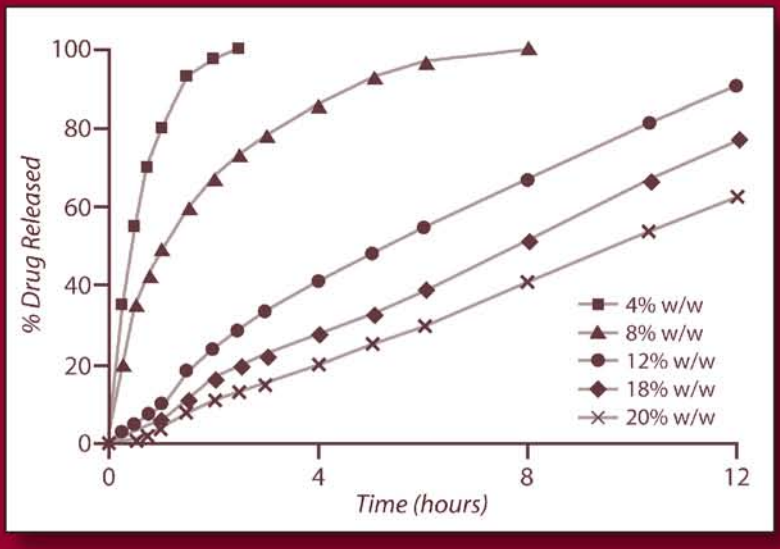
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 176

# Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms

## Third Edition




edited by
James W. McGinity
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# Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms

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# Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms

## Third Edition


Edited by

James W. McGinity

*University of Texas at Austin*

*Austin, Texas, USA*

Linda A. Felton

*University of New Mexico*

*Albuquerque, New Mexico, USA*



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*To Kitty, Rachel, and Michael*
*and*
*in loving memory of Mary Deveise and Phareaux Felton*

# Preface

The elimination of organic solvents from a film-coating system circumvents problems associated with residual solvents and solvent collection. The use of aqueous-based coatings, however, presents its own challenges to the pharmaceutical scientist. While aqueous film-coating technology has advanced to a level where it has become a matter of routine, there are still factors and parameters that must be considered and controlled for the development and commercialization of an optimized finished product. During the past ten years, since the second edition of *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms* was published, considerable advances in aqueous-based film-coating technologies have been made and new polymeric coating materials have been introduced. Publications in the scientific literature have focused on many issues, including the interaction of drugs with functional polymers, the influence of processing parameters on coating quality, and the stabilization of polymeric film coats, as well as basic properties of latex and pseudolatex colloidal dispersions.

The third edition has been revised and expanded to capture the most recent scientific advancements from the literature. Some of the world's leading experts in aqueous film-coating technology have contributed to this edition. Chapters from the second edition have, for the most part, been updated and expanded considerably. New chapters address subjects such as the adhesion of polymeric films to solid substrates, the influence of pigments on the properties of polymeric coating systems, drug interactions with polymers, and the physical aging of polymeric films. The contributing authors have attempted to explain in detail, using illustrated examples, appropriate steps to be taken in order to solve formulation, processing, and stability problems and to achieve an optimized dosage form.

As with the prior editions, the prime objective of this third edition is to further expand the number of new researchers to this field of pharmaceutical technology and to stimulate new ideas, concepts, and product opportunities. Trade names and chemical names of commercially marketed coatings are used throughout the text to help familiarize the reader with the various polymers available for pharmaceutical applications. This book will be a valuable resource for anyone in the pharmaceutical industry working in the area of aqueous-based film coating.

The editors would like to thank the chapter authors for their contributions and our readers who over the past several years have given us many useful comments and suggestions. As usual, your comments and constructive criticism on this third edition will continue to be appreciated.

*James W. McGinity*
*Linda A. Felton*

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# Contributors

**Roland Bodmeier** College of Pharmacy, Freie Universität Berlin, Berlin, Germany

**L. Diane Bruce** Aptuit Inc., Kansas City, Missouri, U.S.A.

**Brian Carlin** FMC BioPolymer, Princeton, New Jersey, U.S.A.

**Mark D. Coffin** GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.

**Thomas P. Farrell** Colorcon, West Point, Pennsylvania, U.S.A.

**Linda A. Felton** College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, U.S.A.

**Steven E. Frisbee** Biovail Technologies, Chantilly, Virginia, U.S.A.

**Isaac Ghebre-Sellassie** Exxpharma LLC, Morristown, New Jersey, U.S.A.

**Michael R. Harris** College of Pharmacy and Health Sciences, Texas Southern University, Houston, Texas, U.S.A.

**Stephen W. Hoag** School of Pharmacy, University of Maryland, Baltimore, Maryland, U.S.A.

**Yohei Hoashi** Gifu Pharmaceutical University, Gifu, Japan

**Yoshiaki Kawashima** Department of Pharmacy, Aichi-Gakuin University, Nagoya, Japan

**Hiroyasu Kokubo** Cellulose and Pharmaceutical Excipients Department, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan

**Shawn A. Kucera** College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.

**Jian-Xin Li** FMC BioPolymer, Princeton, New Jersey, U.S.A.

**James W. McGinity** College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.

**Atul M. Mehta** Elite Laboratories, Inc., Maywood, New Jersey, U.S.A.

**Nasser N. Nyamweya** Pharma Polymers, Degussa, Piscataway, New Jersey, U.S.A.

**Sakae Obara** Cellulose and Pharmaceutical Excipients Department, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan

**Patrick B. O'Donnell** Neurocrine Biosciences, San Diego, California, U.S.A.

**Ornlaksana Paeratakul** Department of Pharmaceutical Technology, Srinakharinwirot University, Bangkok, Thailand

**Hans-Ulrich Petereit** Research and Development Application Technology, Degussa Pharma Polymers, Röhm GmbH, Darmstadt, Germany

**Ali R. Rajabi-Siahboomi** Colorcon, West Point, Pennsylvania, U.S.A.

**Ray C. Rowe** School of Pharmacy, University of Bradford, Bradford, U.K.

**Florence Siepmann** College of Pharmacy, University of Lille, Lille, France

**Juergen Siepmann** College of Pharmacy, University of Lille, Lille, France

**Brigitte Skalsky** Research and Development Application Technology, Degussa Pharma Polymers, Röhm GmbH, Darmstadt, Germany

**Hirofumi Takeuchi** Gifu Pharmaceutical University, Gifu, Japan

# 1

# Pseudolatex Dispersions for Controlled Drug Delivery

**Brian Carlin and Jian-Xin Li**

*FMC BioPolymer, Princeton, New Jersey, U.S.A.*

**Linda A. Felton**

*College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, U.S.A.*

## INTRODUCTION

Reservoir systems, widely used for oral-controlled or sustained drug release, consist of a polymer coating on solid substrates (reservoir), such as powders, beads, granules, capsules, or tablets. Latex or pseudolatex presentations of water-insoluble polymers have largely superseded the use of organic solvents for applying such coatings. Aqueous polymer dispersions are preferred on environmental and safety grounds, as solvents are not used during the coating process. These dispersions or aqueous polymer emulsions may be prepared by emulsion polymerization of a monomer (latex) or by emulsification of a polymer (pseudolatex). Dispersions of biopolymer derivatives, such as the cellulosics, can only be prepared as pseudolatices.

A number of emulsification procedures can be used to prepare pseudolatices from pharmaceutically acceptable polymers, avoiding the problem of monomer residues (1). They are typically prepared by dissolving the polymer in a water-immiscible solvent and emulsifying the organic phase into water. After homogenization, the solvent is removed by vacuum distillation, leaving a 30% solids dispersion in water. Pseudolatices are colloidal dispersions containing spherical solid or semisolid particles in the nanometer to micron range, typically 0.1 to 0.3 μm (Fig. 1). Because the 30% polymer loading is in suspension rather than in

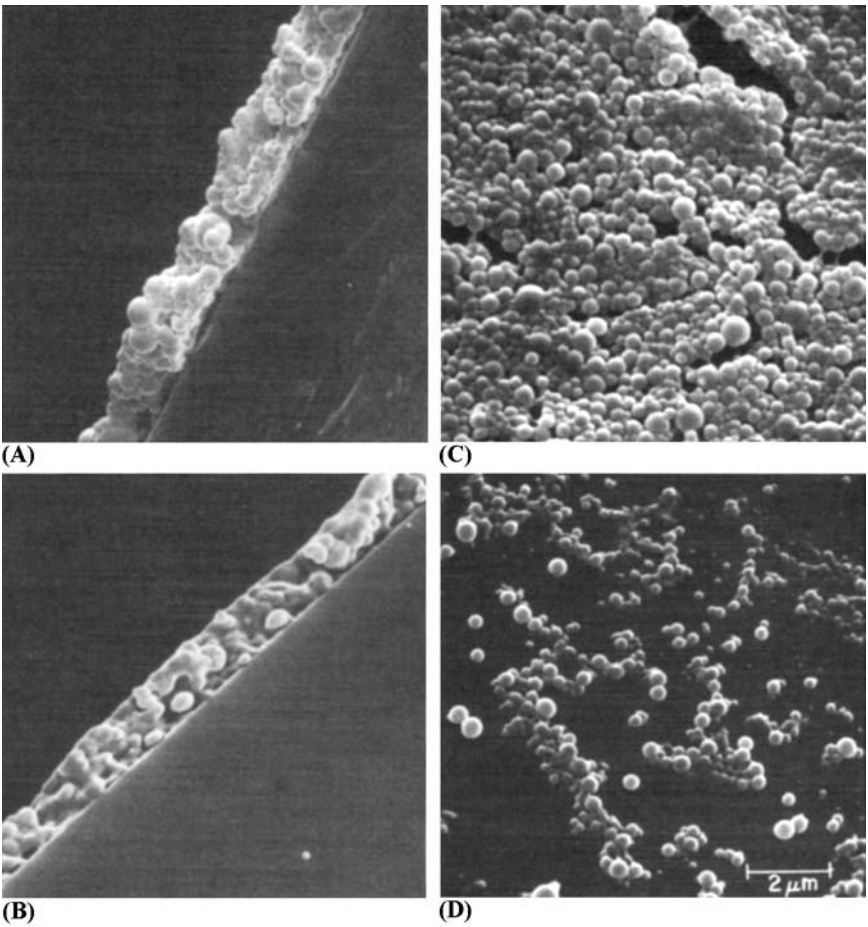


**Figure 1** (**A**) Cross-section: free Aquacoat® ECD film cast on glass, showing discrete polymer spheres. (**B**) Cross-section: same Aquacoat film as coalescence proceeds. (**C**) Top view, free film freshly cast on glass. (**D**) Liquid latex. (Magnification: A, B, D: 8000×).

solution, viscosity is low and the dispersions are free-flowing mobile liquids that can be easily atomized and sprayed. The particle size is also low enough for the particles to be self-suspending.

The Emulsion Polymers Institute, Lehigh University, developed the process for converting water-insoluble polymers into colloidal aqueous dispersions (1) and the Industrial and Physical Pharmacy Department at Purdue University applied the Vanderhoff process to pharmaceutical polymers useful in controlled release technology (2). Ethylcellulose Aqueous Dispersion NF, JP is commercially available as Aquacoat® ECD. A cellulose acetate phthalate (CAP) dispersion for

enteric coating, Aquacoat® CPD, is also available. Both Aquacoat ECD and CPD are plasticizer-free for maximum stability and to afford flexibility to the formulator in terms of performance and regulatory acceptability.

Aquacoat ECD is used to illustrate the formulation, manufacture, and utilization of aqueous polymer dispersions for extended release, taste masking, and moisture barrier applications. Other methods of preparing aqueous dispersions of ethylcellulose have been developed, such as the emulsification of an extrusion melt (ethylcellulose, plasticizer, and oleic acid) into ammoniated water, used for Surelease® (U.S. patents 4,123,403, 4,502,888). Aquacoat CPD is discussed at the end of the chapter for delayed release (enteric) applications and colonic drug delivery.

## ADVANTAGES OF PSEUDOLATEX DISPERSIONS

Aqueous pseudolatex colloidal polymer dispersions offer several advantages over polymers dissolved in organic solvents, including lower spraying viscosities, higher solids loading, higher spray rates, no solvent environmental, toxicity, or flammability issues, and reduced energy requirements relative to aqueous polymer solutions. Wesseling and Bodmeier (3) showed equivalent release profiles of cured plasticized Aquacoat ECD coatings against the corresponding coatings deposited from an organic solvent.

The viscosity advantage is demonstrated by the concentration–viscosity plot (4) in Figure 2. Polymer solution viscosities are dependent on concentration

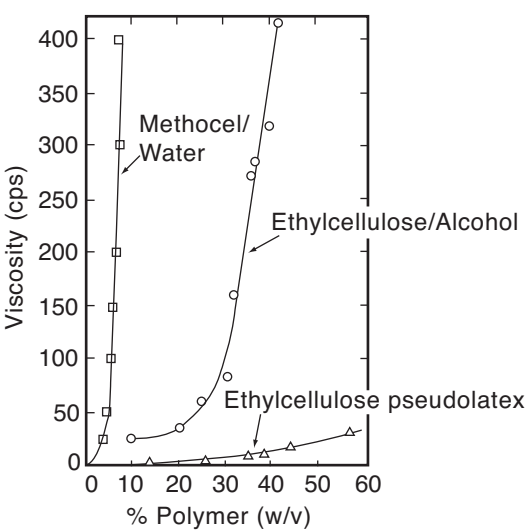


**Figure 2** Concentration–viscosity relationship of ethylcellulose pseudolatex and polymer solutions. *Source*: From Ref. 4.

and molecular weight and usually limit the maximum loading that can be sprayed. With pseudolatices, viscosity is independent of the molecular weight of the polymer in the dispersed system, and greater (undissolved) polymer concentrations (30%) are possible at extremely low viscosities (<150 MPa s).

Water in pseudolatices evaporates more readily compared to aqueous polymer solutions. Figure 3 shows a solvent loss–time curve for a pseudolatex versus an idealized curve for a polymer solution. With a pseudolatex, there is a zero-order loss of water independent of the solids concentration. This is due to the film formation mechanism involving coalescence of discrete submicrometer latex spheres. At about 85% water loss, the curve begins to tail off due to particle–particle contact. Then there is a slow exponential water loss during coalescence. In contrast, the rate of solvent loss from a polymer solution, such as ethylcellulose in an organic solvent, is proportional to the vapor pressure of the solvent. As the concentration of the solids in the solution increases, the vapor pressure drops and there is a concurrent decrease in the rate of solvent loss. Thus, latex dispersions give up water more quickly and completely.

Table 1 compares the water vapor transmission rates (WVTRs) of ethylcellulose films from organic solvents against films from a plasticized ethylcellulose pseudolatex as a function of film thickness. The water vapor pressure across the films was 29.0 mmHg at 30°C in each case. The WVTRs of the pseudolatex films were about one-half the value of the ethylcellulose polymer film from an organic solvent.

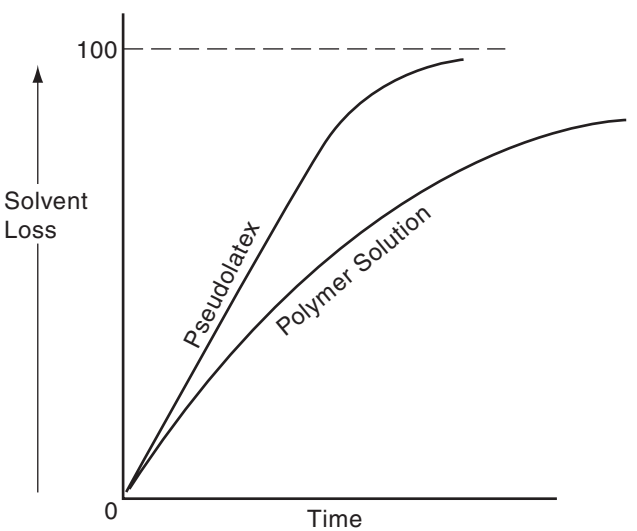


**Figure 3** Solvent loss–time curves for pseudolatex and polymer solution.

**Table 1** Water Vapor Transmission Rates

| Plasticized Ethocel® pseudolatex | | Ethocel 50 cP organosol | | Ethocel-Methocel® E-50 organosol | |
|---|---|---|---|---|---|
| Film thickness (cm) | WVTR[a] ($\times 10^{-5}$) | Film thickness (cm) | WVTR[a] ($\times 10^{-5}$) | Film thickness (cm) | WVTR[a] ($\times 10^{-5}$) |
| 0.0050 | 3.9480 | 0.0046 | 7.5002 | 0.0070 | 13.332 |
| – | – | 0.0078 | 6.0013 | 0.0093 | 11.844 |
| 0.0101 | 3.6824 | 0.0094 | 5.5723 | 0.0105 | 11.023 |
| 0.0120 | 3.3350 | 0.0124 | 5.1478 | 0.0116 | 10.921 |

[a]Water vapor transmission rate in g/hr $cm^2$ mmHg.

## MANUFACTURE OF AQUEOUS POLYMER DISPERSIONS OF ETHYLCELLULOSE

Aquacoat ECD is used for aqueous film coating of solid dosage forms to extend drug release, taste mask, or protect against moisture. It consists primarily of ethylcellulose with a surfactant and a stabilizer from the emulsion stage [sodium lauryl sulfate (SLS) and cetyl alcohol], as shown in Table 2. Traces of dimethylpolysiloxane (<400 ppm) to suppress foaming during distillation may also be present. Ethylcellulose is a cellulose ether made by the reaction of ethyl chloride with alkali cellulose. Each anhydroglucose unit has three replaceable OH groups some or all of which may react with ethyl chloride. Figure 4 shows the molecular formula for ethylcellulose and the method of manufacture is illustrated in Figure 5. The ethylcellulose is dissolved in a water-immiscible organic solvent and cetyl alcohol (cetanol) is added as a dispersion stabilizer. The solution is then emulsified into an aqueous SLS solution. The resulting crude emulsion is passed through a homogenizer to yield a submicron "fine" emulsion, which is then distilled to remove the organic solvent and sufficient water to yield a 30% solids dispersion.

**Table 2** Composition of Aquacoat® ECD

| | Solids (%) | Finished product (%) |
|---|---|---|
| Ethylcellulose | 87.1 | 26.1 |
| Cetyl alcohol | 8.7 | 2.6 |
| SLS | 4.2 | 1.3 |
| Water | – | 70.0 |
| | 100.0 | 100.0 |

*Abbreviation*: SLS, sodium lauryl sulfate.

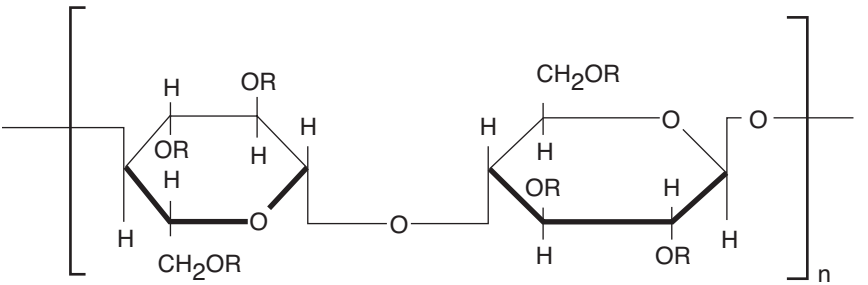


**Figure 4** Ethylcellulose polymer.

## MECHANISM OF FILM FORMATION

The mechanism of pseudolatex film formation is different from that of polymer deposition from a solvent and must be understood in order to avoid unanticipated effects. Polymer and plasticizer deposited from a solution are intimately mixed on a molecular scale. In contrast, a pseudolatex is initially deposited as discrete polymer spheres, which must coalesce to form a continuous film. A plasticizer is often included in the formulation to promote the coalescence process. Chevalier et al. (5) defined four stages of the film formation process for pseudolatices:

1. ordering and close packing of the particles due to water evaporation to give a face-centered cubic construction;

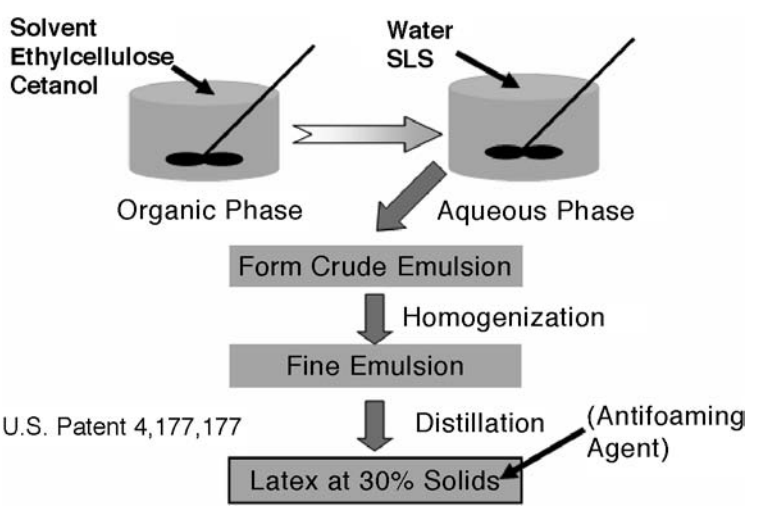


**Figure 5** Manufacturing process of Aquacoat® pseudolatex. *Abbreviation*: SLS, sodium lauryl sulfate.

2. deformation and filling the voids left by the removal of water to give a foam structure;
3. coalescence or fusion of the particles due to fragmentation of the hydrophilic layers between particle cores, leading to phase inversion where the remaining water is no longer the continuous phase; and
4. Polymer interpenetration between cores, forming a continuous polymer matrix and erasing the original particle identity.

Figure 6 provides an example of film formation from a pseudolatex dispersion (6). As water evaporates, the spheres come in contact as a close-packed array. The capillary force of the interstitial water then deforms the particles, causing the spheres to fuse, resulting in complete coalescence. The properties of partially coalesced films may be radically different from that of the corresponding fully coalesced films. Partially coalesced films are also inherently unstable, as coalescence typically continues slowly over time, resulting in decreases in the drug-release rates. It is essential to ensure complete coalescence for long-term stability. Unfortunately, verification of complete coalescence is not always described in the pseudolatex literature, which complicates interpretation of data.

Figure 7 illustrates the forces exerted on spherical particles as water evaporation proceeds. Energy required for the coalescence of the spheres results from the surface tension of the polymer generated by the negative curvature of the particle surface as approximated by Frenkel's equation (7,8):

$$\theta^2 = \frac{3\sigma t}{2\pi\eta r}$$

where $\theta$ is the half-angle of coalescence (contact angle) at time $t$, $\sigma$ is the surface or interfacial tension, $r$ is the radius of a sphere, and $\eta$ is the viscosity of

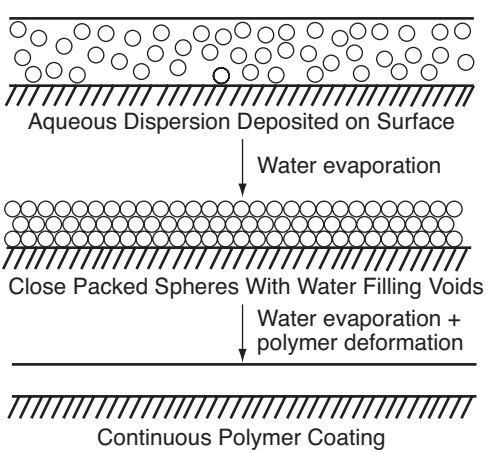


**Figure 6** Film formation from a pseudolatex dispersion. *Source*: From Ref. 6.

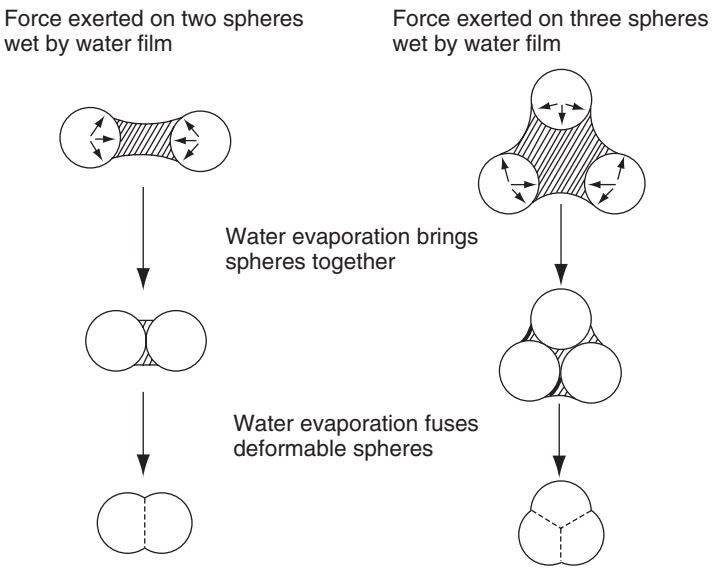


**Figure 7** Particle coalescence during the evaporative phase.

the spheres. The contact angle is initially zero at the point of first contact and increases as the two particles fuse together.

This equation illustrates the inverse relationship between polymer viscosity of the spheres and the degree of coalescence, which is the rationale for adding a plasticizer to the coating formulation to soften the spheres and promote fusion. The equation also illustrates the utility of smaller (submicron) spheres, as less force is required to completely fuse or coalesce the particles. The Frenkel equation uses the air–polymer interfacial tension (dry sintering) as the driving force for coalescence, but Brown (9) proposed that the capillary pressure of interstitial water between the closely packed spheres is the driving force. This is consistent with the presence of surfactants in aqueous polymer dispersions, which would otherwise reduce the driving force implied by the Frenkel equation. According to Brown, when the force due to the capillarity of the interstitial water is large enough to overcome the resistance of the polymer spheres, coalescence to form a continuous film will occur, as shown in Figure 7. "Porous, incompletely coalesced films may be formed from many polymers simply by maintaining, during water evaporation, a temperature lower than a certain critical value. It is observed that for certain polymers a higher temperature exists which is insufficient for coalescence of the porous structure previously formed at a lower temperature, but is adequate for complete coalescence if applied during the entire course of water evaporation. In addition to the plasticization of polymers by the water, the water exerts a strong force responsible for coalescence. The role of water in the process

is of extreme importance." Thus, temperature and rate of water evaporation are critical parameters for film formation.

Brown derived the capillary pressure, $P_C$, for the sphere of radius $R$, between three contiguous latex particles (Fig. 8), in terms of the latex particle radii, $r$:

$$P_C = 2\gamma_w/R = 12.9\gamma_w/r$$

where $\gamma_w$ = polymer–water interfacial tension.

Whether attributed to dry sintering or capillary pressure, both mechanisms share the same pseudolatex particle size dependency. The smaller the particle size, the greater the driving force for coalescence, as shown in Figure 9 (9). Various authors have further refined the Brown equation, as reviewed by Steward (10) in his thesis. Steward provides a very comprehensive online review and discussion of the relevant detailed theory on his Web site (11).

Sperry et al. (12) used predried controls to investigate the role of water in film formation using the transition from an opaque to a clear film [the minimum film-forming temperature (MFFT)]. Latices predried at temperatures below their MFFT were compared to wet latices. Using hydrophobic polymers, the dry MFFT was virtually identical to the wet MFFT, indicating that capillary forces contributed little to film formation. However, the author was unable to rule out that capillary forces may have an effect in more hydrophilic systems. Plasticization by water was said to be the cause of hydrophilic polymers yielding wet MFFTs, which were lower than the dry MFFTs by up to 10°C.

Lissant (13) postulated that closely packed spheres above the maximum packing volume (74%, face-centered cubic configuration) will deform at a constant volume to fill all of the space, forming a rhomboid dodecahedron. Joanicot et al. (14) showed that such polyhedra formed when a latex had lost most of its water, creating a structure similar to that of a foam.

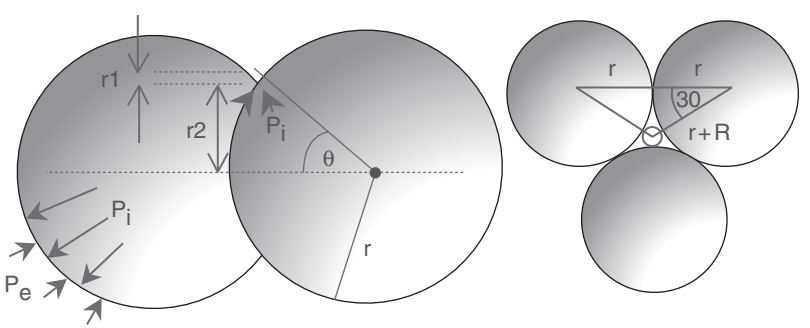


**Figure 8** A cross section of sintered latex particles and a plane view showing the interparticle capillary.

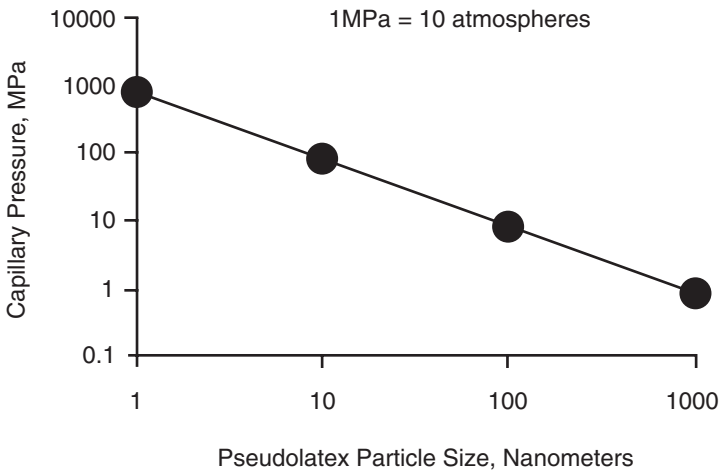


**Figure 9** Capillary pressure is inversely proportional to particle size.

Using small-angle neutron scattering (SANS), Chevalier et al. (5) demonstrated a reversible compression of the latex-in-water dispersion to a latex-in-water foam, followed by irreversible coalescence of the foam with inversion to a water-in-latex topology. Water is involved in both stages. Coalescence depends on the fragmentation of the foam membranes. The phase inversion involves connection of latex domains and fragmentation of water domains, driven by the spontaneous curvature of membranes according to their water content. This work thus differentiated between coalescence, which was defined as the break-up of the hydrophilic layer, and subsequent polymer chain interdiffusion.

Nicholson and Wasson (15) divided coalescence mechanisms into two groups: (*i*) those dependent on sintering or capillarity processes, which dominate when there are polar repulsions present; and (*ii*) those dependent on polymer chain interdiffusion, when there is very little repulsion between particles. According to Voyutskii (16), interdiffusion of polymer chains (autohesion) across what was the interface between discrete polymer spheres is the final step in the formation of integral homogeneous latex films. Voyutskii and Vakula (17) provided a comprehensive review of the effects of self-diffusion and interdiffusion in polymer systems. This is consistent with the strength and cohesiveness of films obtained immediately when deposited from good organic solvents due to complete solvation and maximum extension of polymer chains. Interdiffusion may take longer in latex films, especially if coalescence is not complete. Bradford and Vanderhoff (18) studied the changes in structure occurring in an uncured, continuous, transparent film as a function of film age. Using transmission electron microscopy, within hours of casting, vestiges of the original latex particles could be seen, which disappeared over a 14-day period, accompanied by the exudation of material from within the film, assumed to be a hydrophilic stabilizer.

Bradford and Vanderhoff (19) coined the term "further gradual coalescence" and showed that it occurred at the film–substrate and film–air interfaces as well as within the film's interior where a stabilizer was exuded into "pockets." The size of the holes and porosity due to the leaching of surfactant was reduced if the film was aged or heat-treated before testing. Interdiffusion requires temperatures above the glass transition temperature ($T_g$), as there will be insufficient polymer segment mobility in the glassy state.

Using SANS, Hahn et al. (20,21) demonstrated "massive" interdiffusion of polymer chains from different latex particles during particle coalescence. A 30-fold increase in diffusion coefficients was observed on increasing the "tempering" or curing temperature from 70°C to 90°C. Also using SANS, Sperling et al. (22) concluded that the rate of coalescence was dependent on where the polymer chain ends lie with respect to the particle surface and that films form faster when the ends lie on the particle surface.

Distler and Kanig (23) postulated that upon deformation of the particles into a film, hydrophilic surface boundary layers would interdiffuse to form an interconnected hydrophilic "honeycomb," which might inhibit further hydrophobic polymer interdiffusion. The authors pointed to the fact that a normally transparent film may turn opaque, or even show Bragg diffraction iridescence, when swollen with water, both of which require latex-particulate-sized features to cause the necessary difference in refractive index and crystalline structure, respectively.

The increased water absorbency, reduced surfactant leachability, and reduced tendency to whiten (swell) in water were attributed by Aten and Wassenburg (24) to the redistribution of surfactant molecules from the surfaces of the latex particles to a more even distribution throughout the film, following a period of secondary "drying" above the polymer $T_g$. Such redistribution was ascribed to the increased polymer chain mobility, which was not apparent in films annealed below the $T_g$.

## PRACTICAL ASPECTS OF PSEUDOLATEX FILM COATING

Pseudolatex film coating is a complex process, and the formulation scientist must carefully consider the coating formulation, the physicochemical properties of both the dosage form and the drug, and the processing parameters used. In addition to the pseudolatex dispersion, a coating formulation often includes plasticizers to enhance the flexibility of the film and facilitate polymer sphere coalescence, antiadherents to prevent substrate agglomeration during both the coating process and storage, surfactants to promote spreading of the atomized droplets own the substrate surface, and pigments. The addition of other excipients can significantly impact the physical stability of the dispersion, drug release, and film quality. The dosage form should be strong enough to withstand attrition during coating. The drug itself must be stable to the temperatures used during processing. For these aqueous-based systems, the drug should also be stable to the moisture challenge of aqueous film coating or a seal-coat must be used to

protect the active. Processing parameters must be carefully controlled to optimize film formation. This section discusses some of the most critical concerns during pseudolatex coating processes.

## Drying and Curing

Aqueous pseudolatices have the appearance and consistency of milk and are therefore easily sprayable using conventional aqueous coating techniques, such as fluid bed (Wurster) or perforated pan coating. The coated substrate is dried in situ during the coating process and may or may not require subsequent heat treatment (curing) to complete coalescence of the polymer spheres, depending on the coating formulation and conditions employed during coating. This additional curing may sometimes be described as "drying" at elevated temperature.

As discussed previously, the mechanism of film formation from aqueous pseudolatices of water-insoluble polymers, such as Aquacoat ECD, is very different from simple deposition of a polymer from solvent-based coatings. Water evaporation concentrates the polymer particles in a closely packed arrangement on the substrate surface, and the capillary force of the interstitial water deforms the particles to cause coalescence and produce a dense, continuous film. When the coated substrates are cured at a temperature higher than the MFFT, the interstitial water in the coating layer will ensure an adequate capillary force for the completion of film coalescence. Unfortunately, the warnings against overdrying given by Brown (9) are not always heeded, and overdrying remains a leading cause of partial coalescence and associated problems, particularly decreasing release rates on storage due to further gradual coalescence.

The rate of heat transfer not only affects the rate of evaporation of the solvent, but also, in the case of latex and pseudolatex systems, regulates the rate and degree of coalescence of the polymeric material. Rapid drying rates, though generally desirable, may at times have a negative effect. The rapid loss of water will not permit sufficient capillary pressure to develop, and the latex particles cannot coalesce to form coherent films. Excessive drying conditions also do not allow the coating formulation to spread evenly over the substrate and thus inhibit particle deformation and coalescence (25). The drying rate is determined by several parameters, including the latent heat of vaporization and the relative humidity (RH) of the incoming drying air (26).

Ideally, humidity should be controlled during the coating or curing process itself to avoid such overdrying, as illustrated in Figure 10. Curing at elevated temperatures using ambient humidity may not be sufficient to complete coalescence of overdried particles. The resulting drug-release profiles may decrease on high-humidity storage. When high-humidity curing gives lower release profiles than the corresponding dry curing, this may be a sign of overdrying during coating, resulting in partial coalescence. High-humidity coating conditions facilitate pseudolatex coalescence and can be created by using low-dispersion solids (e.g., diluting the Aquacoat ECD to below 15%) and humidifying the inlet drying air.

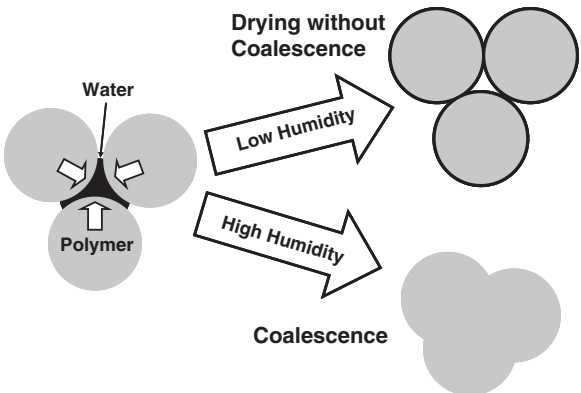


**Figure 10** Film formation from aqueous lattices.

Curing to achieve complete coalescence and provide stable drug-release profiles can thus be minimized or eliminated (27).

To determine if a curing step is necessary, the coated substrates may be challenged with heat and humidity. There should be no decrease in release rate if the film has fully coalesced during coating, with the caveat that thermal stressing alone (i.e., without elevated humidity) will not distinguish overdried partially coalesced from fully coalesced films. Both should give thermostable release profiles, but the overdried profile will be faster and potentially could decrease on long-term storage, especially on humidity challenge. This interplay is demonstrated in Figure 11, where the challenge times (24–48 hours) are significantly higher than the curing

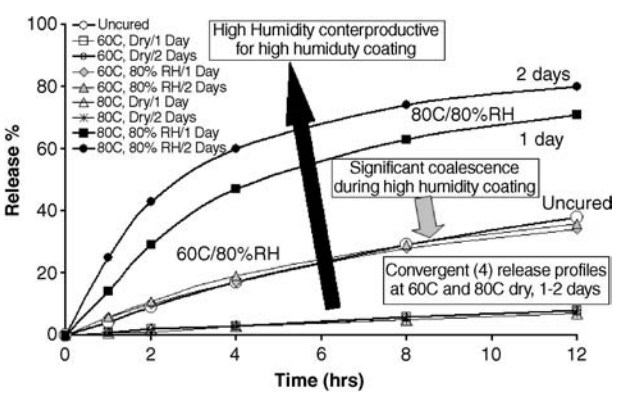


**Figure 11** Effect of curing conditions on theophylline release from coated pellets (15% solids, high-humidity coating, TEC/ECD = 1:4, 4% weight gain). *Abbreviation*: TEC, triethyl citrate. *Source*: From Ref. 30.

time used in practice. High humidity was maintained during coating by direct humidification of inlet air and the use of low solids in the coating dispersions (i.e., higher water spray input). The substrate was 70% theophylline pellets coated with Aquacoat ECD plasticized with triethyl citrate (TEC) (1:4 TEC: Aquacoat ECD solids). Although a significant degree of release retardation was achieved during coating (40% released at 12 hours), curing with dry heat further reduced the release rate to approximately 10% at 12 hours. This profile shows no further time or temperature dependence, as demonstrated by the convergence of the four profiles: 24 hours, 48 hours, 60°C, and 80°C. No further retardation was achieved on high-humidity challenge at the same temperatures, which indicates convergence to a true minimum release rate. In this case, the elevated humidity challenge proved detrimental to coating performance as evidenced by the time- and temperature-dependent increases in release rate. High-humidity curing has been claimed as being necessary for stable release profiles (28), but if humidity is adequately controlled during coating (29), curing may not be required at all, or simple dry curing may suffice.

Results from a dry counter-example are shown in Figure 12. Note the essentially immediate release of the uncured pellets and the sensitivity of the "false" thermostable dry-cured profile to the humidity challenge. Full-strength plasticized Aquacoat was used without humidification of inlet air.

The ideal release profile should not exhibit time, temperature, or humidity dependence on short-term challenges, as shown in Figure 13. This example used low solids loading to maintain high humidity (no humidification of inlet air). Note that during this and the two preceding examples, the coating loading was simultaneously lowered from 4% to 3% to 2% to maximize the amount of drug released. Fully coalesced films of Aquacoat ECD provide significant release retardation,

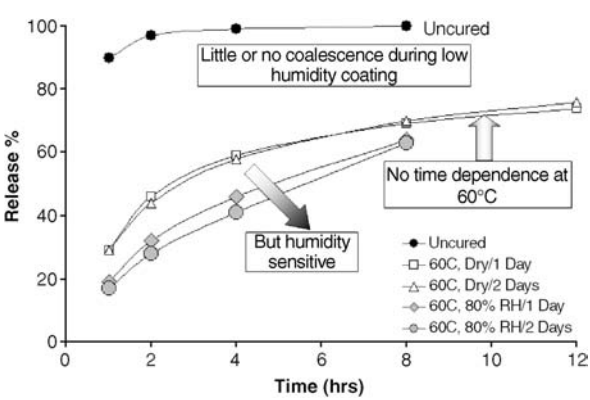


**Figure 12** Effect of low-humidity coating and curing conditions on drug release (35% solids, TEC/ECD = 1:4, 3% weight gain). *Abbreviation*: TEC, triethyl citrate. *Source*: From Ref. 30.

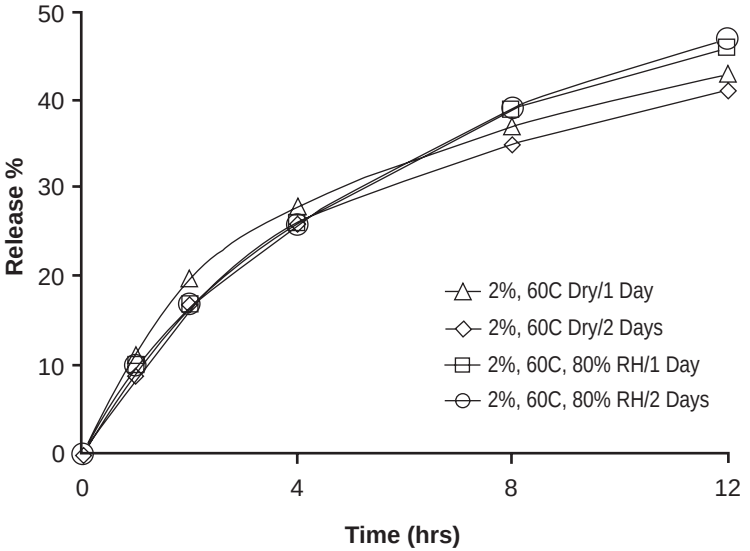


**Figure 13** Drug-release profiles independent of time, temperature, and humidity. 15% solids, low humidity coating, TEC/ECD = 1:4, 2% weight gain. *Abbreviation*: TEC, triethyl citrate. *Source*: From Ref. 30.

which may be too much for some poorly permeable drugs, requiring precision coating using very low loadings. To increase permeability in such cases, pore-forming excipients may be added to the coating formulation.

Typically, curing for one to two hours at 60°C will be sufficient, as shown in Figure 14. Curing can be carried out by oven heating or in situ heating in a fluid-bed coater using increased fluidization to avoid pellet agglomeration. Coating is normally carried out below the $T_g$ of the film to minimize tackiness, especially under the low bulk fluidization conditions in the slowly percolating pellet bed outside the Wurster column. If necessary, a conventional clear (e.g., LustreClear®) or colored (e.g., Opadry®) water-soluble polymer top coating can be applied to enable low fluidization curing above the $T_g$. If maximum retardation is ensured initially, then the long-term storage stability should be good, including elevated humidity, as shown in Figure 15, which is the same batch as in Figure 14 retested after storage at 40°C/75% RH for periods of up to eight months.

It should be noted that Aquacoat ECD contains SLS, which tends to reside on the surface of the dried polymer spheres. Faster release of nonionic or basic drugs from ECD-coated substrates at high pH is strongly indicative of partial coalescence. Because SLS is insoluble in acid but soluble at neutral pH, pH-dependent SLS channels in partially coalesced ECD films may be observed (3). Such pH dependency is not seen in fully coalesced Aquacoat ECD or ethylcellulose spiked with SLS and deposited from organic solvents.

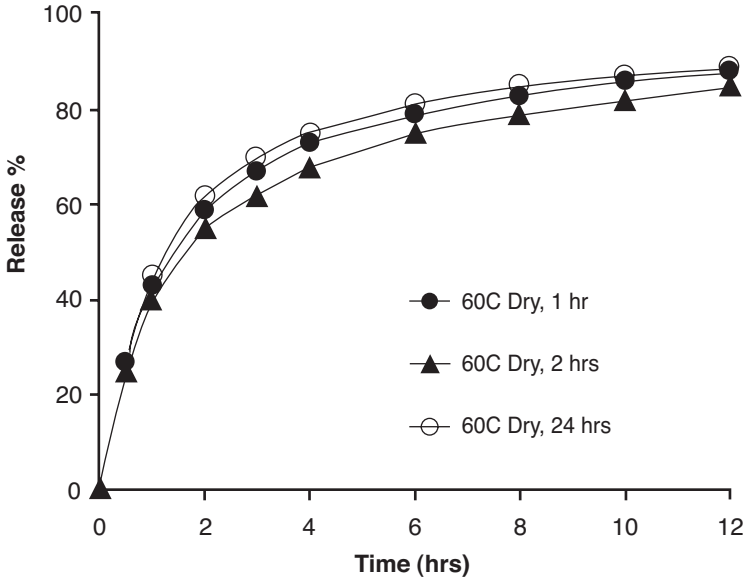


**Figure 14** Drug release as a function of curing time (1.5% weight gain, TEC/ECD = 1:4, 15% solids, high-humidity coating). *Abbreviation*: TEC, triethyl citrate. *Source*: From Ref. 30.

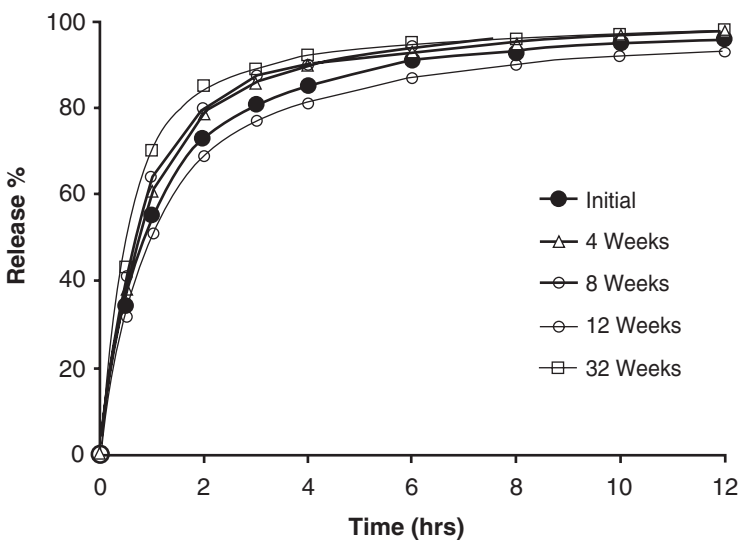


**Figure 15** Drug release as a function of long-term stability at 40C/75% RH (high-humidity coating, 15% solids, 1.5% weight gain, cured at 60°C, dry/1 hr). *Abbreviation*: RH, relative humidity. *Source*: From Ref. 30.

## Plasticizers

Plasticizers are commonly added to film coating formulations to increase the flexibility of the film, decrease the $T_g$ and MFFT, and for pseudolatex dispersions, to facilitate coalescence. The type and level of plasticizer may also affect the drug release by changing the diffusivity of the film. Plasticizer effects are due to a decrease in the cumulative intermolecular forces along the polymer chains (reduction in cohesion), which generally lowers the softening temperature and decreases the $T_g$ (31). Plasticizers impart flexibility and reduce brittleness, as shown in Figure 16, where insufficient plasticizer was used in the batch on the right and the coating cracked upon drying. Pseudolatex spheres of Aquacoat ECD have a $T_g$ of ~89°C and must be adequately plasticized to reduce the film-forming temperature to within the processing temperature range.

The basic requirements of any plasticizer in a polymer system, including latex emulsions, are compatibility and permanence. To be compatible, the plasticizer should be miscible with the polymer. To be permanent, plasticizers should be nonvolatile, with a high boiling point. The effectiveness of a plasticizer can be evaluated by measuring the $T_g$ of the film. Table 3 gives data for six plasticizers useful in sustained or prolonged release applications of pseudolatices for oral solid dosage forms. These plasticizers are all high-boiling organic materials, have low vapor pressures, and, with the exception of TEC, are relatively insoluble in water.

### Glass Transition Tempe rature and MFFT

The $T_g$ is the temperature at which a polymer changes from a glassy state to a rubbery state. Below the $T_g$, the polymer is rigid and glassy, with very limited polymer segment movement. Above the $T_g$, the polymer is in a soft rubbery state, with significant segmental mobility of the polymer chains. If the polymer $T_g$ is

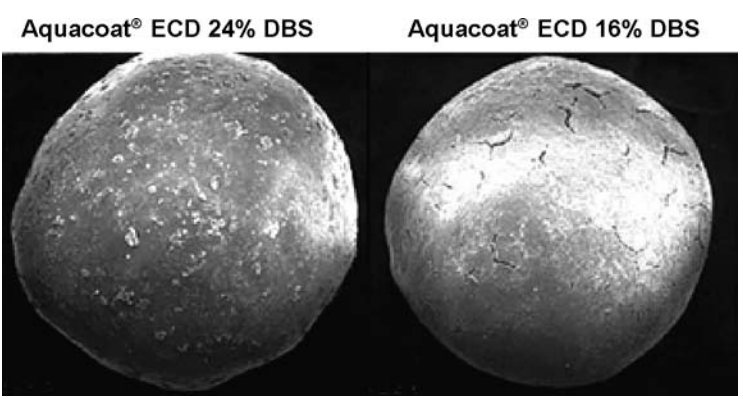


**Figure 16** Effect of sufficient/insufficient plasticizer content on coating morphology. *Abbreviation*: DBS, dibutyl sebacate.

**Table 3** Plasticizer Physical Constant Data

| | BP (°C) | Vapor density (air = 1) | Vapor pressure (mmHg) | Water solubility |
|---|---|---|---|---|
| DBS | 349 | 10.8 | 10 at 200°C | Negligible |
| DEP | 298 | 7.66 | 100 at 220°C | Insoluble |
| TEC | 294 | 9.7 | 1 at 107°C | 6.5% |
| TBC | 170 (1 mmHg) | 12.4 | 1 at 170°C | Insoluble |
| ATBC | 173 (1 mmHg) | 14.1 | 0.8 at 170°C | Insoluble |
| Myvacet 9-45 | >500 | NA | Nonvolatile | Negligible |

*Abbreviations*: DBS, dibutyl sebacate; DEP, diethyl phthalate; TEC, triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate.

higher than the desired operating temperatures for coating, it is necessary to add a plasticizer to the dispersion to obtain good film formation. The formation of a continuous film (i.e., transparent and crack free) also depends on the MFFT of the polymer film, which in turn depends on the elastic modulus (resistance to particle deformation). Above the MFFT, coalescence of latex particles can occur, giving clear films, while friable discontinuous opaque powdery films result when the temperature is below the MFFT. A balance must be struck, however, as too low a $T_g$ or MFFT may cause tackiness and particle adhesion during coating (32).

Figure 17 and Table 4 show the effect of plasticization on the $T_g$ of an ethylcellulose latex. Aquacoat ECD films containing various plasticizers were cast, dried at room temperature overnight, and then oven-dried at 60°C for eight hours. These films were evaluated after 12-hour equilibration at room temperature. The study was conducted on a Perkin-Elmer TMA7, initially at 20°C/min heating rate and then at 5°C/min, resulting in more detailed data collection. All measurements were replicated. It can be seen that as the concentration of the plasticizer was increased, the $T_g$ for the ethylcellulose pseudolatex was lowered, thereby promoting coalescence and film formation. The rank order of effectiveness was TEC > dibutyl sebacate (DBS) > diethyl phthalate (DEP) > acetylated monoglyceride (Myvacet 9-45). For the first three, the optimum level is about 20% to 24%, and for Myvacet 9-45, approximately 30%. These percentages are with respect to Aquacoat ECD solids (i.e., parts plasticizer to 100 parts Aquacoat ECD solids) and not the percentages in the final coating formulation. For example, 25% wrt Aquacoat ECD solids (1:4) is 20% of the total.

### Solubility Parameter

The compatibility or miscibility of a plasticizer can be determined by the solubility parameter as investigated by Hildebrand and Scott (33). These can be calculated

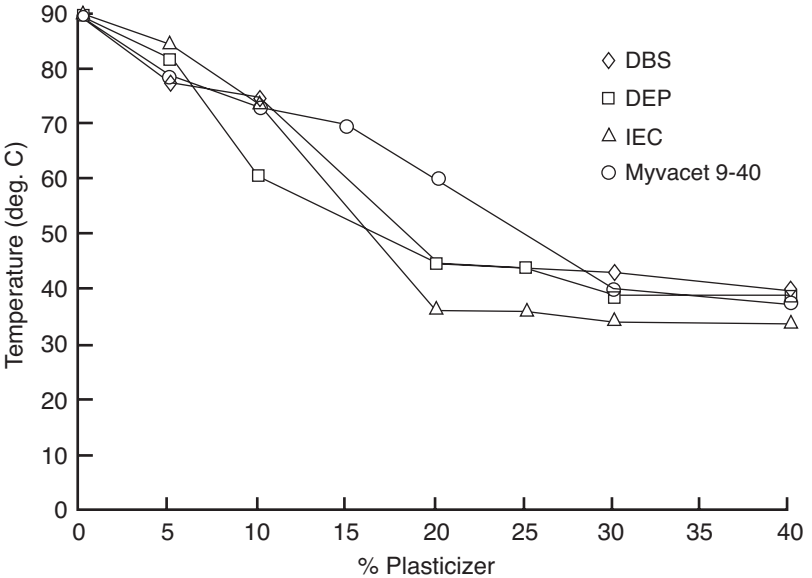


**Figure 17** Glass transition ($T$) of plasticized ethylcellulose latex.

for the polymer and plasticizer or found in the literature. In their calculations, Hildebrand and Scott relied on the molar energy of evaporation and the density of cohesive energy to define the solubility parameter of a known plasticizer. For nonpolar systems, the enthalpy of polymer–plasticizer mixing depends on their respective solubility parameters, $\delta_1$ and $\delta_2$. Onions (6) explored in more detail the Hildebrand-Scott and Flory-Huggins approaches to characterizing the extent of polymer–plasticizer affinity. With a known latent heat of evaporation for

**Table 4** Glass Transition Temperature ($T_g$) Study for Ethylcellulose Latex

| Plasticizer (%) | Temperature (°C) | | | Myvacet 9-40 |
|---|---|---|---|---|
| | DBS | DEP | TEC | |
| 0[a] | 89 | 89 | 89 | 89 |
| 5 | 77 | 81.5 | 84 | 78 |
| 10 | 74 | 60 | 73 | 72.5 |
| 20 | 44 | 44 | 36 | 59 |
| 25 | – | 43 | 35.5 | – |
| 30 | 42.5 | 38 | 33.3 | 39 |
| 40 | 39.5 | 38 | 33.3 | 37 |

[a]Ethylcellulose (neat) $T_g$ = 129°C.
*Abbreviations*: DBS, dibutyl sebacate; DEP, diethyl phthalate; TEC, triethyl citrate.

solvent or plasticizer, Hildebrand proposed that the solubility parameter δ could be calculated as:

$$\delta = \left(\frac{\Delta E_V}{V}\right)^{1/2} - \left(\frac{\Delta H_V RT}{V}\right)^{1/2}$$

where $\Delta E_V$ is the molar energy of evaporation of the plasticizer in its pure state, $\Delta H_V$ is the latent heat of evaporation of the plasticizer, $R$ is the ideal gas constant, $T$ is the absolute temperature, and $V$ is the molar volume of the plasticizer. The term $\Delta E_V / V$ is usually referred to as the density of cohesive energy and represents the energy required to vaporize 1 $cm^3$ of liquid.

Once the solubility parameters of the polymer itself (ethylcellulose) and the candidate plasticizer are known, the enthalpy of the mixture ($\Delta H$) can be determined:

$$\Delta H = V_m \left[\left(\frac{\Delta E_1}{V_1}\right)^{1/2} - \left(\frac{\Delta E_2}{V_2}\right)^{1/2}\right]^2 \phi_1\phi_2 - V_m\left(\delta_1 - \delta_2\right)\phi_1\phi_2$$

where the subscripts 1 and 2 refer to the polymer and plasticizer, respectively. The total molar volume of the mixture is $V_m$, $V_1$, and $V_2$ are molar volumes, $\Delta E_1$ and $\Delta E_2$ are molar energies of vaporization, $\phi_1$ and $\phi_2$ are volume fractions, and $\delta_1$ and $\delta_2$ are the respective solubility parameters.

The mixture enthalpy, $\Delta H$, depends on the relative solubility parameters ($\delta_1 - \delta_2$), and the best theoretical case is a binary mixture miscible in all proportions ($\delta_1 = \delta_2$). Mixture entropy is positive and the Gibbs free energy ($G = H - T\Delta S$) is negative. The solubility parameters for a range of plasticizers and ethylcellulose are given in Table 5. Plasticizers with solubility parameters close to that of the polymer are generally considered to be more miscible.

**Table 5** Solubility Parameters

| Polymer/plasticizer | Solubility parameter $(cal/cm^3)^{1/2}$ |
|---|---|
| Ethylcellulose | 8.5–10.1 |
| DEP | 8.9–9.9 |
| DBS | 7.7–9.2 |
| TEC | 8.6–9.5 |
| Glyceryl triacetate (Triacetin) | 8.8–9.9 |
| Caster oil | 8.53 |
| TBC | 9.04 |

*Abbreviations*: DBS, dibutyl sebacate; DEP, diethyl phthalate; TEC, triethyl citrate; TBC, tributyl citrate.

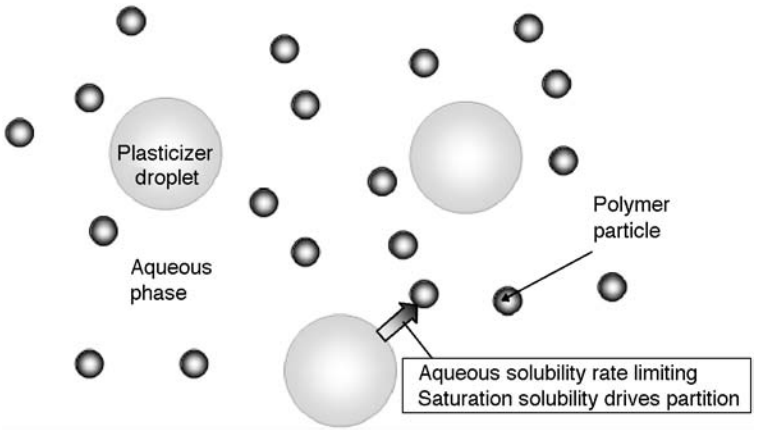


**Figure 18** Plasticizer uptake in aqueous polymer dispersions.

## Plasticizer Incorporation: Mixing Time

The mechanism of plasticization of pseudolatex dispersions needs to be contrasted with that of solvent systems. In a solvent system, the polymer and plasticizer are dissolved together. On stirring into aqueous pseudolatex dispersions, a water-insoluble plasticizer forms a coarse emulsion due to the presence of the

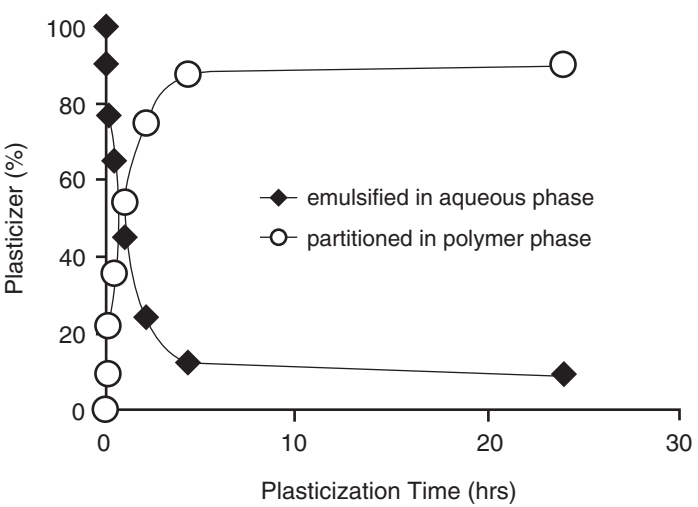


**Figure 19** ATBC uptake in aqueous ethylcellulose dispersion (solids content, 15%; plasticizer/polymer, 1:5). *Abbreviation*: ATBC, acetyl tributyl citrate. *Source*: From Ref. 35.

**Table 6** $T_{85}$ Calculated from Homologous Series

| Plasticizer | $T_{85}$ (min) | Plasticizer | $T_{85}$ (min) |
|---|---|---|---|
| ATBC | 220 | ATEC | 50 |
| TBC | 100 | TEC | (25)[a] |

[a]Predicted.
*Abbreviations*: DBS, dibutyl sebacate; DEP, diethyl phthalate; TEC, triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; ATEC, acetyl triethyl citrate.

pseudolatex process surfactants, as shown in Figure 18. High shear dispersion of a plasticizer is not recommended due to potential destabilization of the pseudolatex.

For the plasticizer to be effective, it must partition into the polymer spheres. Due to their low aqueous solubility, transfer via the aqueous medium is rate limiting. Siepmann et al. (34) quantified the rates of partitioning of various plasticizers into Aquacoat ECD, as exemplified in Figure 19, and the authors considered a minimum uptake of 85% to be reasonable with respect to common curing conditions. The greater the aqueous solubility, the faster the time to reach 85% partitioning ($T_{85}$). $T_{85}$ values for a range of citrate homologs are shown in Table 6. Although Siepmann et al. did not measure a $T_{85}$ for TEC, a reasonable estimate can be made from the other homologs.

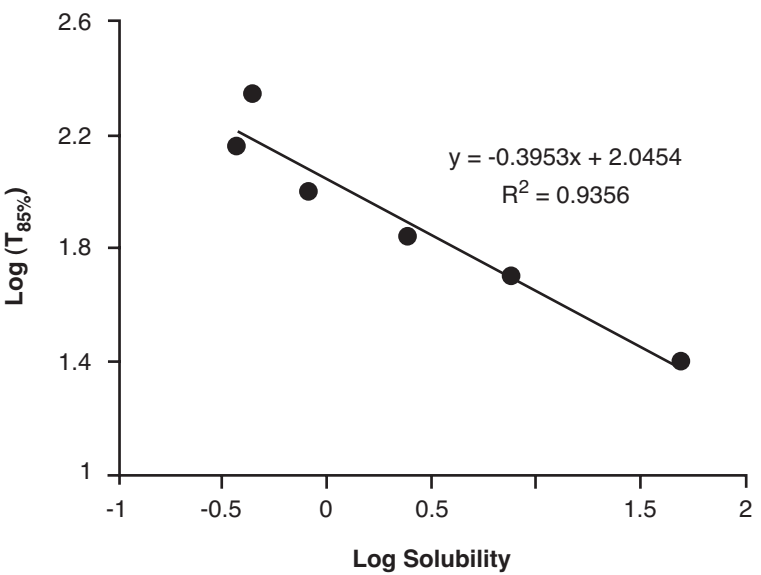


**Figure 20** Effect of plasticizer solubility on $T_{85\%}$.

Correlation of the aqueous solubility of the plasticizer with the $T_{85}$ is shown in Figure 20. The practical significance of extended plasticizer mixing times depends on the degree of coalescence of the plasticized film. If fully coalesced, the degree of partitioning (or plasticizer mixing time) is not of practical significance, and the time allowed for plasticizer mixing with the Aquacoat ECD does not affect the release rates (35). Siepmann et al. measured partitioning in an aqueous system but, even if not fully partitioned in the mixing tank, partitioning will still proceed during coating, especially as the water is progressively removed.

## APPLICATIONS DATA

As shown in Table 7, variables that greatly affect the release-rate profiles through a pseudolatex film relate to both the substrate and the drug physicochemical characteristics, most notably solubility. The release patterns for coated beads were analyzed for two model drug systems: phenylpropanolamine (PPA) HCl and anhydrous theophylline. Aquacoat ECD was applied at various levels and the in vitro drug-release rate was shown to be inversely proportional to film loading (thickness), suggesting that constant drug diffusion through the film is maintained. Such zero-order release is characteristic of a reservoir and rate-limiting barrier, as long as a concentration gradient is maintained in the bead.

Flux of drug across the membrane where a water-insoluble membrane encloses a core reservoir (containing the drug) is given by Fick's first law:

$$\frac{dM}{dt} = \frac{ADK\Delta C}{l}$$

where $A$ is area, $D$ is the diffusion coefficient, $K$ is the partition coefficient of drug between membrane and core, $l$ is the diffusional path length (film thickness), and $\Delta C$ is the concentration difference across the film. The surface area available for drug diffusion is a critical variable where the mechanism of drug release is diffusion controlled by a thin film membrane and the kinetics are apparently zero order and Fickian. It is necessary to control particle size and size distribution of the nonpareil beads to be coated, otherwise batch-to-batch differences in release rates might be observed for a given film loading under identical coating

**Table 7** Variables Affecting Release Rate from Drug Beads Coated with Ethylcellulose Aqueous Dispersion

| | |
|---|---|
| Bead size distribution | Film continuity |
| Bead diameter/surface area | Drug solubility |
| Bead surface | Coated bead sample uniformity |
| Bead moisture content | Film thickness |

conditions. Variability can be minimized by the use of beads of the same sieve fraction, same manufacture, narrowest size distribution, and regular geometry (sphericity). It has been demonstrated by mathematical analysis that as the thickness of coating increases from zero, the release profile will gradually decrease and change from first order to zero order, since the release mechanism of the coated sphere changes from a matrix-dominant mechanism to diffusion from a reservoir through a rate-limiting membrane (36,37).

Figure 21 shows the effect of various coating (pseudolatex) levels applied to beads of a fairly regular geometry containing anhydrous theophylline. The plasticizer was DBS at a level of 24% (pseudolatex solids:DBS ≈ 4:1). Coating levels of 6% to 8% were necessary on nonpareils of 18 to 20 mesh size (0.84–1.00 mm) in order to sustain apparent zero-order drug release. The level of plasticizer, shown at 24%, is not an arbitrary amount, as seen in Figure 22. Here, cumulative release curves for identical beads coated to constant film weight addition (6%) were compared as a function of the level of DBS in the coating formulation. At lower plasticizer levels, there is insufficient plasticizer to soften the ethylcellulose spheres and promote coalescence and film formation at the processing temperatures employed.

PPA HCl represents a more water-soluble drug, which poses an additional dosage design challenge when coating with a water-based polymeric dispersion. Coating conditions employed in the application of an aqueous film to such water-soluble drugs must be modified to minimize partitioning into the coating. An example is given in Table 8, where the ethylcellulose pseudolatex was applied at 30% coating solids to a 10% theoretical coating level. A slow/fast technique was employed, whereby fluid spray rates were held at 2 to 3 mL/min until the

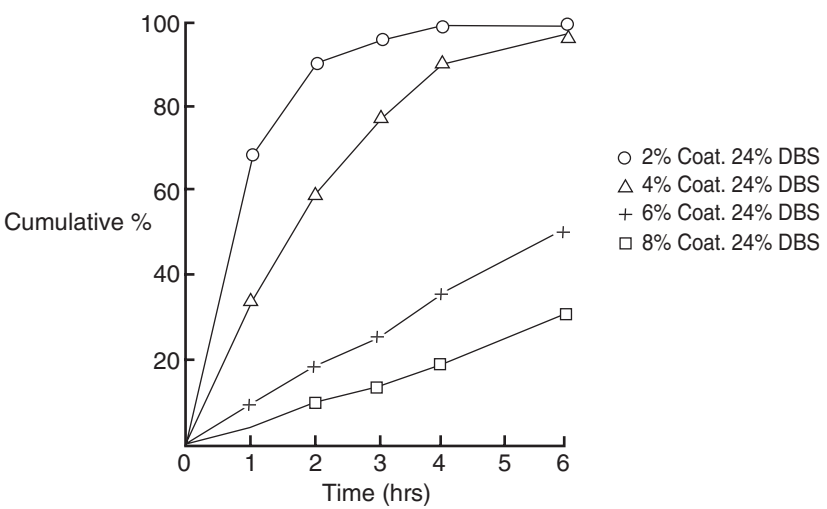


**Figure 21** Effect of film coat level on dissolution.

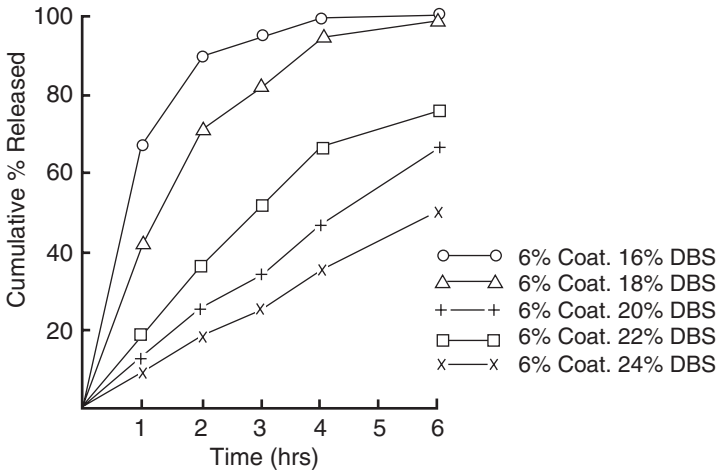


**Figure 22** Effect of plasticizer level on dissolution.

beads were sealed and the coating system stabilized; then the rate was increased to up to 10 mL/min. The time, temperature, and humidity parameters were not optimized in this comparative study, so the degree of coalescence may have varied.

Six plasticizers were studied at a constant film weight addition and incorporation level (30% based on latex solids) to ascertain effects on in vitro release of PPA HCl as shown in Figure 23. The three slowest formulations employed the more hydrophobic butyl ester plasticizers. Faster release was obtained from formulations with ethyl ester or acetylated monoglyceride plasticizers. The stability of drug release after storage at room temperature and at 35°C for three and six months was determined for three formulations as shown in Figures 24 to 29.

Figure 24 shows the room temperature stability profile for PPA beads coated with an ethylcellulose latex plasticized with tributyl citrate, while elevated temperature (35°C) stability is shown in Figure 25. An increase in release was observed when stored for three months at 35°C, the profile remaining unchanged between three and six months of storage. The increase in release rate for these coatings could not be explained by loss of plasticizer (Table 9) or changes in film porosity (Table 10).

Figures 26 and 27 show the corresponding room temperature and 35°C stability profiles for PPA release using TEC as plasticizer. For beads stored at either condition, the drug-release rate slowed at three months, with a further slight slowing at six months. This decreased release rate on storage is characteristic of an incompletely coalesced film at the time of initial dissolution testing. Pseudolatex coating containing TEC showed the largest loss (Table 9) in plasticizer content after six months of storage at both room temperature and at 35°C, which did not correlate with the decrease in release rates.

(*Text continues on page 30.*)

**Table 8** Coating Conditions Employed in Application of Aqueous Pseudolatex to Water-Soluble Drug

| | |
|---|---|
| *Process equipment* | |
| Column | Wurster 4 in./6 in. |
| Nozzle | Spraying systems $^{1/4}$J series 285070SS |
| Partition | 3/8 in. setting |
| Pump | Masterflex 16 pump head |
| *Coating conditions* | |
| Bead load (kg) | 1.0 |
| Process air temperature (°C) | 55–56 |
| Pumping rate (mL/min) (normal) | 10 |
| Pumping rate (mL/min) (slow coating) | 2–3 |
| Atomizing air (psi) | 15 |
| *Coating time* | |
| 10% film weight (min) | 65–73 |
| Slow coating (min) | 29–34 |
| Normal coating (min) | 32–41 |
| Postdrying (min) | 30 |

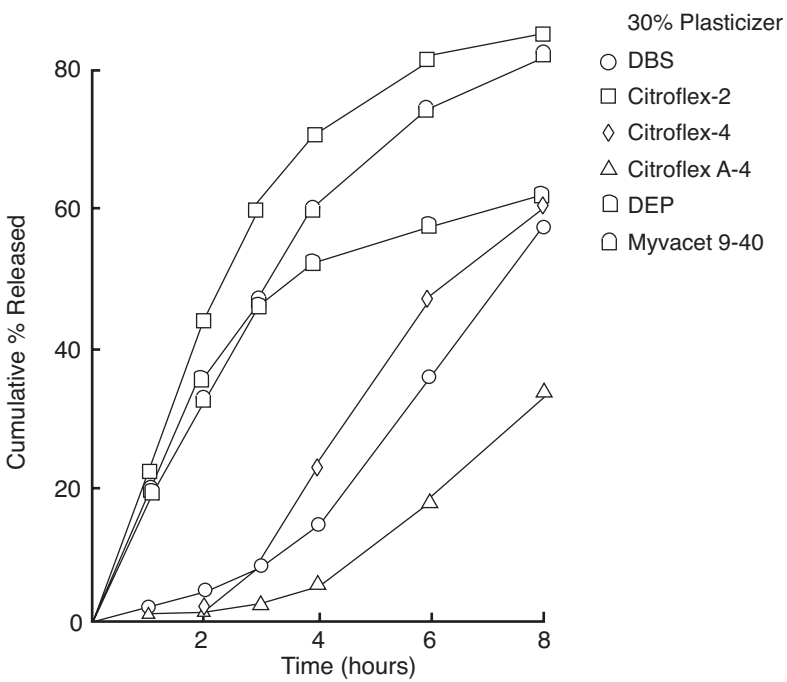


**Figure 23** Effect of various plasticizers on drug release from ethylcellulose latex.

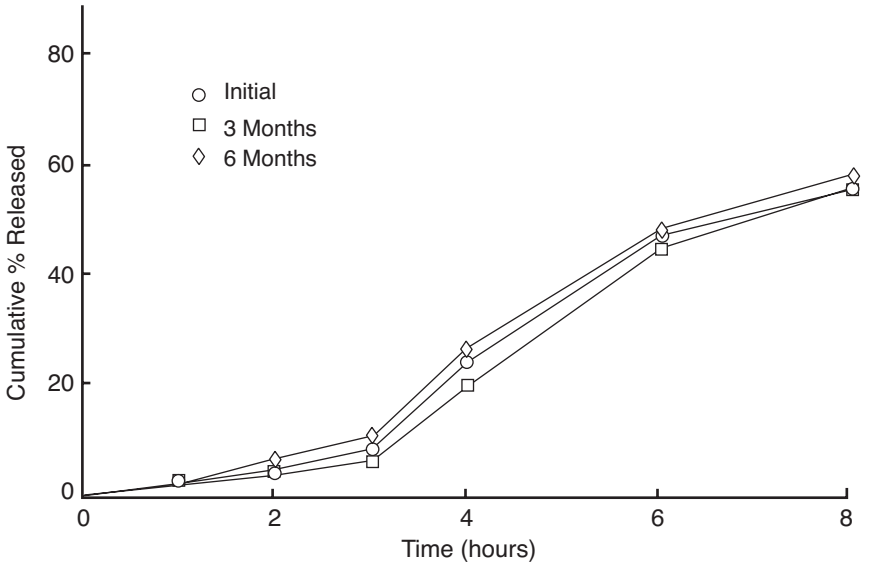


**Figure 24** Stability profile (room temperature) of phenylpropanolamine released from beads coated with TBC-plasticized Aquacoat® ECD. *Abbreviation*: TBC, tributyl citrate.

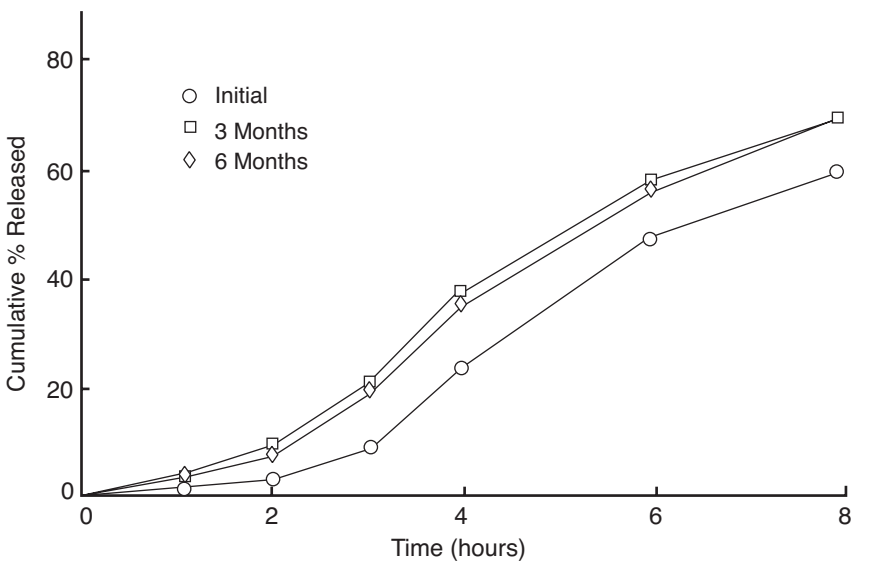


**Figure 25** Elevated temperature (35°C) stability for beads coated with TBC-plasticized Aquacoat® ECD. *Abbreviation*: TBC, tributyl citrate.

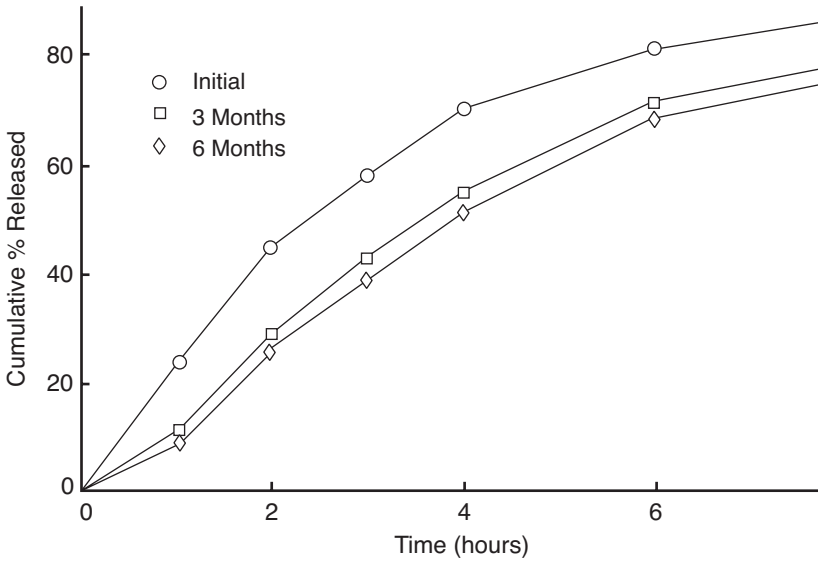


**Figure 26** Stability profile (room temperature) of phenylpropanolamine released from beads coated with TEC-plasticized Aquacoat® ECD. *Abbreviation*: TEC, triethyl citrate.

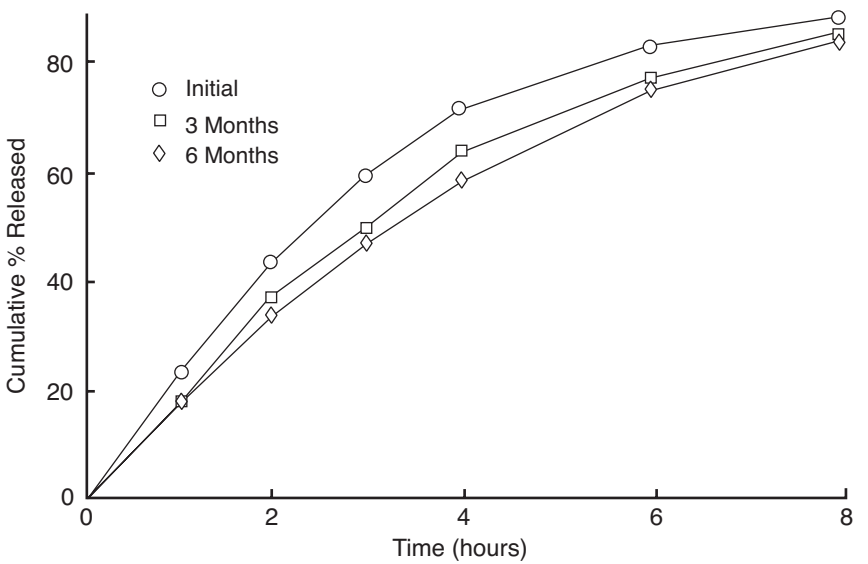


**Figure 27** Elevated temperature (35°C) stability for beads coated with TEC-plasticized Aquacoat® ECD. *Abbreviation*: TEC, triethyl citrate.

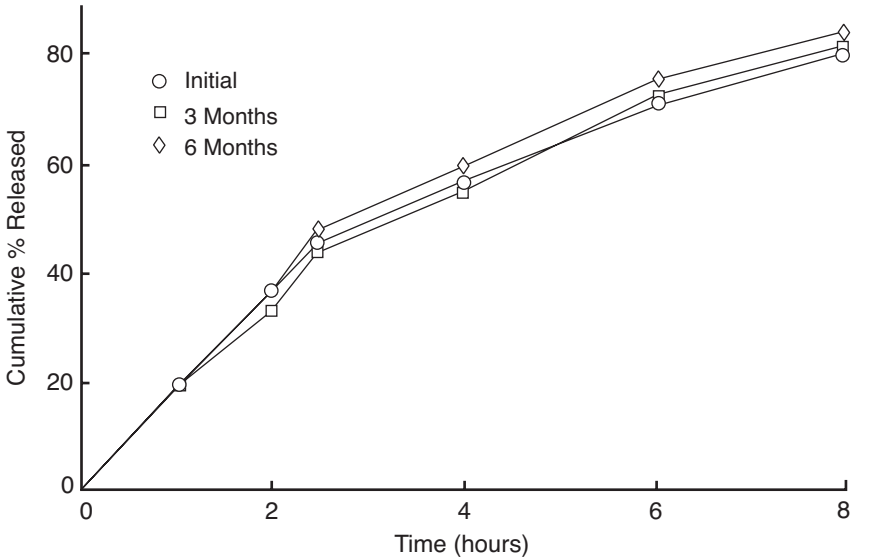


**Figure 28** Stability profile (room temperature) of phenylpropanolamine released from beads coated with acetylated monoglyceride-plasticized Aquacoat® ECD.

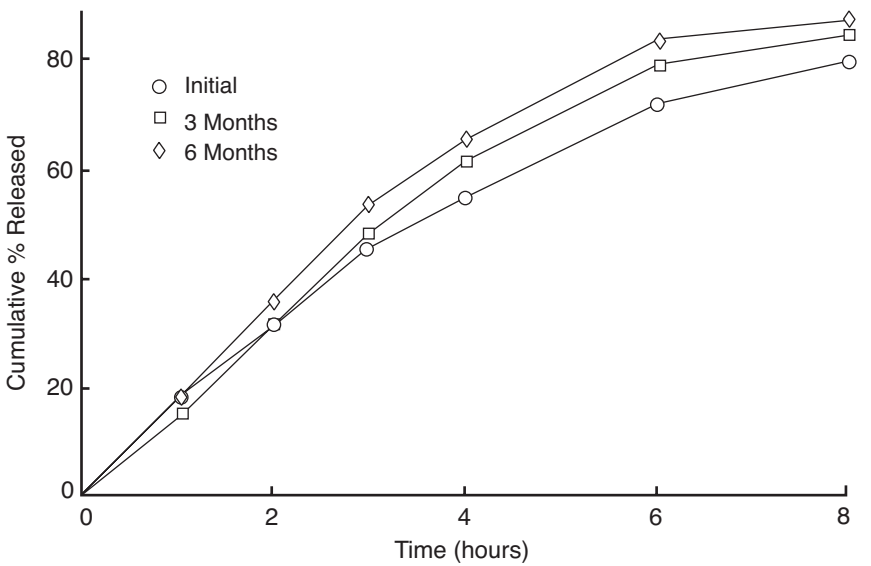


**Figure 29** Elevated temperature (35°C) stability for beads coated with acetylated monoglyceride-plasticized Aquacoat® ECD.

**Table 9** Analysis (Gas Chromatography) of Plasticizer Content in Ethylcellulose Pseudolatex Film

| | | 3 mo | | 6 mo | |
|---|---|---|---|---|---|
| Plasticizer (% remaining) | Initial | RT | 35°C | RT | 35°C |
| DBS | | | | | |
| | 100 | 106 | 106 | 99 | 103 |
| Citroflex-2 | | | | | |
| | 100 | – | – | 92 | 82 |

*Abbreviations*: DBS, dibutyl sebacate; RT, room temperature.

Results using acetylated monoglyceride (Myvacet 9-40) as plasticizer are shown in Figures 28 and 29. These profiles showed a slight increase in release rates, which was more pronounced at 35°C storage.

To further investigate the differences in drug release on storage, the porosity of the coated beads was measured by mercury porosimetry (Table 10). The coated beads had been stored for approximately six months at room temperature or 35°C when submitted for analysis. The porosity of the beads was calculated from cumulative pore volume ($cm^3/g$) and particle density ($g/cm^3$) using intrusion porosimetry. The coated beads were of low porosity, varying from 1.6% to 2.0%, with no significant difference between samples stored at room temperature or 35°C. The pore surface area ($m^2/g$) generally correlated with the porosity; i.e., as the porosity decreases, so does the pore surface area. The pores that were present were very small.

**Table 10** Mercury Intrusion Porosimetry Data for Drug Beads Coated with Aqueous Polymeric Dispersion

| Plasticizer (30%) | | Porosity ($E$) | Surface area of pores ($m^2/g$) |
|---|---|---|---|
| DBS | RT | 0.018 | 2.07 |
| | 35°C | 0.018 | 1.97 |
| TEC | RT | 0.019 | 1.94 |
| | 35°C | 0.016 | 1.81 |
| TBC | RT | 0.020 | 1.90 |
| | 35°C | 0.019 | 1.89 |
| ATBC | RT | 0.019 | 2.04 |
| | 35°C | 0.018 | 1.87 |
| DEP | RT | 0.019 | 1.93 |
| | 35°C | 0.018 | 1.96 |
| Myvacet 9-40 | RT | 0.020 | 2.05 |
| | 35°C | 0.019 | 1.81 |

*Abbreviations*: DBS, dibutyl sebacate; DEP, diethyl phthalate; TEC, triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; RT, room temperature.

Unanticipated pH-dependent release from aqueous ethylcellulose coatings (38,39) may be attributed to partial coalescence (3). Dressman et al. (40) demonstrated that heating pellets coated with ethylcellulose above the $T_g$ of the film stabilized the release profile with respect to the pH of the test media. Additional studies were conducted (41) to identify changes in the film that would explain the stabilization of the release profile. Curing converted the film from a surface having a finite contact angle to a surface instantly wetted by the dissolution media. Scanning electron micrography indicated that film morphology changed during curing with latex particles less distinctly after heating, which they called "film relaxation," i.e., coalescence. It was concluded that film wetting is an important determinant of the release profile of dosage forms coated with ethylcellulose aqueous dispersions, and these properties are changed when the film is relaxed or coalesced by heating above the $T_g$. This is consistent with the phase inversion and expulsion of the hydrophilic components (including surfactant) from the coalesced ethylcellulose film (5).

Nesbitt et al. (42) published release rates of pseudoephedrine HCl and diphenhydramine HCl from pellets coated with ethylcellulose pseudolatex. They concluded that drug release through a pseudolatex film occurs through a capillary network whose porosity varies with drying conditions, driven by solubility-dependent osmotic and diffusive forces.

Ozturk et al. (43) cited as possible mechanisms for release solution/diffusion through the continuous polymer phase and/or plasticizer channels, diffusion through aqueous pores, and osmotically driven release through aqueous pores. To distinguish among these mechanisms, the release rate was studied as a function of coating thickness, plasticizer content, and osmotic pressure in the dissolution medium. As the coating thickness was increased from 9 to 50 μm, the rate of release fell from $9.93 \times 10^{-3}$ to $1.71 \times 10^{-3}$ g PPA/100 mL/hr (Fig. 21). Release as a function of plasticizer content was studied over the range of 12% to 24% DBS (Fig. 22). At 18% or 24% DBS, the release rates were virtually identical, about 50% in six hours. At 12% DBS, over 80% was released in the first hour, and these results were attributed to the presence of cracks in the coating. Release was also studied as a function of the osmotic pressure in the medium (Fig. 30). A plot of release rate versus osmotic pressure revealed a linear relationship with a nonzero intercept (Fig. 31). The steep dependency of release rate on osmotic pressure of the medium suggested that osmotically driven release is a major mechanism for release, whereas the nonzero intercept indicated some contribution from diffusion mechanisms. For all batches, SEMs indicated that the film exhibited pores approximately 2 μm in diameter, consistent with these mechanisms. Ozturk et al. concluded that the release of PPA from pellets coated with the ethylcellulose-based pseudolatex formulation was mainly driven by osmotic pressure, with a minor contribution by diffusion through aqueous pores and perhaps solution/diffusion through the polymer membrane. Osmotic pressure measurements showed that the osmotic pressure generated by both PPA·HCl and the sugar (Nu-pareils) would contribute significantly to

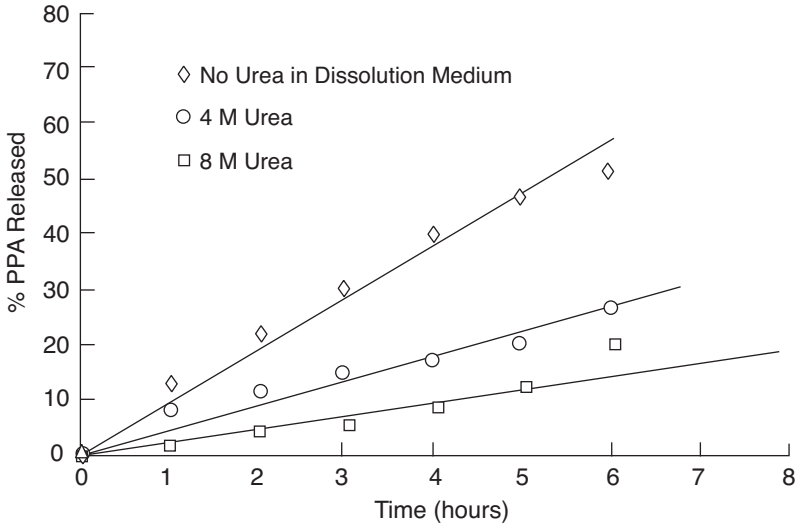


**Figure 30** Effect of osmotic pressure on PPA•HCl release profiles (at a 10% coating loading). *Abbreviation*: PPA, phenylpropanolamine.

the driving force for release. Assuming that these mechanisms operate independently and in parallel, the release of PPA from pellets coated with the ethylcellulose-based film (J) can be mathematically described by an equation that combines these mechanisms:

$$J = \left[\sigma\Delta\Pi + \frac{P_P + P_M}{\delta}\right](C_S - C_B)$$

where σ is the osmotic driving force, ΔΠ is the osmotic pressure difference across the coating, $P_P$ and $P_M$ are the permeability coefficients for aqueous pores and membrane, respectively, $\delta$ is the film thickness, and $C_S$ and $C_B$ are the core surface and bulk drug concentrations, respectively. The same mechanism is operative over a coating range of 5% to 16%, so film thickness may be used as a means of modifying the release rate without changing the release mechanism (within the range of 10–50 μm). Important factors in determining the release rate from these systems include the volume fraction and size of pores generated during processing, the permeability of the film to water, the rate of core dissolution, and the ability of the core constituents and drug to generate osmotic pressure.

## Fluidized Bed Processing

Ethylcellulose latices function well not only in Wurster-type coating equipment but also in other types of fluidized bed equipment, e.g., conventional air suspen-

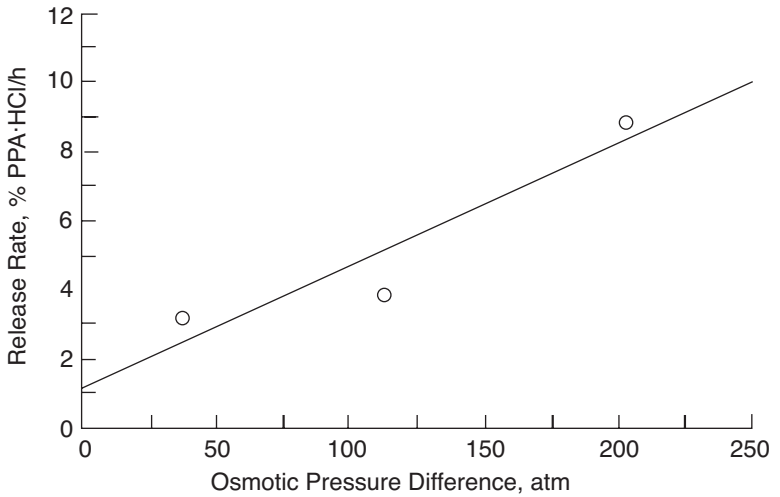


**Figure 31** Effect of osmotic pressure difference on PPA•HCl release rate (at a 10% coating loading). *Abbreviation*: PPA, phenylpropanolamine.

sion chamber or granulator and the rotary fluid bed coater. Conventional air suspension chambers or fluidized bed granulators are characterized by a random or turbulent movement of particles and by spray nozzles positioned at or near the top of the processing chamber. PPA·HCl beads were coated with an ethylcellulose latex in two types of fluidized bed equipment, e.g., Wurster versus top/bottom granulating spray inserts (44). The coating trials are summarized in Tables 11 and 12. PPA release from beads coated by the top or bottom spray methods were faster than beads coated by the Wurster method (Fig. 32). The difference in drug-release profiles between the two coating process techniques can be explained on the basis of the method of application of coating and on film formation and structure. In the Wurster process, the coating liquid is applied concurrently with the flow of the product. The Wurster system combines a partition (column) and an air distribution plate to organize the flow of particles in close proximity to the spray nozzle. Because the nozzle is immersed in the air flow in order to spray concurrently into the fluidized particles, the dispersion droplets travel only a short distance before impinging on the product. As a result, the film is applied more evenly. On the other hand, spray drying of the coating dispersion is most severe in the counter-current top spray granulating insert. SEM examination showed the top spray samples to be much rougher in surface appearance and more porous than the Wurster-coated samples, as shown in Figures 33 and 34.

Ethylcellulose latex dispersions have also been successfully applied to beads by a rotary fluid bed coater. In the rotor (tangential spray) method, the

**Table 11** Summary of Coating Process Conditions

| Constants | Wurster insert | Granulating insert |
|---|---|---|
| Pump type | Peristaltic | Peristaltic |
| Atomizing air pressure | 1.5 bar | 1.5 bar |
| Inner partition height | 3/8 in. | |
| Port size | 1.0 mm | 1.2 mm |
| Nozzle height | Bottom | 0.7 |
| Spray angle | | 0.7 |
| Coating level | 10% (2% slow/8% fast) | |
| Coating suspension | Aquacoat® ECD with DBS 24%[a] applied at 30% solids concentration | |

[a]Based on ECD solids.

coating dispersion is sprayed tangentially in the same direction as the moving beads in the bed. The beads are rotated in a homogeneous, spiral motion by the combined action of the fluidized air, centrifugal force, and gravity. The differences in action between the two coating process techniques again accounts for the faster release shown in Figures 35 and 36. Examination of the coated drug beads by SEM showed similar morphological differences as the top spray versus Wurster.

Figure 37 shows how release patterns can be modified by the addition of a water-soluble polymer hydroxypropyl methylcellulose (HPMC). However HPMC destabilizes the aqueous ethylcellulose dispersion, which can result in

**Table 12** Batch-specific Details of Fluid Bed Coating Trials

| Equipment (insert) | Wurster | Granulating | Granulating |
|---|---|---|---|
| Spray mode | Up | Down | Up |
| Product | 1 kg PPA beads | 1 kg PPA beads | 1.4 kg PPA beads |
| Inlet set temperature (°C) | 55–64 | 55–64 | 60–64 |
| Actual temperature (°C) | 60–80 | 52–80 | 62–81 |
| Outlet temperature (°C) | 44–47 | 44–48 | 33.5–42 |
| Product temperature (°C) | 27–38 | | |
| Spray time (min) | 46 | 50.5 | 51 |
| Dry time (min) | 30 | 30 | 30 |
| Spray rate (mL/min)—slow | 3.4 | 3.4 | 5.6 |
| Spray rate (mL/min)—fast | 11.7 | 9.9 | 12.4 |
| Recovery (%) | 99.5 | 98.6 | 98.3 |
| RH (%) | 10 | 14 | 12 |

*Abbreviations*: RH, relative humidity; PPA, phenylpropanolamine.

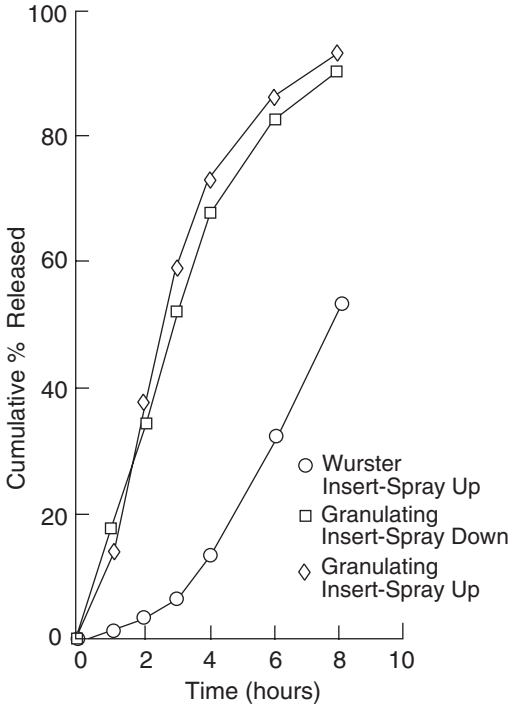


**Figure 32** Release of PPA•HCl from seeds coated by top spray method versus Wurster method. *Abbreviation*: PPA, phenylpropanolamine.

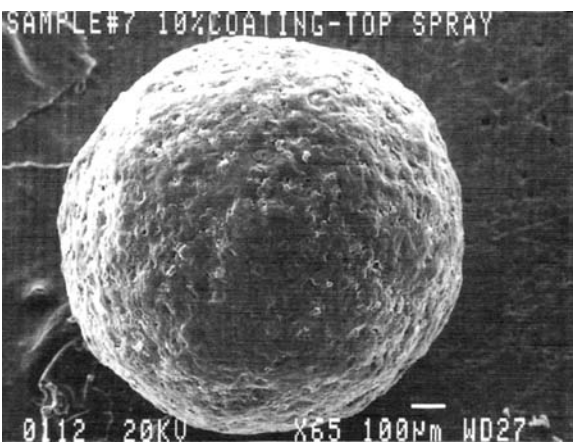


**Figure 33** Surface view of PPA•HCl seed coated by top spray (granulating) method. *Abbreviation*: PPA, phenylpropanolamine.

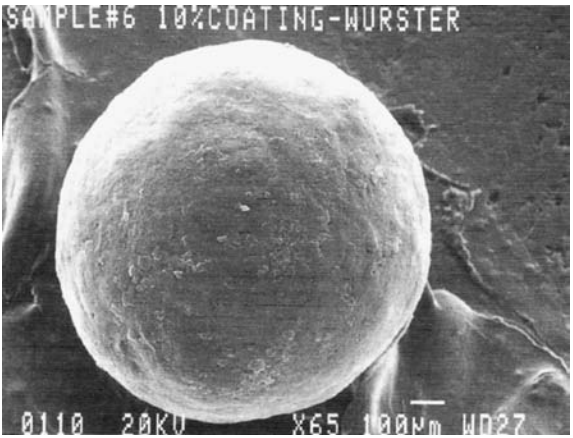


**Figure 34** Surface view of PPA•HCl seed coated by Wurster method. *Abbreviation*: PPA, phenylpropanolamine.

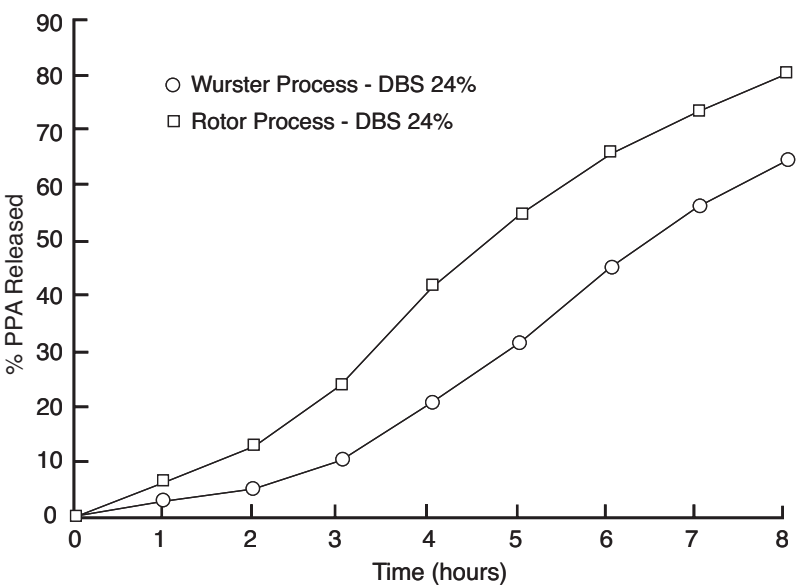


**Figure 35** Release of PPA•HCl from seeds coated by the rotor process versus Wurster process. DBS plasticizer. *Abbreviations*: PPA, phenylpropanolamine; DBS, dibutyl sebacate.

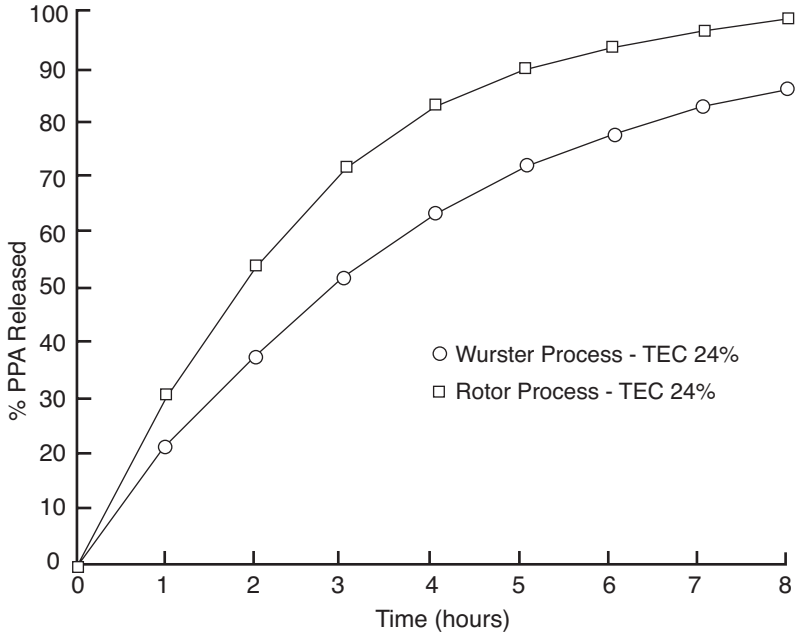


**Figure 36** Release of PPA•HCl from seeds coated by the rotor process versus Wurster process. TEC plasticizer. *Abbreviations*: PPA, phenylpropanolamine; TEC, triethyl citrate.

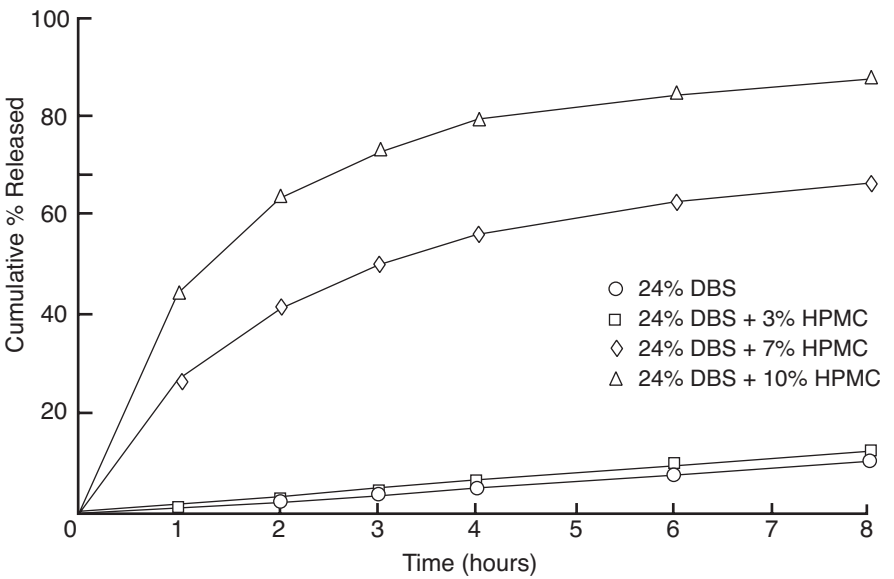


**Figure 37** Effect of water-soluble polymer incorporation on dissolution.

partial coalescence and unpredictable release profiles. Siepmann et al. have identified soluble polymers physically compatible with aqueous ethylcellulose dispersions, such as polyvinyl alcohol (PVA)–polyethylene glycol (PEG) copolymer, propylene glycol alginate (PGA), and carrageenan, which are better suited to giving concentration-dependent release modulations (45–47).

## AQUEOUS ENTERIC POLYMER DISPERSIONS

Enteric film-forming polymers such as CAP contain ionizable functional groups and exhibit pH-dependent solubility (48–50). At low pH, the functional groups are unionized and the film is insoluble. At elevated pH, these functional groups ionize and the polymer becomes soluble. These systems are typically used to protect a drug from the harsh environment of the stomach, to prevent a drug from irritating the stomach mucosa, or to target drug release to the small intestine or colon. Aquacoat® CPD is an aqueous dispersion of CAP and consists primarily of CAP together with a surfactant from the emulsion stage, as shown in Table 13. Traces of dimethylpolysiloxane to suppress foaming during distillation may also be present. CAP is prepared by reacting a partial ester of cellulose acetate with phthalic anhydride. CAP (Fig. 38) is a cellulose ester with three hydroxyl groups per glucose unit available for substitution. About half the hydroxyl groups are acetylated, and another quarter esterified with one of the two acid groups of phthalic acid. The dispersion is manufactured by an emulsion process in which the CAP polymer is converted to a pseudolatex in a procedure similar to that used in the production of Aquacoat® ECD.

Table 14 defines the processing conditions used to apply plasticized aqueous CAP dispersion to aspirin tablets in a 24-in. Accela-Cota (Thomas Engineering, Hoffman Estates, IL, U.S.A.). Peristaltic pumps are typically used to minimize stress on the latex material and to accurately measure unit fluid rates. Bed temperatures are fairly low (36–38°C) for water-based film application.

According to the United States Pharmacopeia, enteric-coated products should resist 0.1 N hydrochloric acid, such that not more than 10% of the active is released in two hours. When placed in pH 6.8 phosphate buffer, the film coating should dissolve rapidly to release the active, typically in less than 10 minutes. Enteric tablets containing alkaline actives may disintegrate prema-

**Table 13** Composition of Aquacoat® CPD

| | Solids (%) | Finished product (%) |
|---|---|---|
| CAP | 78 | 23.3 |
| Pluronic F68 | 22 | 6.7 |
| Water | | 70.0 |

*Abbreviation*: CAP, cellulose acetate phthalate.

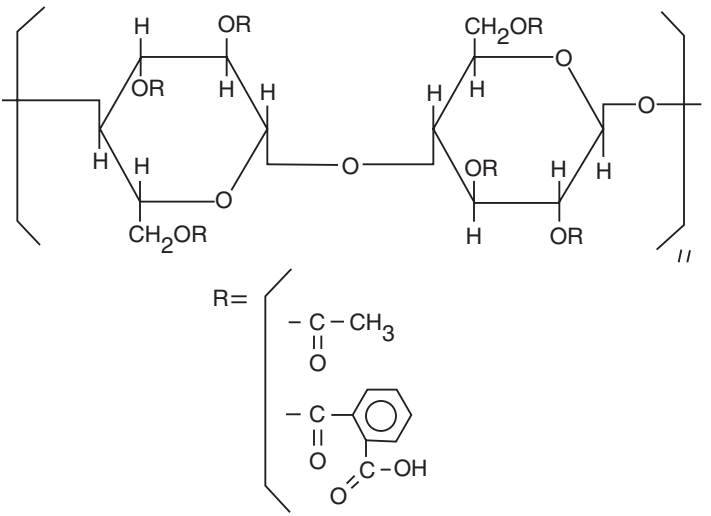


**Figure 38** CAP polymer. *Abbreviation*: CAP, cellulose acetate phthalate.

turely in acid as the coating solubilizes due to a high pH microenvironment. To prevent the formation of soluble alkali phthalate salts, the substrates can be seal-coated first with HPMC before applying the Aquacoat® CPD.

As with sustained-release coatings, film thickness is of critical importance to the functional performance of enteric coated products. Too thin a coating can result in tablet failure in an acidic environment. Too much enteric coating may lengthen the intestinal disintegration time. In fact, high loadings of Aquacoat® CPD can be utilized for colonic drug delivery systems. A film level of at least 5% w/w was required to ensure the integrity in acid of coatings made from either aqueous CAP dispersion or CAP applied from an organic solvent system (Fig. 39). At levels higher than 5% film weight, the CAP pseudolatex coatings exhibit slightly faster disintegration times than the corresponding CAP/solvent coatings applied at the same coating level.

In Figure 40, the disintegration time for aspirin cores coated with CAP pseudolatex and CAP/solvent formulations are compared. It was found that at pH 6.4 and higher, no significant differences in disintegration time were noted for aspirin tablets coated with either the aqueous latex or the organic solution of CAP. However, disintegration time increased substantially as the pH dropped below 6.4, and a significant difference in disintegration time was observed between the two film-coating systems. Table 15 shows that there was no significant change in disintegration time for the latex product after 12 months of storage at room temperature and 35°C, whereas the aspirin product coated from organic solvent exhibited a substantial increase in disintegration time upon aging.

**Table 14** CAP Pseudolatex Enteric Coating—Equipment and Conditions

| | |
|---|---|
| *Equipment:* | Accela-Cota 24 in. |
| Baffles | Four straight bar and four scoop |
| Pump | Masterflex 7562-10 |
| Pump heads | 2 Masterflex 7015 |
| Tubing size | 0.1925, 0.3920 in. o.d./in. i.d. |
| Spray guns | Two spraying systems, 7310-1/4 JAU |
| Fluid cap | 40100 SS |
| Air cap | 134255-45° SS |
| *Conditions:* | |
| Tablet charge | 9.5 kg |
| Fluid rate | 64 mL/min (total) |
| | 32 mL/min per gun |
| Atomizing air | 35 psi per gun |
| *Air temperature:* | |
| Inlet | 80–82°C |
| Outlet | 36–38°C |
| Pan speed | 9.5–10.5 rpm |
| Magnehelic | 1.5 in. $H_2O$ |
| Tablet bed warming | 10 min jogging |
| Coating time | 120 min |
| *Postdrying:* | |
| Accela-Cota pan | Intermittent jogging |
| Air temperature, inlet | 60°C |
| Time | 60 min |
| Film weight addition | 8.9% w/w |

Figure 41 shows the disintegration time of tablets coated with Aquacoat CPD as a function of plasticizer content and plasticizer type. Two plasticizers were investigated: DEP, which is water insoluble, and the water-soluble propylene glycol. Twenty-five percent by weight of either DEP or propylene glycol was insufficient to achieve adequate film quality, and the coatings failed in 0.1 N HCl. However, when the plasticizer level was increased to at least 30% (based on pseudolatex solids), the coatings were resistant to the low pH test media. At higher (54%) levels of propylene glycol, the enteric film coatings failed in acid medium, which was attributed to plasticizer leaching.

Another study evaluated aspirin release at various pH media using the USP (basket) method I at 100 rpm. Aspirin release was shown to increase with increasing pH. The USP enteric dissolution specification is not more than 10% release of aspirin after two hours of testing in a pH 1.5 acid medium. Figure 42 shows that aspirin tablets coated with CAP pseudolatex do not show any significant release of aspirin until pH 6, the pH at which the acid functional groups of the CAP polymer begin to ionize (51).

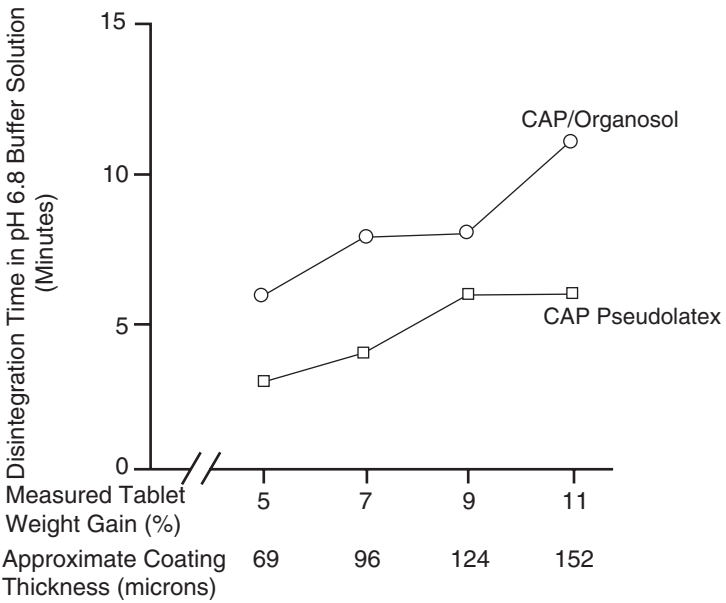


**Figure 39** Disintegration time of aspirin tablets coated with CAP pseudolatex or CAP/organosol in phosphate buffer as a function of film thickness. *Abbreviation*: CAP, cellulose acetate phthalate.

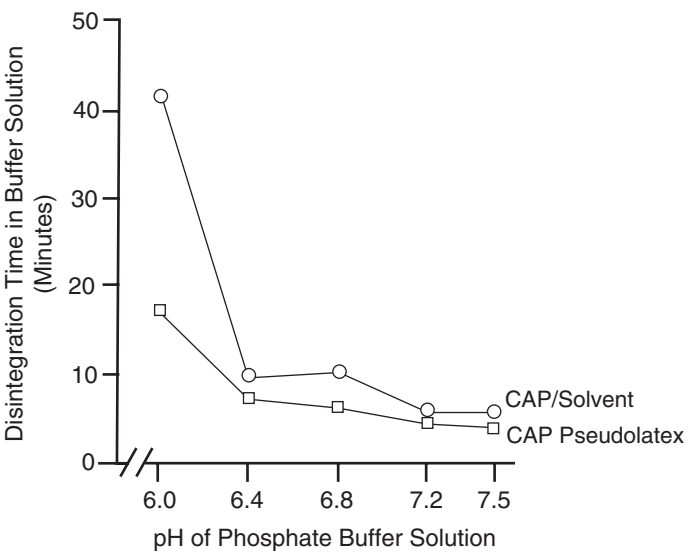


**Figure 40** Disintegration time of aspirin tablets coated with CAP Pseudolatex or CAP/solvent coating as a function of pH. *Abbreviation*: CAP, cellulose acetate phthalate.

**Table 15** Stability Profiles for Aspirin Tablets Coated with Enteric Latex

| Time | Condition | Disintegration time (min) | |
|---|---|---|---|
| | | Aspirin with CAP Pseudolatex coating | Commercial CAP/organosol coated aspirin |
| Initial | | 6–8 | 3–4 |
| 6 mo | RT | 5 | 11.5 |
| | 35° | 6.5 | 12 |
| 9 mo | RT | 4–7 | 6–19 |
| | 35° | | |
| 12 mo | RT | 4–6 | 8–10 |
| | 35° | 4–6 | 8–16 |

*Abbreviation*: CAP, cellulose acetate phthalate.

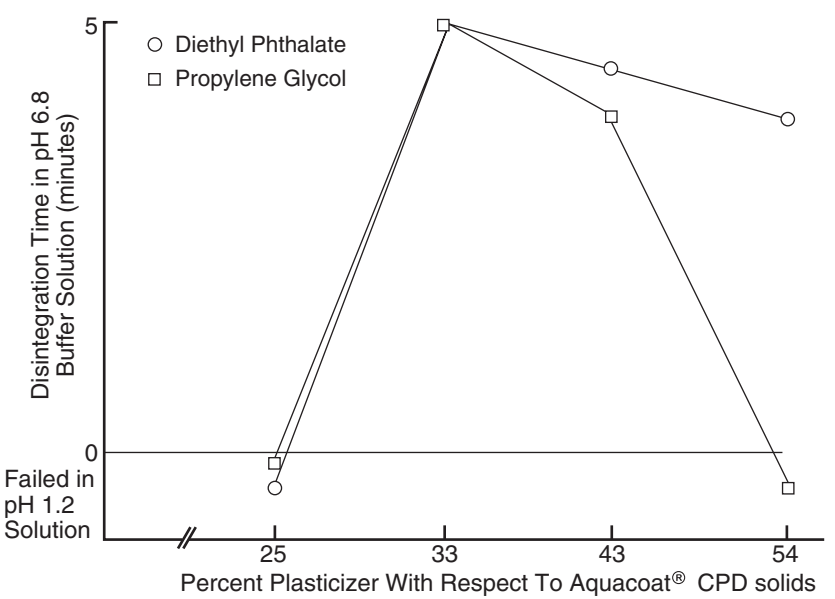


**Figure 41** Disintegration time of aspirin tablets coated with CAP pseudolatex as a function of plasticizer content.

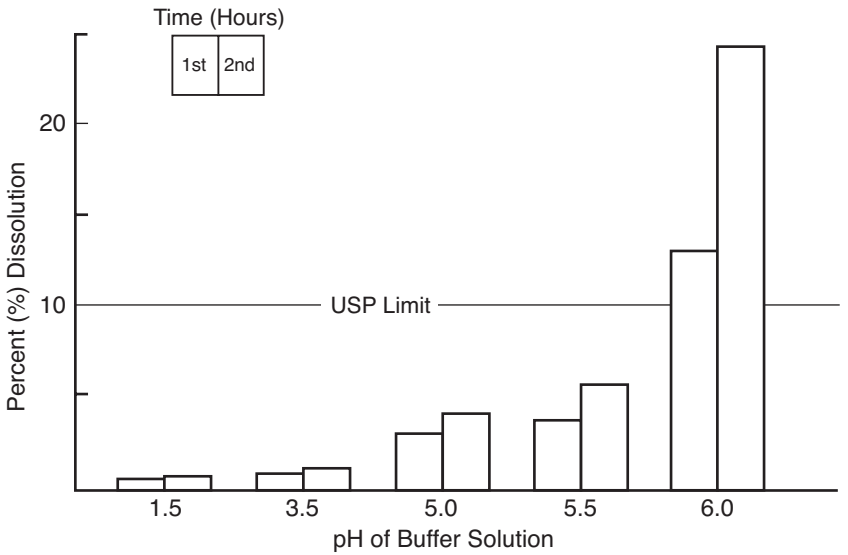


**Figure 42** Dissolution of aspirin tablets coated with CAP pseudolatex as a function of changing pH media.

## SUMMARY

Colloidal aqueous dispersions of ethylcellulose and CAP provided effective and versatile rate-controlling membranes in the design of modified-release oral solid dosage forms. Aqueous pseudolatex coatings avoid the environmental, safety, and toxicological problems associated with organic solvents. The formulation scientist must understand the mechanisms of film formation from such aqueous-based systems in order to achieve stable drug-release rates. Interactions between the coating formulation, substrate, and processing parameters require the formulator to give careful consideration to the entire coating process.

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# 2

# Aqueous Polymeric Coating for Modified-Release Oral Dosage Forms

**Michael R. Harris**

*College of Pharmacy and Health Sciences, Texas Southern University, Houston, Texas, U.S.A.*

**Isaac Ghebre-Sellassie**

*Exxpharma LLC, Morristown, New Jersey, U.S.A.*

## INTRODUCTION

Technology is constantly advancing to improve efficiency and lessen overall cost. Therefore, it is incumbent on the pharmaceutical development scientist to be aware of and become proficient in the use of these new technologies. Although aqueous film coating has been employed in pharmaceutical development for several years, the use of the technology to enhance the performance of drugs to optimize delivery from dosage forms will forever be an emerging application due to the fact that no two drug molecules will have the same physicochemical properties. Thus, to achieve the desired results, formulations and processes must be tailored to the specific drug entity and dosage form. The term "enabling technologies" has become part of the conversation during the drug development process. These are the technologies that are being applied to enhance the properties of drugs ranging from enhancing stability to improving absorption in order to improve the pharmacological outcome. Modifying drug release by applying aqueous film-coating technology to achieve optimum therapeutic benefits can be considered an enabling technology.

The objective of preformulation research is to characterize the physicochemical properties of new drug substances and provide a rational basis for subsequent dosage-form development. In addition, preclinical pharmacokinetic

studies are conducted in animals to provide insight into the absorption and elimination characteristics of the compound. Currently, a high level of emphasis is being placed on the economics of health care, and the impact of pharmaceuticals has become an area of study (pharmacoeconomics). Therefore, it is now more important than ever to consider these early findings about the potential new drug substance during the development phase, particularly when designing the dosage form. That is, the overall cost of therapy is becoming a very important aspect in new drug development, and the optimum therapeutic regimen requires careful consideration of the cost of goods even at this early stage of development. For example, if the therapeutic class that the compound is being developed for requires long-term therapy, and the compound demonstrates good gastrointestinal absorption properties but has a short plasma half-life, effective dosage form design could enhance the beneficial aspects of the compound. Compounds with short plasma half-lives require several doses per day, and this could potentially be a competitive disadvantage in the marketplace. Modified-release dosage forms have always been more effective therapeutic alternatives to conventional or immediate-release dosage forms. By reducing side-effect profiles of drug entities and allowing for less frequent dosing regimens, these dosage forms may improve the overall cost of drug therapy. Therefore, modified-release dosage forms for new chemical entities are being considered on a more routine basis than ever before. In the past, new chemical entities were typically formulated and developed clinically as immediate-release dosage forms and introduced to the marketplace as such. A modified-release dosage form of the same compound usually found its way to the market after several years of dosing experience with the immediate-release version. In today's environment, it has become prudent to consider the physicochemical and pharmacokinetic properties of the compound from the outset of new drug development.

The objective of developing a modified-release dosage form for oral administration is to control the release of the therapeutic agent and thus control drug absorption from the gastrointestinal tract. Such a dosage form effectively reduces adverse effects associated with a peak plasma concentration beyond that needed for therapeutic effectiveness, and at the same time, it maintains the plasma level above or at that needed to achieve the therapeutic effect for a longer period of time. Thus, the number of times the medication has to be administered is reduced without compromising efficacy. The dosage form, in effect, controls the amount of drug available for absorption from one dose administration to the next, with the result being a more stable plasma level profile. Target drug-release profiles for oral administration are achieved either by applying a release-controlling barrier around drug-loaded granules, pellets, and/or tablets, or by incorporating polymeric or wax systems in formulations.

It is essential that these types of dosage forms are manufactured in a reproducible manner in order to deliver the drug at a controlled and consistent rate. Release rate reproducibility within a given batch and between batches is critical for both the patient and the manufacturer. The manufacturer must meet rigid spec-

ifications set for the product not only to satisfy regulatory agencies, but also to avoid the loss of profits if a batch fails to meet these specifications and cannot be salvaged. In addition, the patient loses the therapeutic benefits of the specialized dosage form if the product fails. It can even have a detrimental effect on the patient if the failure is associated with dose dumping, i.e., release of the entire drug load all at once. It is precisely this critical end-product performance that has led to the use of coated pellets and/or granules in the development of controlled-release dosage forms. Such a dosage form is made up of multiple units with controlled-release properties, and thus the dose is divided up into several units as opposed to a single unit. This is accomplished by combining these units into either a capsule or tablet for ease of administration. Since the dose is divided into several units, failure of a few pellets or granules does not significantly impair the performance of the dosage form as a whole, and a larger margin of safety against dosage form failure is realized.

Modified-release dosage forms have been fabricated by a variety of methods including forming a slowly eroding matrix made up of mixtures of polymers, waxes, gums, sugars, talc, or other components (1). In the case of pellets, this was accomplished by ladling solutions or suspensions and dusting solid components onto starter seeds or granules in coating pans equipped with external drying air and heat sources. The technique employed was somewhat analogous to the sugar coating of tablets. The process was laborious and tedious and required experienced artisans to achieve reproducibility. Even then, reproducibility was still difficult to accomplish. Therefore, to attain the target release rates, pellets of different release rates were blended before filling into capsules. The ratio of pellets that are blended to make up the final dosage form was determined by conducting dissolution testing on the pellets and inputting the results into equations. This method of manufacture would clearly be a difficult process to carry out in today's regulatory environment where reproducibility of a manufacturing step is critical for the establishment of a validated process.

Pellet technology as applied to controlled release has advanced with the advent of new processing equipment and the development of film coating as a technique for pharmaceutical applications. These developments have given the pharmaceutical scientist the opportunity to apply scientific principles to the development of well-designed and predictable controlled-release dosage forms. The design of the dosage form is driven by the desired dosing regimen and more importantly, the pharmacokinetic properties of the drug substance. During the development phase, an attempt is made to attain a certain degree of flexibility to vary the release properties of the dosage form with minimum changes to the basic composition of the formulation. This in turn would shorten the development time and provide the formulation development scientist as well as scientists in pharmacokinetics and clinical research to optimize the delivery of the drug substance at the desired site of absorption.

Drug-loaded pellets are manufactured today mainly by solution, suspension, or powder layering of the drug substance onto starter sugar spheres (e.g., Sugar

Spheres NF) or granules. In some cases, pellets may be formed by blending the drug substance with appropriate excipients followed by the application of a binder liquid onto the powder blend in a rotary equipment. Most or all of these applications now employ sophisticated high-speed rotary granulation fluid bed equipment, although to some extent, dish pelletizers are also used. Another technique that is widely used to manufacture pellets is extrusion-spheronization. Extrusion-spheronization is a multistep process that is time consuming and labor intensive; however, in certain instances, it is preferred since it is capable of generating a highly concentrated matrix core and/or higher density drug pellets, which are critical requirements for higher-dose drugs. The pellets formed by all of these methods are generally spherical in shape and do not exceed 1.7 mm in diameter. Although matrix pellets with inherent controlled-release properties can still be manufactured in a single step, the prevailing climate in the pharmaceutical industry favors the development of core pellets coated with a rate-controlling membrane (2,3). This is because the release characteristics of the pellets can be easily modulated by simply altering the composition or thickness of the film coat.

While the formulation and processing variables of pellets were being refined and optimized, research in the area of membrane technology was also intensified and led to significant discoveries. Natural and synthetic polymers such as ethylcellulose have been incorporated in coating formulations employing organic solvents to provide rate-controlling membranes. Although the technique has become increasingly popular, the flammability and toxicity of organic solvents and stringent government regulations that restrict and control their applicability are hurdles that constrain their use. These restrictions, coupled with the ongoing quest to become as environmentally friendly as possible in all of our actions, have prompted some pharmaceutical companies to prohibit the use of organic solvents in dosage form manufacture. As a result, water became the solvent of choice for dosage form development, and consequently, various aqueous polymeric dispersions that have applicability in modified-release dosage forms were developed.

The utility of the water-based polymeric dispersions depends to a great extent on the manufacturing conditions of the dispersions. Equally important are the coating conditions, which could determine the success or failure of the final product. Since the formulation development scientist does not have control over the manufacture of the dispersion, he or she must carefully and systematically characterize the commercially available products and optimize the formulation and processing variables in order to develop well-defined and reproducible dosage forms. It is in this context that Aquacoat® ECD, a dispersion of ethylcellulose in water that is manufactured and distributed by the FMC Corporation (Philadelphia, Pennsylvania, U.S.A.), is discussed in this chapter. Nevertheless, other polymeric dispersions are also available for use as film-coating materials, such as Surelease®, Eudragit®, and Kollicoat® (4).

## DESCRIPTION AND METHOD OF PREPARATION

### Description

Aquacoat ECD is an aqueous dispersion of ethylcellulose, a polymer generally recognized as safe and approved for use in food and pharmaceutical products. Because of its safety, ethylcellulose has been widely used in pharmaceutical formulations. The Aquacoat ECD dispersion conforms to the specifications for Ethylcellulose Aqueous Dispersion USP/NF. It exists as a milky white liquid with the characteristic odor of ethylcellulose. It contains 29% to 32% solids. Sodium lauryl sulfate and cetyl alcohol are included as stabilizers. Their concentrations are in the ranges of 0.9% to 1.7% and 1.7% to 3.3%, respectively. Ethylcellulose is present in the dispersion as spherical particles in the size range of 0.1 to 0.3 μm. The pH of the dispersion ranges from 4.0 to 7.0, and the specific gravity ranges from 1.025 to 1.040. These properties are tabulated in Table 1 (5).

The key items to note regarding the properties of Aquacoat ECD from a formulation point of view are (*i*) the high solids content of a water-insoluble polymer, (*ii*) the low viscosity, (*iii*) the inclusion of an anionic surfactant, and (*iv*) the pH of the dispersion. The impact of these properties on dosage form development will be discussed later in the chapter.

The dispersion is stable and has a shelf-life of 12 months when stored at room temperature; it will rarely settle upon standing because of the colloidal nature of the dispersed solids. As a precaution, however, the manufacturer's label suggests that the dispersion be shaken before use. Since the dispersion has properties similar to those of an emulsion, the normal precautions applicable to emulsions should be adhered to with Aquacoat ECD.

**Table 1** Aquacoat® ECD Specifications

| Component or property | Specification |
|---|---|
| Total solids | 29–32% |
| Ethylcellulose content | 24.5–29.5% |
| Sodium lauryl sulfate content | 0.9–1.7% |
| Cetyl alcohol content | 1.7–3.3% |
| pH | 4.0–7.0 |
| Viscosity | NMT 150 cps |
| Heavy metals | NMT 10 ppm |
| Total aerobic microbial count | NMT 100 cfu/g |
| Total yeast and mold count | NMT 20 cfu/g |

*Abbreviation*: NMT, not more than.
*Source*: From Ref. 1.

## Method of Preparation

Aquacoat ECD is classified as a pseudolatex as opposed to a true latex because of the differences in the methods of preparation of the two systems. Nevertheless, a pseudolatex has the same general properties as a latex. A latex is prepared by emulsion polymerization, where the chemical reactions to form the polymer are carried out in an emulsified state. In contrast, a pseudolatex is made from an already existing thermoplastic water-insoluble polymer. Emulsion polymerization techniques have been used for many years to generate latexes suitable for paints and other industrial applications. The basic technology used to make pseudolatexes was developed at the Center for Surface and Coating Research at Lehigh University. This technology was further refined to develop pseudolatexes for use in pharmaceuticals at the Industrial and Physical Pharmacy Department of Purdue University (6,7). The ethylcellulose pseudolatex is made by first dissolving the ethylcellulose polymer and cetyl alcohol in an organic solvent. The polymer solution is then emulsified in water with the aid of the anionic surfactant, sodium lauryl sulfate. The emulsion is homogenized to reduce the particle size of the polymer droplets, and then the organic solvent is removed by steam distillation, leaving a dispersion of 30% w/w solids content. The dispersion is low in viscosity and fluid, even at the high solids content. In contrast to polymer solutions, the viscosity of latex dispersions is independent of polymer molecular weight. Moreover, the pseudolatex is strongly resistant to microbial attack, a property that is unmatched by aqueous solutions of polymers, which generally require preservatives or have to be prepared immediately before use to preclude microbial contamination.

## Mechanism of Film Formation

Ethylcellulose generates very hard or tough films and needs a plasticizer to soften the film, i.e., to improve flexibility and reduce brittleness. The glass transition temperature of ethylcellulose is 120°C. The glass transition temperature is defined as that temperature below which the polymer is in a glassy state and above which it is in a rubbery state. Thus, an unplasticized ethylcellulose film would be in the glassy state, i.e., brittle, at temperatures at which pharmaceutical products are manufactured and stored and would not perform its intended function. The plasticizer must be able to dissolve the polymer to promote chain mobility and flexibility. Thus, a comparison of the solubility parameters of plasticizers with that of ethylcellulose would help predict the effectiveness of a given plasticizer (8,9). Alternatively, free films can be prepared with various plasticizers at different levels and examined thermomechanically to determine effectiveness (10). Free films can also be used to investigate the release properties employing in vitro techniques, although caution must be exercised during interpretation of the results (11). Table 2 lists some selected plasticizers with their solubility parameters and softening effects on Aquacoat ECD films.

Aquacoat ECD is compatible with a number of plasticizers, some which are listed in Tables 2 and 3. The ideal plasticizer should not only be compatible

**Table 2** Solubility Parameters and Film-Softening Effects on Aquacoat® ECD Films of Selected Plasticizers[a]

| Plasticizer | Solubility parameter $(j/m^3)^{1/2} \times 10^{-3}$ | Level in film (percentage of Aquacoat ECD solids) | Softening temperature (°C) |
|---|---|---|---|
| Diethyl phthalate | 20.5 | | NT |
| Dibutyl phthalate | 19.0 | | NT |
| Dibutyl sebacate | 18.8 | 24 | 54 |
| | | 30 | 46 |
| | | 40 | 45 |
| Triethyl citrate | | 24 | 59 |
| | | 30 | 52 |
| | | 40 | 48 |

[a]The solubility parameter for ethylcellulose is 21.1.
*Abbreviation*: NT, not tested.

with Aquacoat ECD but must also (*i*) be safe for use in pharmaceuticals, (*ii*) be compatible with the drug and the other components, and (*iii*) remain permanently in the resultant film. Also, since the film is to be used as a barrier membrane for controlling drug release, the plasticizer's aqueous solubility should preferably be low to avoid its dissolution, which eventually leads to disruption of the film in an aqueous environment.

The plasticizer serves a dual role in the formation of Aquacoat ECD films. It does not only render hard and brittle films flexible, as it does with films derived from solutions, but it also softens the dispersed polymeric particles and facilitates their deformation and eventual coalescence. Film formation from a pseudolatex is different from that from a polymer solution (9). Film formation from a polymer solution occurs through a series of phases, where initially the bulk of the solvent evaporates, which then increases the viscosity of the solution, and leaves the polymer chains in close proximity. Upon more complete evaporation

**Table 3** Plasticizers that Are Suitable for Use with Aquacoat® ECD Formulations

| | |
|---|---|
| Castor oil | Tributyl citrate |
| Diethyl sebacate | Triethyl citrate |
| Dibutyl sebacate | Glyceryl tributyrate |
| Diethyl phthalate | Myvacet 9-40 |

*Note*: Numerous other plasticizers have been studied with Aquacoat ECD.
*Source:* From Ref. 12.

of the residual solvent, the individual polymer chains align themselves in such a way that they form a cohesive film. In the case of a pseudolatex, the water serves only as a carrier for the dispersed particles and not as a solvent. As water evaporates, the dispersed particles, which contain numerous polymer chains, become closely packed. Upon further evaporation, the softened particles deform, due to capillary pressure effects, and coalesce to form a continuous film. The plasticizer then embeds itself between the layers of polymer chains to enhance flexibility as it would with solutions. Because plasticizers have a dual role in the mechanism of film formation from pseudolatexes, the level of plasticizer required to achieve equivalent film properties may be higher for a pseudolatex than for a solution.

The formation of an acceptable film for controlling drug release is also dependent on numerous other parameters such as the processing conditions and substrate effects. Examples of the impact of these parameters on drug release will be covered later in the chapter.

## Free Film Evaluation

In cases where the suitability of a film composition for membrane application is unknown, it may be prudent to study film properties by utilizing laboratory techniques such as thermomechanical analysis, tensile strength measurements, microscopic examination, and diffusion experiments. A free film may be prepared by pouring or spraying the dispersion mixture onto an inert substrate, e.g., a glass slide or Teflon® plate. The film is allowed to dry completely and then gently removed from the substrate. Subjective examinations for such properties as flexibility can be easily conducted. More quantitative analyses can also be performed as demonstrated by the following examples.

Free films were prepared by spraying triethyl citrate or dibutyl sebacate–plasticized Aquacoat ECD formulations onto a rotating Teflon plate (the Teflon plate was attached to a conventional rotating coating pan) (10). The films were lifted off the plate with a Teflon-coated spatula. Areas of similar thicknesses were isolated from the various films and used for thermal analysis. A thermomechanical analyzer was used to measure the temperature at which a load of 2 g began to penetrate the film. This laboratory experiment allowed comparison of the effects of a plasticizer and plasticizer concentration on Aquacoat ECD films, as shown in Table 2.

Several plasticizers were incorporated in Aquacoat ECD formulations to evaluate the effect on the mechanical properties of Aquacoat ECD–free films (12). The films were cast by spraying the plasticized dispersion onto Teflon tape. The results demonstrated that the plasticizer type (chemical class) and amount as well as the storage conditions influence the mechanical strength of Aquacoat ECD films.

The microscope can also be a valuable tool to characterize and compare films. The homogeneity of the components of a film, which is a critical property

for a rate-controlling film, can be studied with the use of a scanning electron microscope (13). Various other characterization tests that can assist in the selection of suitable film-coating systems are reported in the literature (14). A judicious laboratory procedure for the characterization of films intended for use as a release rate–controlling membrane is the diffusion test. This test can be utilized to determine the diffusivity of the drug through films of various compositions prior to application of the film coating on the substrate. The application of such a method for the determination of the diffusion process was carried out employing theophylline as the model drug (11). This technique provides the formulation development scientist another tool to evaluate and characterize the formulation of the rate-controlling membrane. However, the results could be misleading unless proper care is taken when extrapolating to actual processing conditions as mentioned earlier. A dramatic difference in a drug permeation was observed between the diffusion test results from a free film and dissolution data derived from pellets coated using the same formulation (15,16). The difference was attributed to migration of the water-soluble substances into the film during the coating process. During dissolution testing, the soluble components dissolved to create water-filled pores that served as channels for drug release. In addition, the osmotic pressure difference between the solubilized core and the dissolution medium leads to an increase in the release rate of the film-coated pellets as compared to the diffusion properties observed with free films. Free film evaluations have also been conducted to study the effect of the solubility of the drug in the film on membrane performance (17).

## FORMULATION VARIABLES

### Dispersion Concentration

Aquacoat ECD is available at a 30% solids content and it may or may not be applied as is in a plasticized formulation. The manufacturer recommends that the dispersion be diluted with water after the addition and mixing of the plasticizer. However, experience has shown that the addition of water to Aquacoat ECD before the addition of plasticizer has not made a significant difference in either film properties or film stability as long as the plasticizer is thoroughly mixed into the dispersion. The typical working solids content after the addition of plasticizer in our laboratories is 15% to 24% w/w. This range is intended for the coating of pellets and may vary depending on the particle size of the cores. Therefore, determination of the optimum solids content of the dispersion for a particular application or product is a critical step that needs to be carried out on a case-by-case basis. The solids content in a pseudolatex formulation, even after dilution of the dispersion, is usually higher than the concentrations employed with solutions. Also, the viscosity is always lower. With these highly concentrated formulations, care must be taken to optimize the spray pattern and drying efficiency of the process in order to allow the proper spreading of the droplets onto the substrate, which, in turn,

leads to an optimum film formation. Otherwise, the capillary pressure required to deform and coalesce the polymer particles will not be fully developed, and the coating efficiency will be drastically reduced. As indicated earlier, the choice and level of plasticizer determines the behavior of the film and should be evaluated carefully. The plasticizer level in a modified-release formulation is typically 20% to 30%, expressed as a percentage of Aquacoat ECD solids. However, levels as high as 35% plasticizer have been studied (16). No steadfast rule is appropriate, as each drug and/or application will have different properties, and thus the choice and level of plasticizer should be optimized with respect to processing, release, and stability properties.

### Water-Soluble Additives

In some cases, water-soluble additives are incorporated into plasticized dispersions or formulations to aid in modifying the release characteristics of the pellets. Since ethylcellulose is completely insoluble in water, its film is impermeable to most drugs. As a result, a film formed from Aquacoat ECD may not be permeable enough to provide the target release profile. Therefore, a water-soluble additive may be included in the film to increase the permeability of the membrane when the product is exposed to an aqueous environment during the dissolution phase. The additives dissolve in the medium, leaving behind water-filled channels, which increases the release rate. Water-soluble polymers such as hydroxypropylcellulose and hydroxypropyl methylcellulose (HPMC) as well as other small molecule substances such as sucrose and mannitol have been used for this application. The use of carrageenan has also been explored for this purpose (18). The use of electrolytes should be avoided since electrolytes tend to disrupt the colloidal nature of the dispersion and lead to coagulation. Invariably, the amount of the additive is optimized at a certain coating level to achieve the targeted release rate. For example, a coating level of 10% weight increase may have been determined to be the level necessary to achieve a uniform coating on the substrate. However, if the release rate of the drug is too slow, it can be increased with the addition of a water-soluble substance in the film. Often a difference of 1% to 2% w/w in coating level significantly alters the drug-release rate. This is especially true if the permeability of the film is very low and partitioning of the drug through water-filled pores in the film is the major mechanism of release. In this situation, small changes in film thickness translate into large differences in drug-release rate. Thus, the reproducibility of release rates between batches may become difficult. Since there is always the possibility of over- or underspraying during the coating process, the film system should be optimized so that a 1% to 2% difference in coating level will not cause a significant change in the release rate. This task may be accomplished by the addition of a water-soluble additive in the formulation, and increasing the coating thickness. In other words, the addition of a water-soluble additive may improve the reproducibility of release-rate properties and compensate for variability in processing conditions. The water-soluble

additive is usually dissolved in water prior to addition and should be thoroughly mixed into the dispersion.

## Water-Insoluble Additives

Certain processing aids may be necessary to reduce tackiness during film coating. These components are sometimes termed "separating agents." Talc is the most common of these agents used in tablet coating. Kaolin has proved to be valuable as a separating agent for Aquacoat ECD in that it is insoluble yet hydrophilic and easily remains suspended in the dispersion with little agitation. This is important because the amount of shear intended to disperse the additive may coagulate the Aquacoat ECD dispersion.

The separating agent should be inert with respect to the drug and the release characteristics of the film. That is, the ideal separating agent should be chemically compatible with the drug substance, not have an impact on the release properties of the film, and function only as a processing aid during manufacture. The amount of separating agent required to exert this function must be optimized without exceeding the maximum carrying capacity of the polymer in the film. The effect of adsorption capacity of a polymer on film behavior is illustrated in Figure 1, where the critical pigment volume concentration is identified for a hypothetical film. At low levels of pigment, there is a small effect on water vapor transmission (slowly decreasing rate) until a critical concentration is reached. At this concentration,

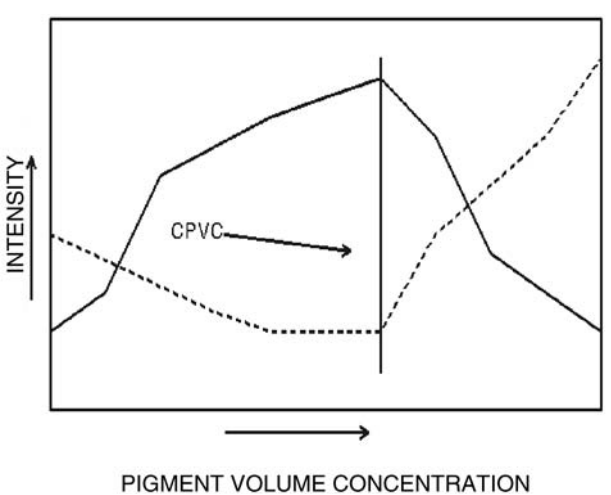


**Figure 1** The effect of pigment volume concentration on film properties. *Solid line*, tensile strength; *dashed line*, moisture permeability. *Source*: From Ref. 1.

the film properties change dramatically, and the water vapor transmission rate increases rapidly. Although the example demonstrates the effect of pigment concentration on water vapor transmission rate, it can easily be translated to drug-release characteristics, and thus emphasizes the need to evaluate the effects of separating agents on release rate. This criterion also applies to the inclusion of lake dyes and any other insoluble additive to the film. As with water-soluble additives, the usual order of addition involves suspension of the water-insoluble additive in water, followed by mixing the suspension with the polymeric dispension.

### pH-Sensitive Additives

If the objective is to design a dosage form to achieve drug release independent of the pH of the medium irrespective of the physicochemical properties of the drug, pH-sensitive components may have to be incorporated in the film to compensate for differences in solubility that may occur in gastric and intestinal fluids. For example, a coated pellet formulation of a weakly basic drug that exhibits poor dissolution in media of pH 5 or higher may show different release rates in simulated gastric and intestinal fluids, the most common media used for dissolution testing. Based on dissolution properties, the release rate in this case would probably be faster in the acidic media and slower in the neutral to alkaline media. However, the release rate could be made to remain constant by adjusting the film composition. One way of accomplishing this is to include an enteric coating material in the Aquacoat ECD formulation. A mixture of Aquacoat ECD and Eudragit L 30 D (an aqueous dispersion for enteric coating) was successfully used in our laboratories to address such a problem. Other aqueous-based enteric systems that are commercially available may also be utilized for this purpose. The principle behind this approach is that the enteric polymer remains as integral part of the membrane under acidic conditions and may even contribute to slowing the release rate. However, at pH 5 or higher, the enteric polymer dissolves and leaches out of the film, creating large pores for drug release. Thus, the in vitro release rate superficially remains constant by reducing the impact of reduced drug dissolution rate at the higher pH. Siepmann et al. have examined the use of propylene glycol alginate for the same purpose (19). They found that the release of theophylline from pellets coated with dispersions containing propylene glycol alginate was pH dependent, with the release being higher at the higher pH. One major liability of such an approach is the variability of drug release that may occur in vivo due to differences in stomach-emptying times, and therefore the administration of the dose with regard to the consumption of meals may become an important factor in product performance.

## GENERAL APPLICATIONS

Although the components of the coating formulations and the processing conditions are important variables that need to be optimized to develop modified-release

pellets, they are by no means the only parameters that should be considered. Coating thickness and physicochemical properties of the substrate also play major roles in controlling the rate and extent of drug release from coated pellets.

### Effect of Coating Level

The amount of coating applied to drug pellets or granules is inversely proportional to the release rate. That is, the thicker the film coat, the slower the release rate. The release mechanism obeys the theory of diffusion applicable to reservoir-type systems. Several release rates may be obtained with the same formulation by adjusting the level of coating and hence the diffusional path length. Moreover, a lag time to the initiation of release may be observed at higher coating levels due to the time required for the media to penetrate through the film to the core pellets. Changing coating levels is a convenient way to study the effect of varying release rates on in vivo performance, since the qualitative composition of the formulation remains the same.

### Substrate Effects

Controlling the properties of the substrate is essential to obtaining a reproducible and uniform product. The consistency of core pellets from lot to lot is as important as maintaining the same film-coating conditions. The most critical properties are drug concentration and particle size. According to Fick's first law of diffusion, the release rate depends on, among other variables, the diffusional area and the concentration gradient across the film coat. Therefore, with film-coating level, drug content in the core, and all other variables held constant, the larger the size of monosize pellets, the faster the release rate will be. However, in practice, pellets and granules are not monosize; as a result, pellets or granules of well-defined particle size ranges are used. The ultimate release rate is a composite of the release rates of multisize pellets or granules. Therefore, tolerances on the particle size of the substrate must be established to maintain the consistency of the product. Typical ranges are mesh fractions covering two sizes of standard screens, e.g., 16 to 20. A further tolerance may be applied to define that a certain percentage of these pellets or granules not pass through an 18 mesh screen.

The drug concentration of the pellet also plays a critical role in determining the release rate, since diffusion occurs across a concentration gradient. It is this property that accounts for the first-order release patterns that are routinely observed with membrane controlled–release systems. As drug is released from the core through the membrane into the dissolution medium, the drug reservoir is depleted and the concentration in the medium is increased. The concentration gradient is greatest in the initial phase of drug release and decreases with time. Thus, the release rate decreases with time. This behavior is most prevalent with highly soluble drugs, which are typically formulated into modified-release dosage forms.

Other substrate properties that have significant effects on the release characteristics of coated dosage forms are described in the literature (15–17). Drug solubility in the film and migration of soluble components of the substrate into the film coat during processing may not only affect release rate, but also stability of the product over time. The lipophilic drug ibuprofen was shown to migrate through an Aquacoat ECD film forming drug crystals on the surface over time due to its solubility in the film. This phenomenon can be eliminated or, at least, minimized by the application of a seal coating between the core and the controlled-release film. An example of a polymer that may be used as a seal coating is HPMC. However, the effect of the seal coating on the final release of drug from the dosage form must be studied.

## COATING AND PROCESSING EQUIPMENT

Several types of coating equipment may be used to film coat pellets or granules with Aquacoat ECD. These include fluid-bed equipment, perforated coating pans, and conventional coating pans. Air suspension (fluid-bed) processes are more efficient at removing water due to high air throughput and are characterized by short processing times. This factor, coupled with the small size of pellets, makes air suspension the process of choice for coating pellets with Aquacoat ECD formulations. It is important, however, with fluid-bed machines and any other coating equipment, that specific processing parameters be established to obtain an acceptable film coat. Even within the fluid-bed family of coating machines, different parameters are appropriate for different setups. For example, top spray, bottom spray, and tangential spray processes commonly employed in fluid-bed coating provide coated pellets with surface morphologies that are unique to each process (20). Since this is a property that may ultimately determine the release profiles that are envisioned, judicious selection of processing equipment can help circumvent potentially disastrous coating operations. In some cases, the transfer of processes from one type of equipment to another may require a change in the composition of the formulation to generate matching release profiles.

Once the processing equipment has been selected, coating parameters are established to maximize efficiency and to maintain reproducibility. These parameters include (*i*) the inlet air humidity, temperature, and volume; (*ii*) the batch size; (*iii*) the spray rate; (*iv*) atomization air pressure; and (*v*) any other parameter specific to the equipment such as rotor speed and air slit opening for rotary fluid-bed processes. In addition, product variables such as batch size and substrate properties must be carefully monitored. During film coating with Aquacoat ECD polymeric dispersions, an air-handling system that provides consistent drying air to the product chamber is essential to ensure the reproducibility of the process with a given set of parameters. Whenever a set of processing conditions do not provide the perfect end result, a compromise may be necessary to achieve an acceptable product. For example, if a fast application rate does not provide reproducible results, the application rate may have to be reduced, thereby increasing processing time.

## FILM CURING AND STABILITY

### Curing

Films formed from Aquacoat ECD dispersions require a curing stage before the release rate characteristics of the coated product stabilize (5). As discussed earlier, film formation from a pseudolatex consists of several steps. The coalescence process is initiated during the application stage. However, microscopic coalescence occurs after the coating event has been completed. This process has been termed "further gradual coalescence" (5). Depending on the formulation and the coating conditions, this process has been reported to take as long as two weeks at room temperature. Thus, a formulator would have to wait at least two weeks to determine the true release characteristics of a product.

One way of accelerating the further gradual coalescence process is to use high processing temperatures and/or store the film-coated product at an elevated temperature after coating. However, the processing temperature cannot be much higher than the film-softening temperature during the coating process, because tackiness of the film leads to severe handling problems and agglomeration. Due to the level of plasticizers usually included in Aquacoat ECD formulations, the inlet air temperatures are typically adjusted to keep the product temperature below 45°C. In some cases, even lower temperatures may be required. Storing the coated product in ovens at 60°C for short periods of time has also been shown to further shorten the gradual coalescence time. Based on this premise, a process was developed utilizing fluid-bed technology to film coat and ensure full coalescence of the film coating in a 30-minute curing step (21). The procedure involved the application of an Aquacoat ECD formulation on pellets to impart sustained release characteristics, followed by an overcoat composed of HPMC. The HPMC film, which is derived from an aqueous solution, has a higher glass transition temperature and thus a higher softening temperature than the plasticized Aquacoat ECD film. This allows the product to be exposed to high temperatures (60°C) in the fluid-bed equipment without the creation of a sticky surface, as was true with the plasticized Aquacoat ECD film. Li et al. have studied the effects of temperature and humidity on film coalescence and curing (22). The optimization of temperature and humidity during the curing step may significantly accelerate the process. Naturally, the high curing temperature associated with Aquacoat ECD formulations may not be applicable to substrates containing temperature-sensitive and/or low-melting drugs and formulation aids.

### Storage and Stability of Coated Pellets

Film-coated pellets should not be stored or transported above the softening temperature of the film to avoid an unwanted change in dissolution characteristics, even for cured pellets. Generally, this should not be a problem since most drug products are stored in environments of controlled temperatures, and a change in dissolution characteristics is not expected to occur during the established shelf-life of the product. Experience has shown that the release profiles of Aquacoat

ECD–coated pellets remained stable over a four-year period. To ascertain the dissolution stability of coated pellets, not only during controlled storage but also during transport and patient use, it is critical that the coated product be subjected to elevated temperatures. One could also use the temperature/relative humidity (RH) conditions for stability storage recommended by the International Committee on Harmonization: 25°C/60% RH and 40°C/75% RH. Samples may also be stored at 30°C/60% RH (backup to the 40°C/75% RH condition).

## PRACTICAL EXAMPLES

### Ibuprofen Pellets

Ibuprofen pellets were prepared by solution layering in a Glatt Roto-granulator and film coated with an Aquacoat ECD dispersion in a Glatt WSG-5 unit with a Wurster insert to achieve sustained release of the drug over an eight-hour period in pH 7.2 buffer (23). Myvacet® 9-40 (distilled acetylated monoglycerides) was used as the plasticizer. Successful sustained release was attained with a 13% film coat (Fig. 2); however, no stability data were given.

### Phenylpropanolamine HCl Pellets

Phenylpropanolamine HCl pellets were prepared by the extrusion-spheronization technique and film coated in a laboratory fluid-bed machine (Aeromatic Strea) employing the bottom spray apparatus to achieve sustained release (10). By comparing plasticizers and drying parameters, it was shown that sustained release was attained under a variety of conditions (Fig. 3).

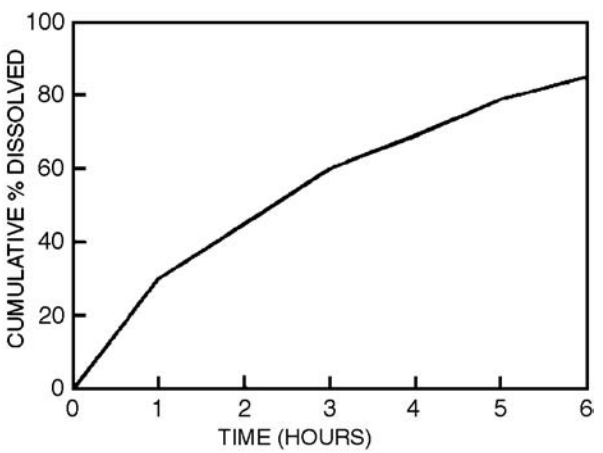


**Figure 2** Dissolution profile of ibuprofen pellets coated with Aquacoat ECD® plasticized with Myvacet® 9-40. *Source*: From Ref. 23.

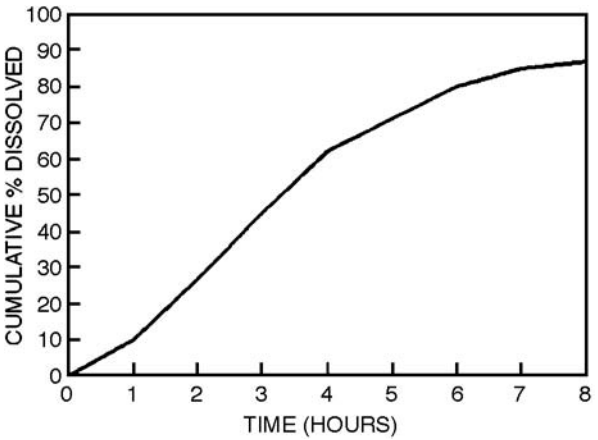


**Figure 3** Dissolution profile of phenylpropanolamine HCl pellets coated with Aquacoat® ECD plasticized with triethyl citrate. *Source*: From Ref. 10.

## Theophylline Pellets

Theophylline pellets of 75% potency and 20 to 40 mesh size were coated with Aquacoat ECD films containing HPMC to obtain the target dissolution profile (24). The coating equipment was the Glatt WSG-5 unit with a Wurster insert. The plasticizer used was dibutyl sebacate at the 24% (based on polymer solids) level. The coating

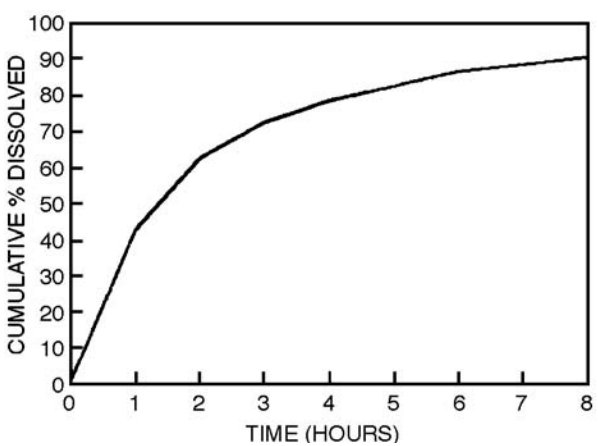


**Figure 4** Dissolution profile of theophylline pellets coated with Aquacoat® ECD and 10% HPMC. *Abbreviation*: HPMC, hydroxypropyl methylcellulose. *Source*: From Ref. 24.

**Table 4** Coating Formulation Containing 10% HPMC and 25% Total Solids

| Ingredient | Amount of solids (g) | Amount of dispersion (g) |
|---|---|---|
| Aquacoat® ECD | 139.5 | 450.00 |
| Dibutyl sebacate | 33.48 | 33.48 |
| HPMC E-5 (14% solution) | 18.58 | 132.71 |
| Water | | 149.97 |
| Total | 191.56 | 766.16 |

*Abbreviation*: HPMC, hydroxypropyl methylcellulose.

level was held constant at 13%, and various release rates were obtained by modifying the level of HPMC in the film (Fig. 4). The total solids concentration of the dispersion formulations was 25% to 30%. The rotating bottle, changing pH method was used to study dissolution. The target release was obtained with formulations containing 7% to 10% HPMC. The coating formulation containing 10% HPMC and 25% total solids is shown in Table 4. Other authors have also shown sustained release with theophylline using dibutyl sebacate as the plasticizer (25).

## EVALUATION OF COATED PELLETS

The most obvious way to evaluate coated pellets physically is to conduct the dissolution test. To date, this is the best physical test available to correlate with in vivo performance. There is no method of choice for conducting the dissolution test. The USP/NF currently recognizes two apparatuses for conducting dissolution testing that would be convenient for pellets. These are the rotating basket and paddle apparatuses. A flow-through apparatus is also now recognized by the USP/NF that could also be used to evaluate the release of drug from coated pellets. Some investigators still utilize the rotating bottle, changing pH method.

Other physical tests that may be used to evaluate film-coated pellets include macroscopic and microscopic observations and porosimetry (26). Application of these tests may or may not lead to a correlation with in vivo performance. The use of the microscope allows the investigator to examine the surface characteristics of the film. Mercury intrusion porosimetry can be used to determine the porosity and pore volume of the film coat. The porosity of the film may be correlated with the release rate. Caution, however, must be exercised when mercury intrusion is used to determine pore size at elevated pressures, since it is difficult to accurately measure pore size in a flexible film. However, the ultimate performance test for the modified-release dosage form is adequate drug bioavailability and sustained pharmacological activity. The goal is to achieve a dosage regimen with less frequency of administration without lowering the overall oral bioavailability relative to an

immediate-release dosage form. Since it is the physicochemical properties of the drug substance that dictate the outcome, it is extremely important that each drug and product be optimized on a case-by-case basis to accomplish this goal (27).

## SUMMARY

Properly formulated and processed, an Aquacoat ECD aqueous polymeric dispersion can provide all the quality attributes of solvent-based ethylcellulose coatings without the concerns associated with the use of organic solvents. It has the added advantage of a high solids content, which facilitates relatively short processing times and is cost effective. Due to the compatibility of the dispersion with a number of plasticizers of different chemical classes of compounds, the formulation development scientist can tailor film coatings that are suitable for a given drug candidate or substrate. It is essential that the coating formulations and coating processes are optimized and carefully controlled to ensure reproducibility of the product from batch to batch.

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# 3

# Processing and Equipment Considerations for Aqueous Coatings

**Atul M. Mehta**

*Elite Laboratories, Inc.,*
*Maywood, New Jersey, U.S.A.*

## INTRODUCTION

Environmental and economic factors have caused an ambitious shift from organic-solvent–based to water-based film coatings for pharmaceutical dosage forms. The significantly higher heat of vaporization of water has required improved efficiency in coating equipment, such that conversion to aqueous systems can be achieved with a minimum of difficulty. The choice of proper equipment and the creation of a suitable processing environment are as essential to achieving a good film coating as is the selection of the appropriate coating formulation. This is particularly true for aqueous film coating.

Initially, aqueous processes were met with skepticism because of the longer process time and the inferior appearance of the coated product. A few desired release functions were obtainable only with organic solvent–soluble films. However, the development and introduction of latex and pseudolatex materials as well as improvements in equipment design have broadened the spectrum of aqueous coating. With correctly selected equipment and processing conditions, it is now possible to apply water-based films to small particles without agglomeration or to tablets containing superdisintegrants without core penetration and dissolution of the tablet surface.

The expanding and competitive market for pharmaceuticals has led to many products with unique forms and release characteristics. Tablets, pellets, granules, and crystals coated for esthetic reasons or for functional release are increasingly being prepared from water-based coating systems. Newly developed films can be

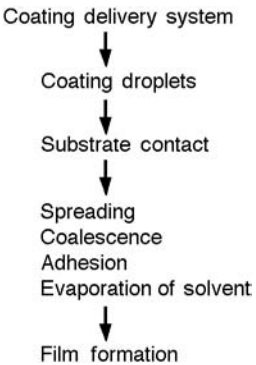


**Figure 1** Dynamics of the coating process.

applied for enteric release, for the masking of unpleasant tastes, and for sustained and controlled release, as well as for protection from environmental conditions. However, it has also placed a greater demand and emphasis on the equipment design and processing conditions for such products.

The film-coating process requires a delicately balanced environment (Fig. 1). Formation of an acceptable layer of film on the substrate requires the following:

1. Formation of appropriate-size droplets
2. Contact of these droplets with the substrate
3. Spreading and coalescence of the droplets
4. Evaporation of the solvent

An equilibrium must be established such that the coating material adheres and coalesces properly upon contact with the surface of the substrate, yet it also must dry rapidly so that core penetration of solvent and dissolved coating material is minimized and agglomeration of core material is prevented. To create the necessary environment for such a process to occur, specialized coating equipment and optimal processing conditions are mandatory.

## EQUIPMENT

Equipment used in film coating can be classified into three general categories: pans, perforated pans, and fluid-bed processors. These systems are used to contain the materials being coated and provide an environment for the coating to dry. They should also provide a means to ensure that an equal amount of coating material is applied evenly to each particle. The delivery system conveys the coating material to the coating equipment in a controlled and desired fashion. Support equipment contributes to automation and includes the control systems. The available coating

equipment systems vary from simple air handlers and manual process control to automated processes and dew point control.

Coating is an old processing technique and has been utilized for centuries. Early coatings were applied to products by rolling the product in a mass of wet coating material and continuing the rolling until it was dry. The rolling action distributed the coating uniformly over the surface of the object being coated as it was slowly drying. Heat was sometimes applied at various stages during the process to accelerate the drying. The process was typically carried out in a shallow pan hung from the ceiling over an open fire. Needless to say, coating was a slow process and achieved inconsistent results.

## Conventional Pan

Approximately 140 years ago, the coating pan was invented. A great many products were and still are being coated in round pans (Fig. 2). Primarily used for sugar coating, this system uses drying air blown onto the surface of the tumbling bed;

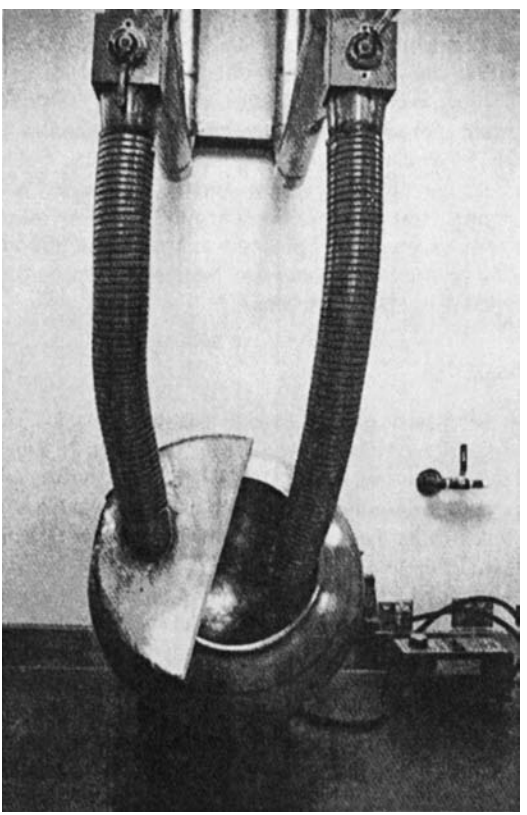

**Figure 2** Conventional pan. *Source*: Courtesy of Colorcon, Inc., West Point, PA, U.S.A.

exhaust air is withdrawn by a manifold situated at the outer perimeter of the pan opening. Much of the heat energy supplied to the bed is deflected off the surface.

Initially a deep pan was placed at the end of a tilted rotating shaft. The shaft was turned at a constant speed by means of a hand crank, and heat was applied by placing an open fire under the pan as it turned. Up until approximately 25 years ago, the only real improvements to this design were the replacement of the hand crank with a motor and the use of forced hot air instead of an open flame. This type of coating equipment was well suited for the kind of coating then being done—sugar coating. Sugar coating is a long and sensitive process, usually defined as "art" as opposed to "science." Validation of this process has been difficult. Although there are now some automated sugar coating processes, film coating is replacing them as the method of choice. When film coating was introduced to improve coating efficiency, attempts were also made to improve the drying efficiency of the coating equipment. Improvements were made to the design of the hot air handling equipment, and better exhaust systems were installed to increase the flow of air in the pans. These alterations proved adequate for film coatings based on highly volatile organic solvents, and this type of coating became the standard of the industry and remained so for many years. Solvent film coating adapted rather easily to conventional pans, but aqueous systems presented serious problems due to the high latent heat of vaporization of water (539 kcal/kg), which is much greater than that of the popularly used organic solvents (e.g., 200 kcal/kg for ethanol). However, as the need to reduce the use of organic solvents became important, it was found that these modifications did not provide adequate drying conditions for coatings using water as a solvent. Core penetration by water is the main concern, especially when the core contains water-soluble drugs or water-sensitive drugs or when the tablets contain superdisintegrants.

To improve the utilization of the drying air, the immersion sword was developed (Fig. 3). This device consisted of a supply and exhaust air manifold,

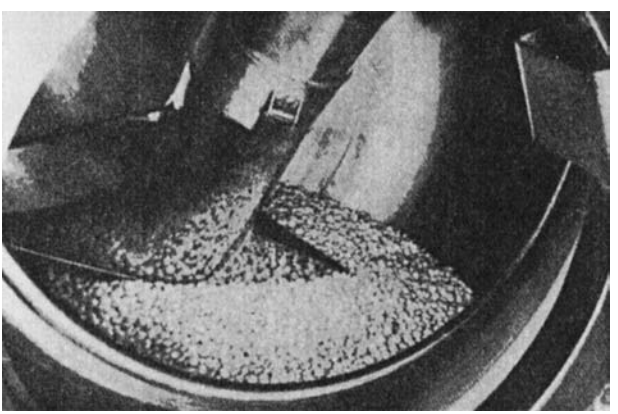

**Figure 3** Immersion sword. *Source*: Courtesy of Glatt GmBH, Binzen, Germany.

which is immersed in the tumbling bed. Drying efficiency is improved but there are some disadvantages. The stationary sword, which displaces some product (reducing batch size), can affect mixing in the pan. Additionally, as tablets cascade into the device, attrition of the core or abrasion of the coating may occur. This problem is minimized by positioning the sword carefully and supplying the drying air in the direction of the tumbling tablets; this provides a cushion of air that reduces the impact of the tablets against the sword. Also, the sword should penetrate the bed so that the tablets pass it only by gravity. If it is too deep and enters the lower bed, which contains tablets being returned to the surface by the pan, abrasion or attrition may result. The sword is applicable to both conventional round pans and the Pellegrini pan (Fig. 4), which is a somewhat angular pan that rotates on a horizontal axis. Typically, the drying air is supplied to the batch surface, as in the conventional pan, but mixing baffles and improved

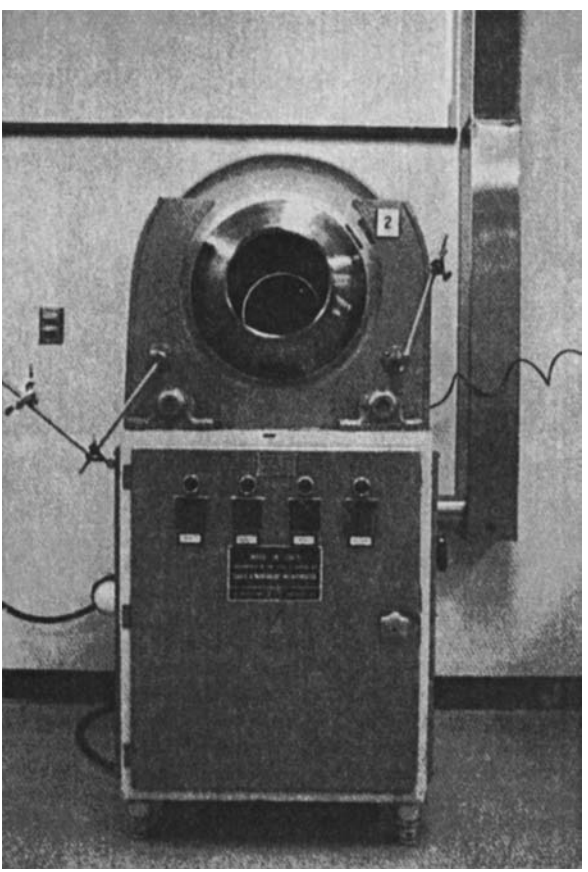

**Figure 4** Pellegrini pan. *Source*: Courtesy of Colorcon, Inc., West Point, Pennsylvania, U.S.A.

design make the Pellegrini better suited for aqueous film coating than the conventional pan. This type of coater is available in batch sizes up to approximately 1000 kg.

## Perforated Pans

The perforated pan was developed to improve drying efficiency, which it does by drawing the air through the bed as opposed to supplying air to the bed surface only (Fig. 5). Drying air is supplied to the bed in several ways. In one type, it is supplied from outside the pan, drawn through the bed, and exhausted by a duct behind the tumbling bed. Another approach supplies air from a duct located just inside the loading or access opening of the pan. Deflector baffles direct the air across the bed, and the air is exhausted from behind the tumbling tablets. Yet another type of system uses a split duct behind the tablet bed, which allows air to be supplied underneath the front of the bed, which may be advantageous for tablets with friability problems. Additional drying air may be supplied to the bed surface. Exhausting is accomplished through the top half of the split duct.

There are variations in these systems (Fig. 6), depending on the vendor, but the intention is to maximize the drying capability of the machine so as to minimize core penetration at high spray rates. Batch sizes in these systems range from 0.5 kg to approximately 800 kg. The choice of one pan over another is a very individual decision, depending on the types of coatings to be performed, the degree to which the system is to be customized, the materials to be coated, and a host of other possible considerations. However, they all can be effectively employed for aqueous film coatings. For example, an equipment evaluation study (1)

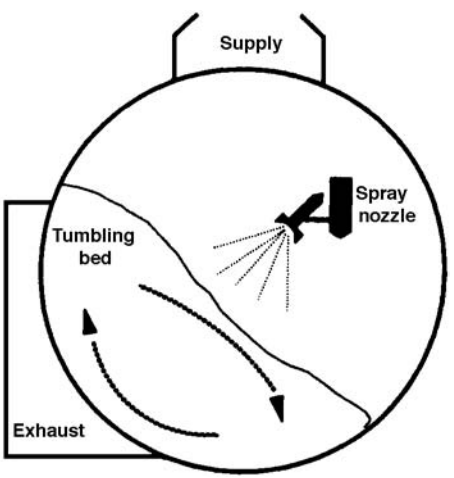


**Figure 5** Perforated pan.

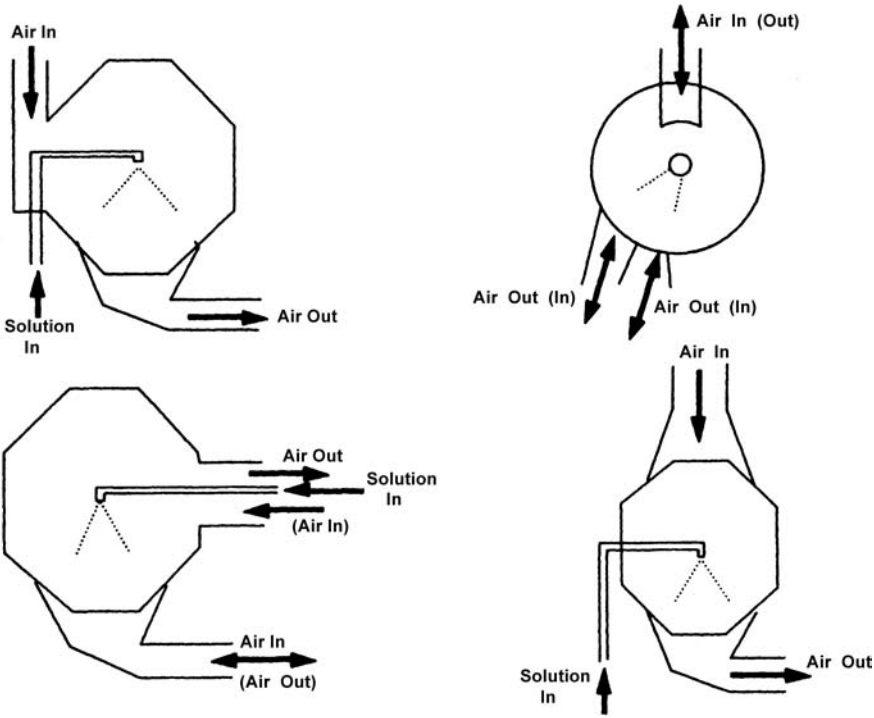


**Figure 6** Various designs of perforated pans.

compared five commercially available pans for aqueous enteric coating of tablets. The pans were evaluated for feasibility, coating application rates, efficiency of application, air utilization efficiency, frequency of gun plugs, and ease of application and cleaning.

For high-volume products, a continuous coating equipment such as that shown in Figure 7 may be utilized. It is a modular design system that enables starting with a basic treater and expanding into a full range coating system. Figure 8 is the schematic of such a system, and Figure 9 depicts an inside view of the coating chamber. The continuous process machine allows the product to flow continuously throughout the product run. New product enters the machine in a steady stream to replace coated product that has exited the machine. The throughput is dependent on product and/or coating treatment objectives. Volumes range from 100 to 30,000 lb/hr.

The process begins with the product entering the machine through an infeed chute. In the first drum, the product is coated and transferred into another infeed chute; the process is repeated in the second drum. At the conclusion of the process, the product should be dry and ready for further treatment such as packaging.

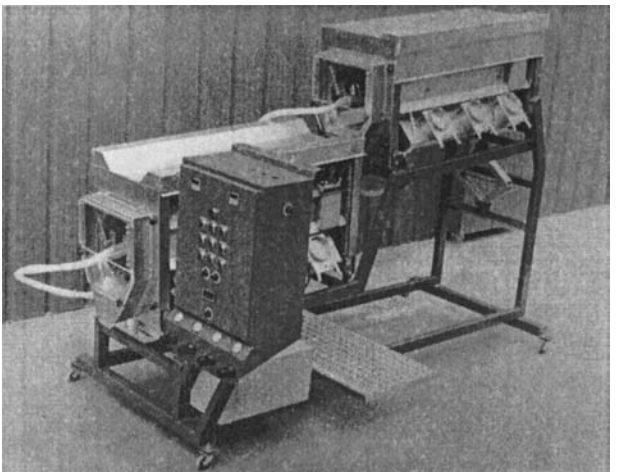

**Figure 7** The Workhorse continuous coating system. *Source*: Courtesy of Vector Corporation, Marion, Iowa, U.S.A.

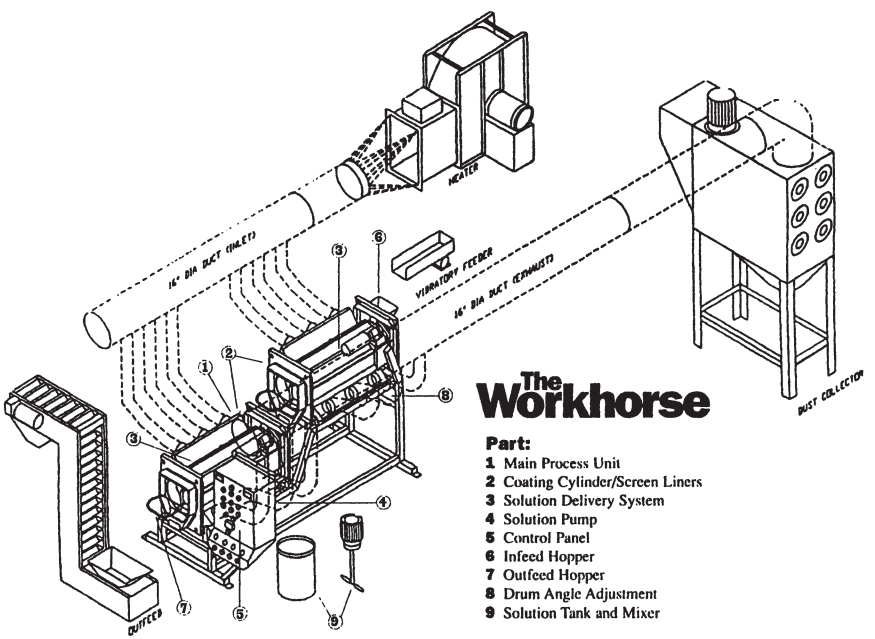


**Figure 8** Typical equipment required to operate continuous coating system. *Source*: Courtesy of Vector Corporation, Marion, Iowa, U.S.A.

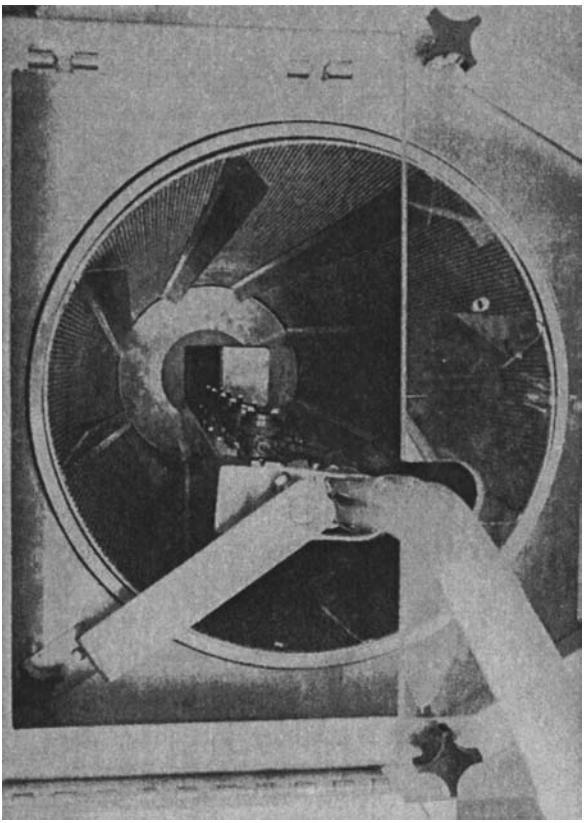

**Figure 9** Main processor unit. *Source*: Courtesy of Vector Corporation, Marion, Iowa, U.S.A.

The continuous series includes an intricate spraying setup that involves 10 spray guns, individually controlled to provide uniform coverage. One gun can be spraying a small amount of coating solution while the next gun is spraying a larger amount and the next might not be spraying any solution at all. The controls enable the operator to adjust the amount of spray on the product.

A complete continuous coating system provides centralized controls for all parameters such as inlet temperature, air flow, drum speed, and differential pressure. Such a system can also monitor dew point.

## Fluid Bed

The fluid-bed equipment is well known for its drying efficiency, having been used for drying and granulating for many years. A typical fluid-bed system is depicted in Figure 10. The use of fluid-bed equipment in applying aqueous coating

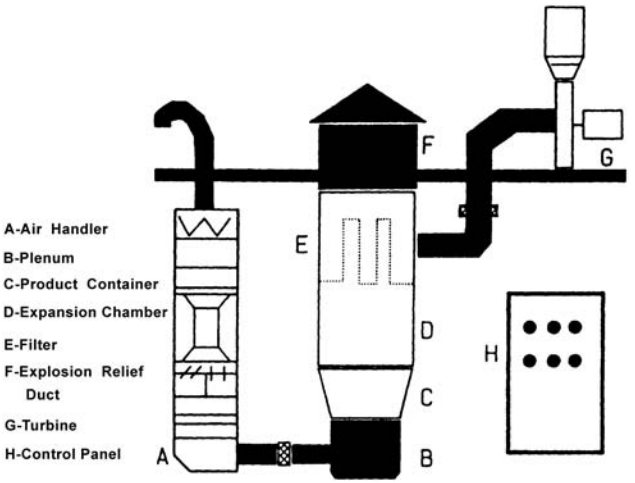


**Figure 10** Typical fluid bed installation.

systems has increased greatly primarily due to (*i*) improved drying efficiency, (*ii*) improved design considerations, and (*iii*) increased experience.

Fluidized-bed equipment is the preferred choice of equipment for aqueous coating systems applied for reasons other than esthetics such as taste masking, enteric coatings, sustained- or controlled-release coatings, and coatings applied

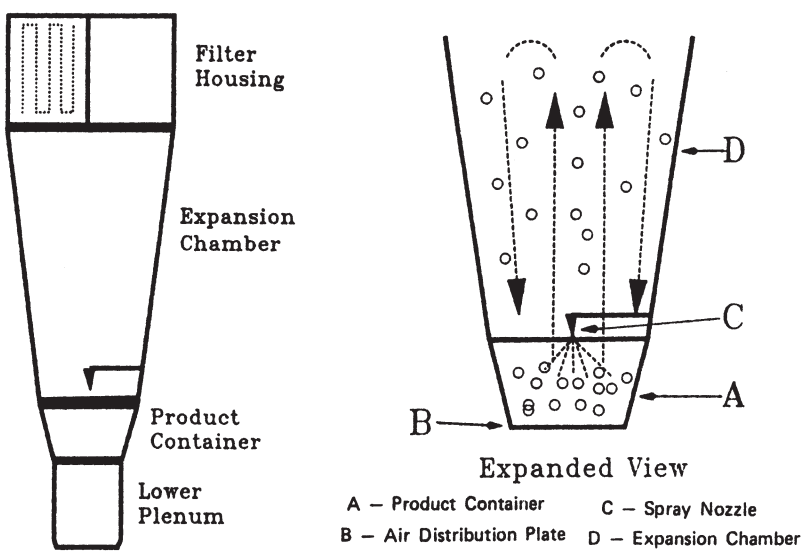


**Figure 11** Top-spray coater. *Source*: Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey, U.S.A.

for protection. Aqueous film coating can be applied to the fluidized material by a variety of techniques, including spraying from the top (granulation or conventional mode), from the bottom (Wurster), or tangentially (rotary granulator).

### Top Spray (Granulator Mode)

Although it is not applicable for tablets, the top-spray granulator can be used to coat small particles successfully. The films formed in this process are not as uniform, but for releases that are not dependent on membrane thickness or perfection (such as taste masking), it is a viable and simple approach. The substrate is fluidized up to the nozzle, which sprays counter-currently into the material (Fig. 11). The high particle velocity and efficient heat transfer allow aqueous coating of small particles with little or no agglomeration. Batch sizes range from 0.5 kg to approximately 1000 kg.

### Bottom Spray (Wurster)

The Wurster coating system, invented about 25 years ago, has had some success in table coating. The flow pattern is formed by a partition and an orifice plate, which control the air flow (Fig. 12). The majority of the air is diverted through

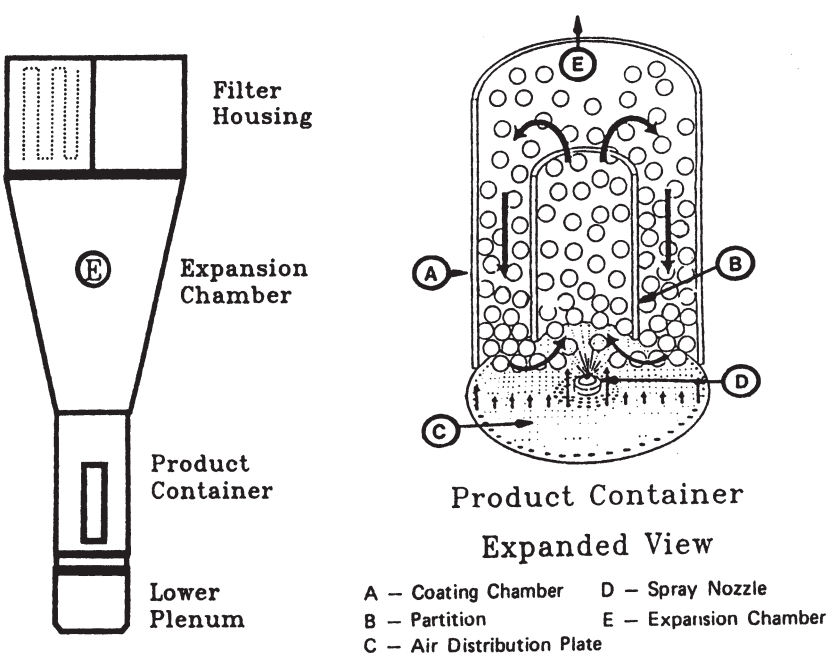


**Figure 12** Bottom-spray (Wurster) coater. *Source*: Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey, U.S.A.

the partition, causing fluidization and upward travel of the cores. As the tablets or particles exit the partition and enter an expansion zone, air velocity decreases and the cores drop outside the partition. The air in this down-bed acts to cushion the tablets as they travel downward to continue their cycling through the coating zone. The balance between the air inside and that outside the partition and the

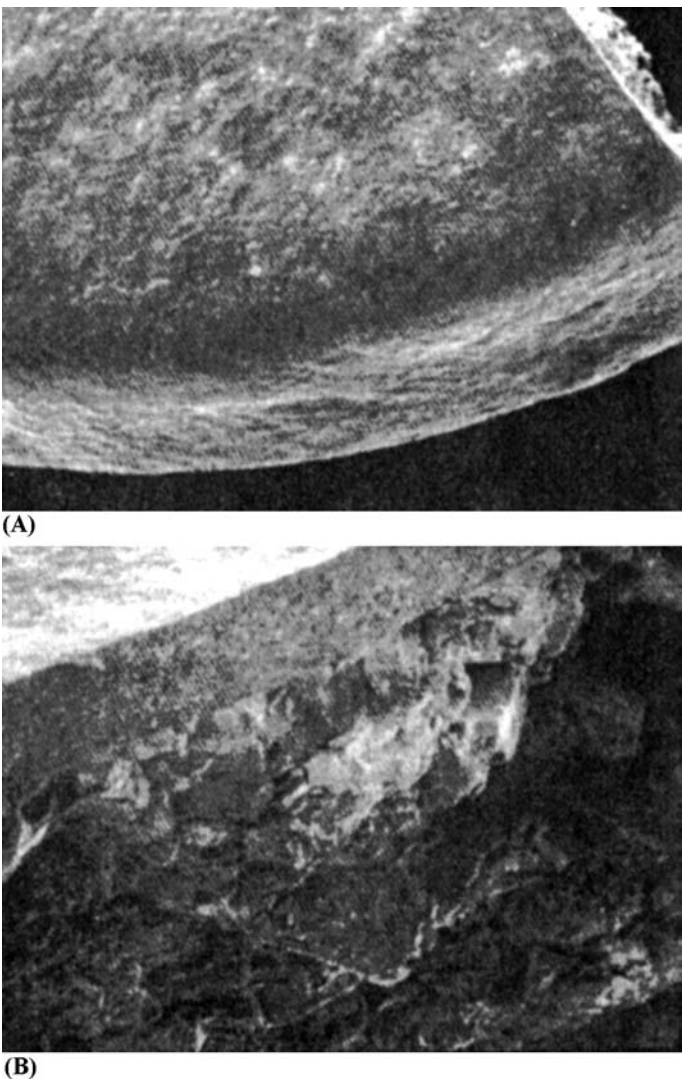


**Figure 13** Cross sections of tablets coated with Eudragit® L 30 D in Wurster coaler (Glatt GPCG-5): (**A**) magnification ×25; (**B**) magnification ×100.

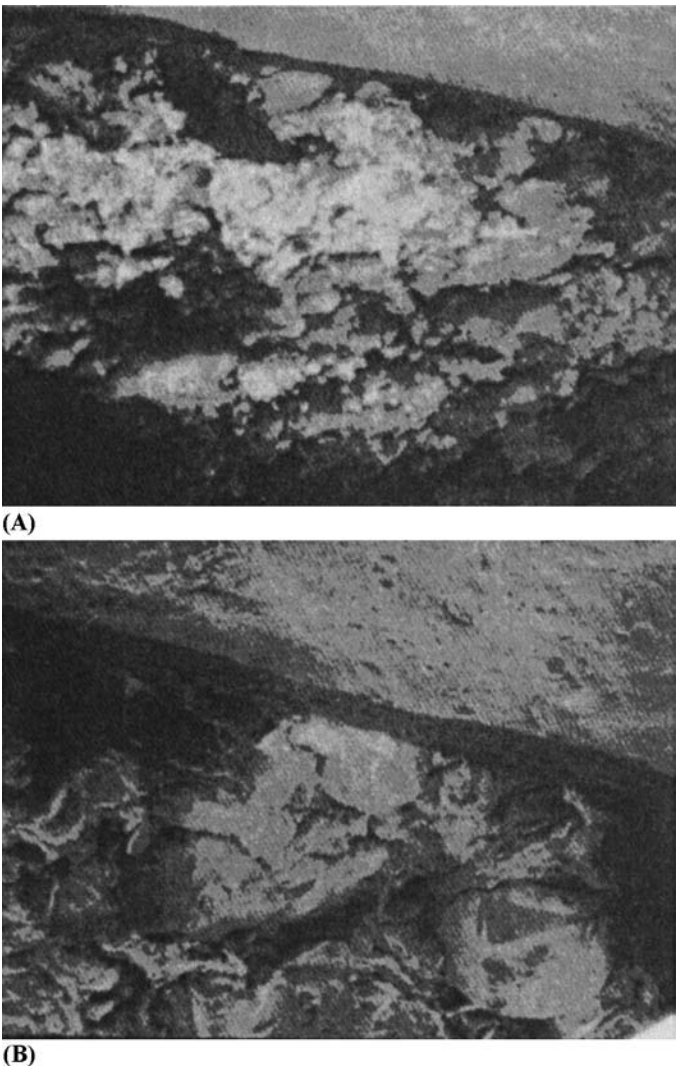


**Figure 14** Cross-sectional views of tablets coated with Opadry in Wurster coaler (Glatt GPCG-5): (**A**) magnification ×25; (**B**) magnification ×100.

gap between the orifice plate and the partition are critical. The proper combination of these factors results in a very dense concentration of core material in the coating zone and a rapid down-bed, indicating a short bed cycle time (under these conditions, liquid application rates may be quite high). Additionally, the up-bed height (the distance the tablets rise above the partition) is small and is the key to

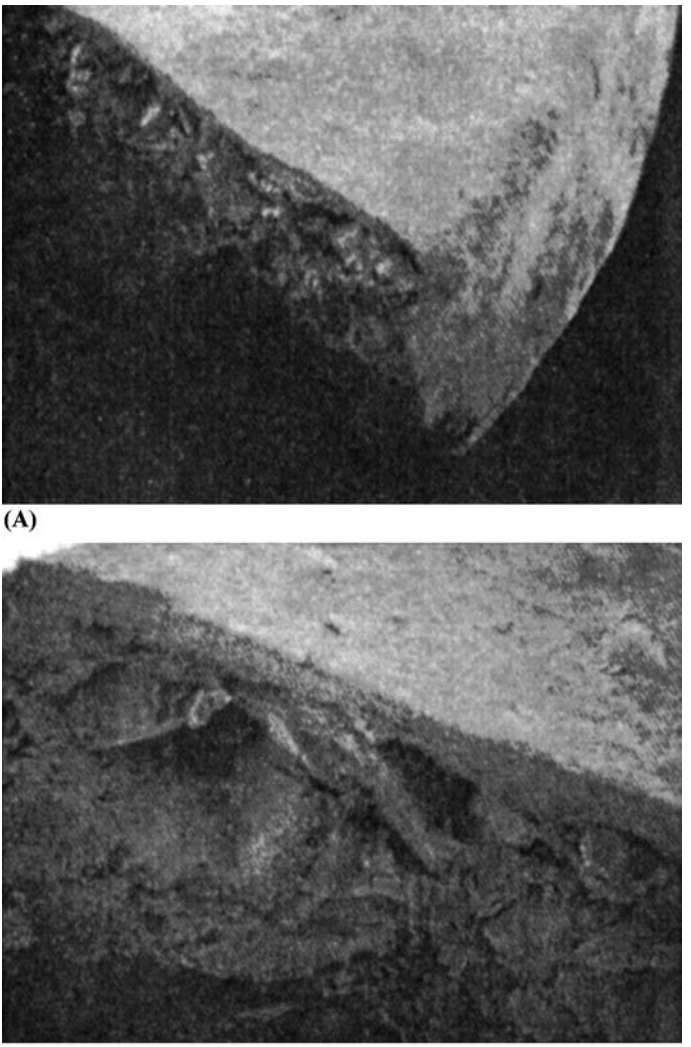


**Figure 15** Cross sections of tablets coated with Aquacoat® in Wurster coater (Glatt GPCG-5). (**A**) magnification ×25; (**B**) magnification ×100.

minimizing the attrition that is usually associated with air suspension tablet coating. Figures 13 to 15 illustrate tablets coated in a Wurster system (Glatt GPCG-5) with three different aqueous polymeric materials.

The Wurster system is growing in popularity in the coating of smaller particles. It is able to apply droplets to the substrate before much evaporation occurs

and rapidly evaporates surface solvent (or water) prior to core penetration. This is evident in Figure 16 where different layers of applied coatings are visible. This is critical for stability as well as endproduct performance of the product. Discretely dividing the particles by air suspension allows the application of films to pellets, granules, and materials as fine as 50 μm with little or no agglomeration (depending on the coating substance). The organization of the particles in close proximity to the liquid nozzle and rapid bed cycle times yield uniform distribution of the film. Depending on the vendor, there are variations in the geometry of the total system. However, it is recommended that longer expansion chambers be used to coat small particles (Fig. 17). The system allows batch sizes from 0.5 kg to approximately 500 kg.

The recently introduced Wurster HS™ technology (U.S. Patent 5,236,503) involves the use of a proprietary device to influence the behavior of the coating zone (Fig. 18). It is designed to keep particles away from the nozzle until the spray pattern is fully developed. As a result, more of the excess drying capacity can be used and the application rate can be substantially increased. The high-atomizing air velocities can provide droplet sizes small enough for coating of particles smaller than 100 μm without causing attrition, since the velocity decreases prior to contacting the substrate. This is because the product is kept away from

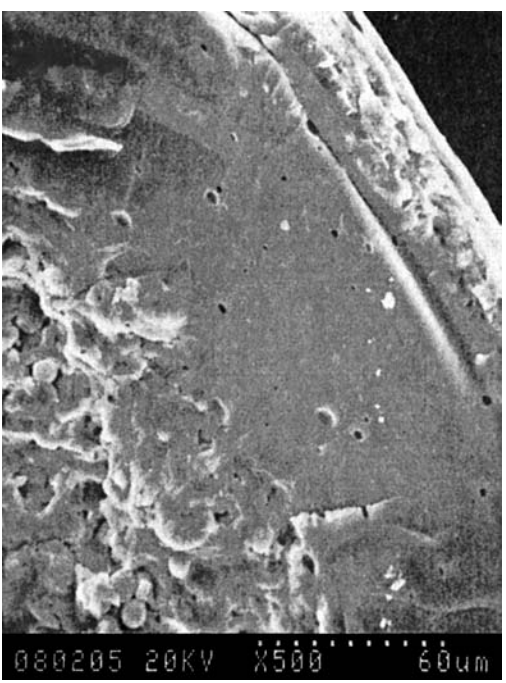


**Figure 16** Cross section of a drug-containing particle coated with polymers in Wurster column. *Source*: Courtesy of Elite Laboratories, Inc., Maywood, New Jersey, U.S.A.

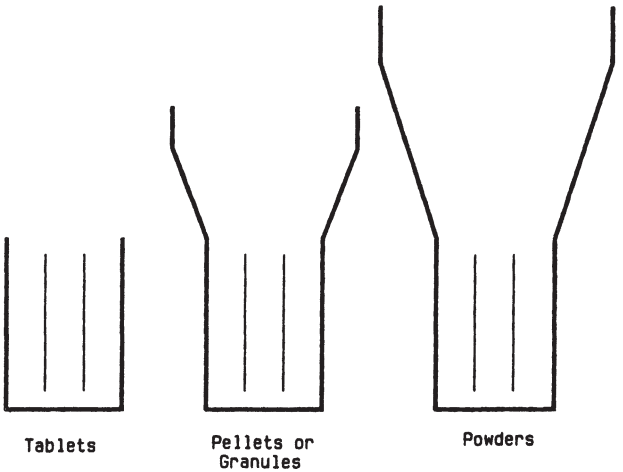


**Figure 17** Expansion chambers for Wurster columns. *Source*: Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey, U.S.A.

the nozzle tip. However, success depends on the type of product to be coated, liquid characteristics which must be amenable to atomizing to well below 10 μm droplets, and the processing conditions employed. It is to be noted that the high surface area of fine particles requires high amounts of coating to ensure adequate coverage of particles.

Another recently developed approach to improve on the coating application in a Wurster column makes use of Swirl Accelerator (particle accelerator; Fig. 19), a guiding system in which the air is accelerated, stabilized, and given a precise amount of swirl. The objective is to provide a highly controlled air flow pattern in the coating zone. Particles are entrained into the swirling air flow, which leads to greater probability of impact with droplets of atomized coating liquid. This can lead to a reduction of the amount of coating material needed, and the process times are reduced as a result. Again, the product and coating liquid characteristics have to be considered and will dictate the ultimate success of the process.

Precision coaters are configured such as to allow removal and inspection of nozzles during processing—a major advantage over conventional Wurster nozzle configuration whereby the process has to be interrupted and the column emptied before access to the nozzles is possible.

### Tangential Spray (Rotary Granulator)

A recently developed fluid-bed system (Fig. 20) uses a rotating disk to add centrifugal force to the forces of fluidization and gravity and offers very rapid mixing. Applicable for coating of pellets, granules, and particles as small as 200 μm,

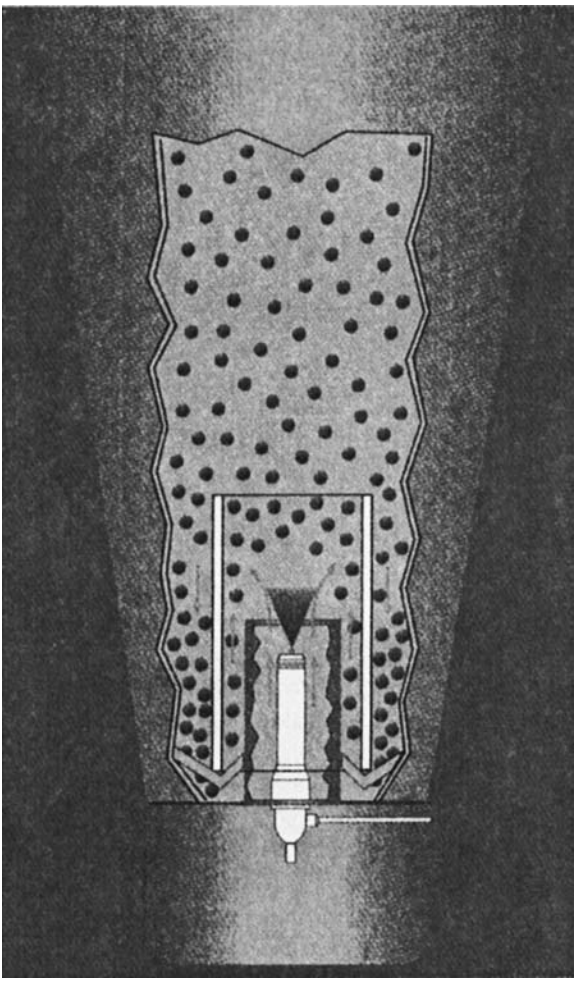

**Figure 18** Wurster HS™ system. *Source*: Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey, U.S.A.

this device is also capable of producing pellets from seed material or powders. A gap between the rotating disk and the wall of the product container allows for fluidization air and controls the liquid application rate. This design achieves greater drying efficiency and hence increased spray rates. The rotary type of air suspension system is available for batch sizes ranging from 1 kg to approximately 500 kg. The particle cycling time in tangential spray fluidized-bed equipment is very rapid, so that the films are uniform in thickness as are those applied using the processes discussed previously.

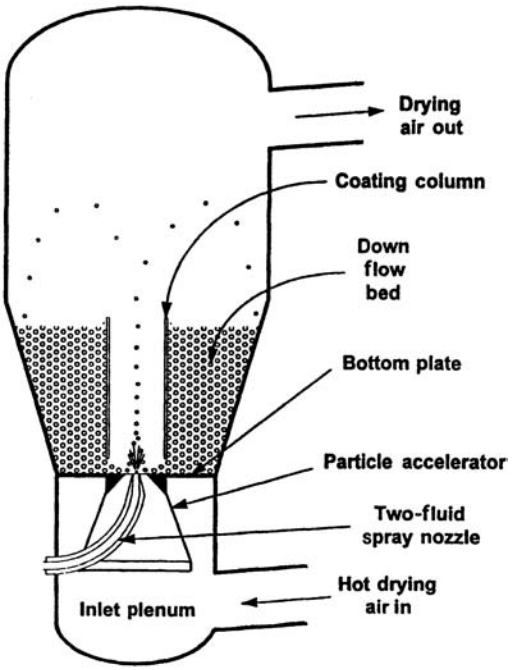


**Figure 19** Precision coater. *Source*: Courtesy of Niro Inc., Columbia, Maryland, U.S.A.

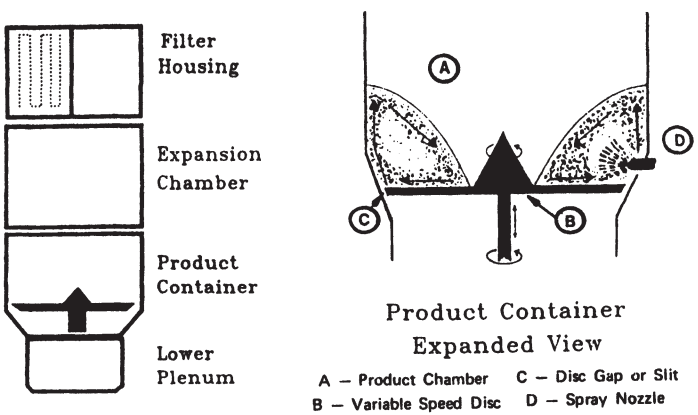


**Figure 20** Rotor tangential spray coater. *Source*: Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey, U.S.A.

The evaluation and advantages and disadvantages of each of these fluidized-bed techniques have been reported in the literature (2,3) and are summarized in Table 1. Figures 21 to 23 illustrate similar morphological characteristics for caffeine pellets coated with the aqueous system (2) in all three fluid-bed techniques, corresponding to similar release profiles (Fig. 24).

### Delivery Systems

The fluid-delivery systems used in film coating consist of the pumping system and the nozzles. Several types of pumps and nozzles are available.

**Pumps:** There are several types of pumps used in coating applications, and the choice may depend on the type of coating material to be applied. The peristaltic pump is the simplest and easiest to clean. It uses a multilobed, adjustable-speed head to deliver liquid through a flexible hose, which is usually silicon rubber. The disadvantages of this pump include pulsation as the lobes change, low liquid pressure, inability to pump viscous liquids, and fluctuations in the liquid delivery rate. Some of the disadvantages can be overcome, and with some coating substances,

**Table 1** Comparison of Three Fluid-Bed Coating Processes

| Processing method | Advantages | Disadvantages | Applications |
|---|---|---|---|
| Top-spray coating (granulator mode) | Large batch sizes<br>Simple setup<br>Easy access to nozzle | Limited applications | For esthetics and enteric coatings; not recommended for sustained-release products or tablet coating |
| Bottom spray (Wurster) | Moderate batch sizes<br>Uniform and reproducible film characteristics<br>Widest application range | Tedious setup<br>Impossible to access nozzles during process<br>Tallest fluid-bed machine for fine particle coating | Sustained release, enteric release, layering, esthetics |
| Tangential spray (rotary mode) | Simple setup<br>Nozzle access during process<br>Higher spray rate<br>Shortest machine | Mechanical stress on product | Very good for layering, sustained release and enteric-coated products; not recommended for friable products and tablets |

the peristaltic pump is the system of choice. Pulsation can be damped by selecting a nozzle port that offers some back pressure to the liquid supply. Since the pump does not develop much pressure, it is ideal for latex and pseudolatex coatings, which are low in viscosity and will coagulate when subjected to the high pressure, or shear, that exists in other types of pumps such as gear and piston pumps.

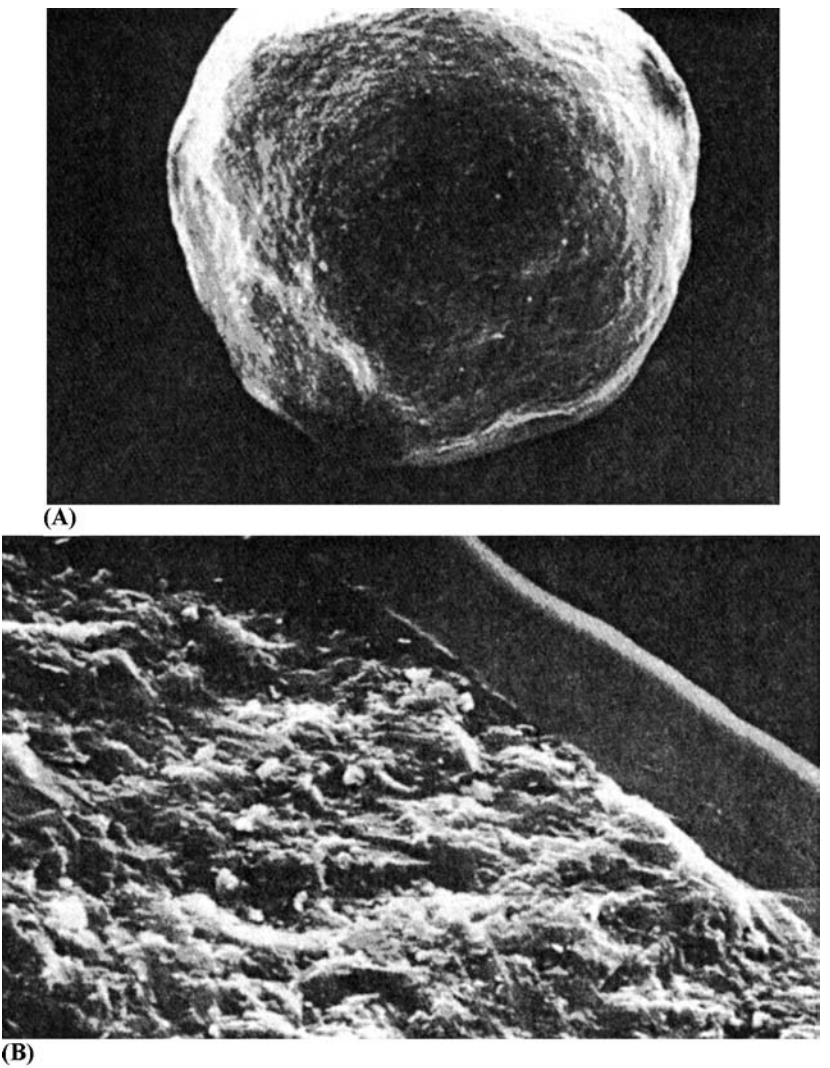


**Figure 21** Caffeine pellets coated to 5% w/w using an aqueous system (Eudragit® L 30 D) and the top-spray method: (**A**) magnification ×70; (**B**) cross section, magnification ×1000. *Source*: From Ref. 2.

The gear pump consists of a cavity of specific volume in which two gears mesh at very close tolerance. This results in very smooth and precise liquid delivery—the major advantage of this type of pump. Cleaning is a bit more difficult, but not overly so. The disadvantage of this system is that the close tolerance between the gears can present a problem when using liquids that contain undissolved solids

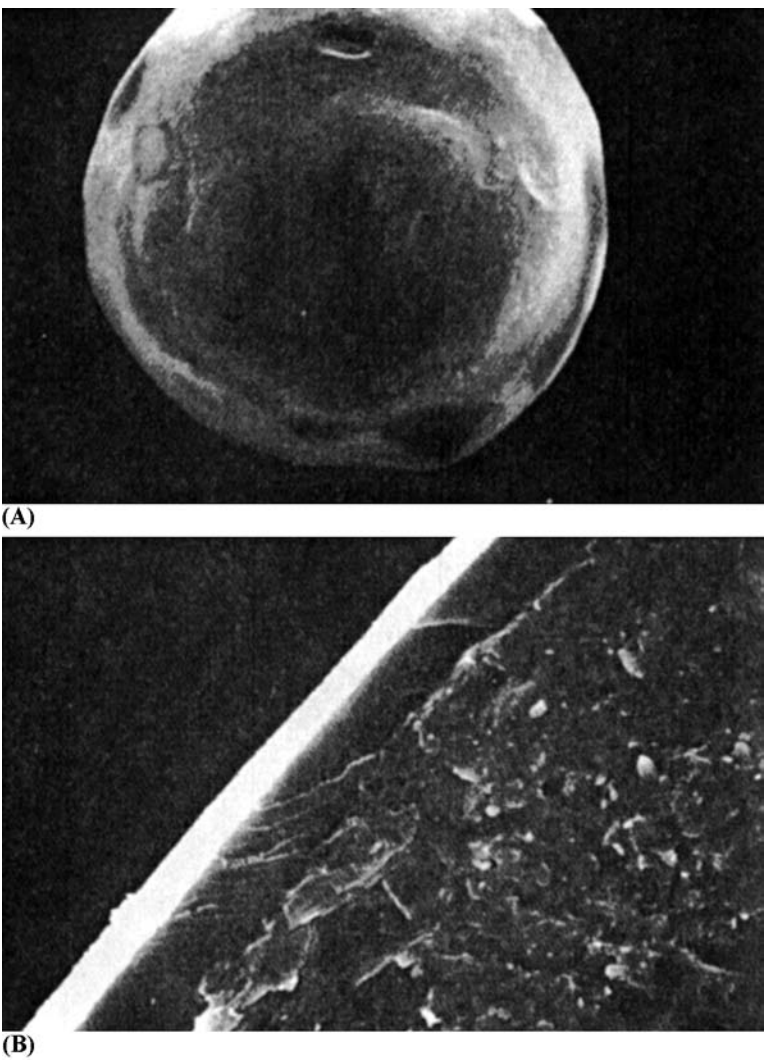


**Figure 22** Caffeine pellets coated to 5% w/w using an aqueous system (Eudragit® L 30 D) and the bottom-spray method: (**A**) magnification ×70; (**B**) cross section, magnification ×1000. *Source*: From Ref. 2.

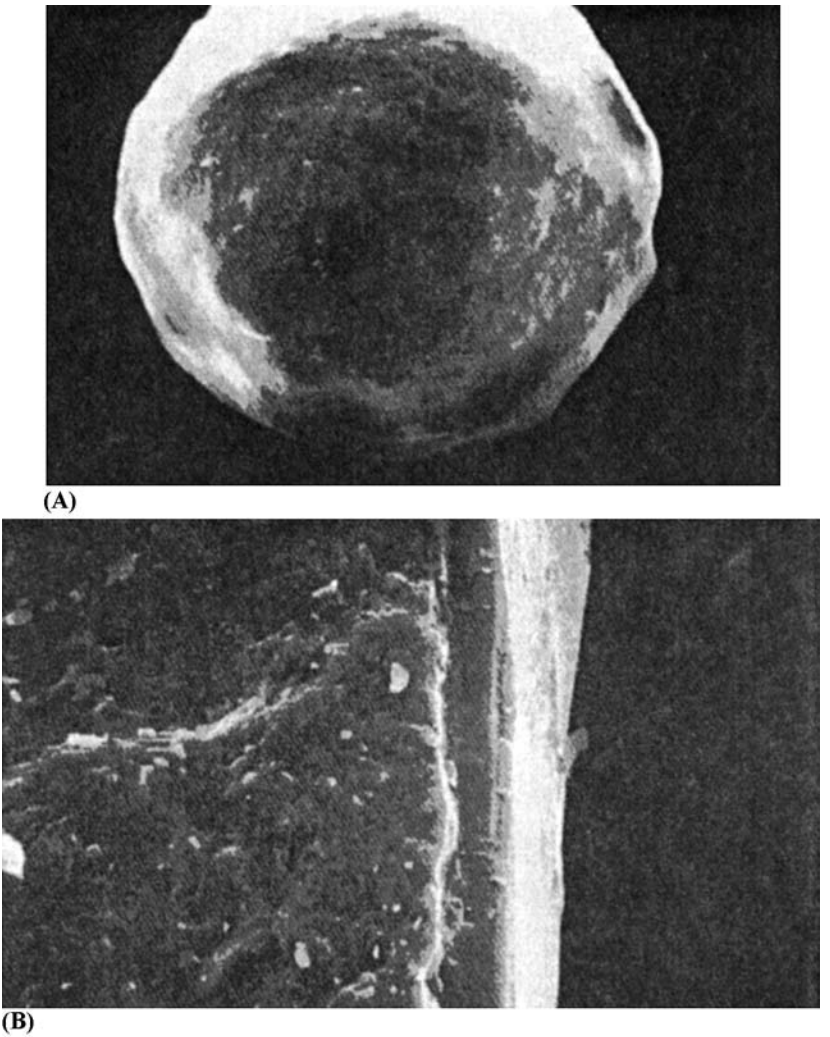


**Figure 23** Caffeine pellets coated to 5% w/w using an aqueous system (Eudragit® L 30 D) and the tangential spray method: (**A**) magnification ×70; (**B**) cross section, magnification ×1000. *Source*: From Ref. 2.

(depending on the particle size). In addition, the pressure developed between the gears may make it unsuitable for use with latex and pseudolatex materials.

The piston pump, used in both air (pneumatic) and airless (hydraulic) systems, uses adjustable stroke length or speed to control flow rate. It has the greatest number of parts and is therefore the most difficult pump to clean. The

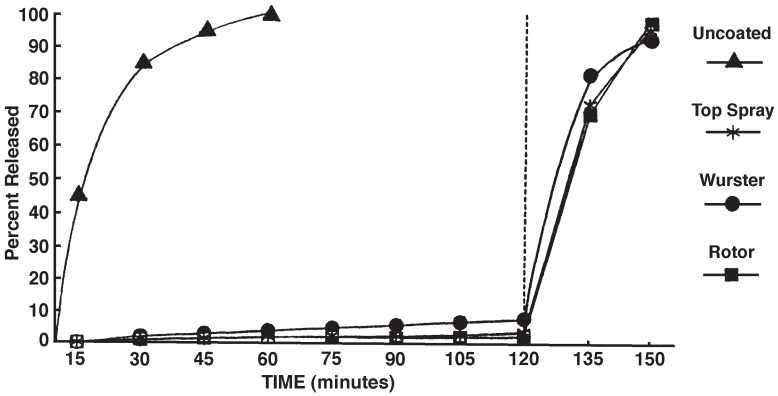


**Figure 24** Dissolution profiles of caffeine pellets coated to a level of 5% w/w using an aqueous system (Eudragit® L 30 D). For 0–120 min, pH = 1.2; for 120–150 min, pH = 6.8. *Source*: From Ref. 2.

advantage of the piston pump is its ability to clear minor clogs in nozzles due to its pressure "reserve." A disadvantage is that there is pulsation in the flow as the piston changes direction (severity varies with the check valve type and travel of the piston). A pulse damper may minimize this effect. Although the line pressure found in the air spray systems is low, the pressure between the contact points in the check valves may cause coagulation of latex and pseudolatex materials, reducing the effectiveness of the valves and resulting in loss of precision of liquid delivery.

In yet another type of system, the container in which the coating liquid is prepared is a pressure vessel. This system is easy to clean and supplies the liquid in a very smooth manner. The delivery rate is controlled by vessel pressure and a flow controller to the nozzle. There are no high-pressure points in this type of "pump"; therefore, it can be used for latex and pseudolatex coating materials.

**Nozzles:** Multiple nozzles are typically used in production coating equipment. It is highly recommended that each nozzle be supplied by a separate pump head or be monitored by a flow meter to assure that if a nozzle clogs, the liquid that would be supplied to the clogged nozzle is not distributed to the other guns or nozzles, which would lead to localized overwetting. Nozzles can be classified as either pneumatic or hydraulic, perhaps better known as air and airless nozzles. The primary difference is the manner by which liquid is atomized by the nozzle.

Most aqueous film-coating systems use pneumatic nozzles. The droplet size can be smaller than with hydraulic nozzles and can be controlled independently of flow rate. The droplet pattern is usually flat fan in coating pans and solid cone in fluidized beds. In the pneumatic nozzles, the fluid is pumped to the nozzle under relatively low pressure, and the outer nozzle opening is larger. Atomization

is achieved by blowing high-pressure air through the fluid stream as it leaves the nozzle opening. These atomization techniques lead to other important differences between the pneumatic and hydraulic nozzles. The advantage of being able to independently adjust the fluid-delivery rate and atomization is very beneficial in the case of pneumatic nozzles. Also, the airstream used for atomization serves to provide an additional drying force during the process. Perhaps the greatest advantage of pneumatic nozzles in aqueous film coatings is that these nozzles can be readily used with pumps that can deliver fluid at an easily measured uniform rate. In the hydraulic nozzle, fluid is pumped at a relatively high pressure through a small nozzle opening, causing atomization of the fluid. It uses the relationship between fluid-line pressure and the nozzle opening to determine the degree of atomization. Thus, changes in the fluid-delivery rate with no corresponding change in the nozzle will result in a change in atomization. An increase in the delivery rate will also increase the atomization and vice versa. This can lead to problems, particularly if a relatively slow delivery rate is desired. With a low delivery rate, a small nozzle opening is required to keep proper atomization, and that may lead to such things as nozzle blockage.

The number of nozzles depends on the surface area exposed to spraying and may range from one to six nozzles in a coating pan, one to seven nozzles in the fluidized-bed Wurster system, one to six nozzles (or nozzle ports in a single nozzle) in the conventional top-spray fluid-bed granulator, and one to three nozzles in a rotary granulator/coaler.

### Filters

A typical fluid-bed machine uses filter bags made of a variety of materials and mesh sizes. They are generally mechanically shaken and can be designed so that the batch continues to fluidize during the shaking mode. This is of particular advantage during coating of small particles to avoid agglomeration and allows continuous spraying. However, the disadvantages include (*i*) tedious setup and clean-up, (*ii*) filters that can rupture, resulting in product loss, and (*iii*) coating material that can deposit into the filter, causing occlusion of filters leading to loss in fluidization.

Alternately, fluid-bed machines can be fitted with a cartridge filter system (Fig. 25). It can filter down to 2 μm, resulting in higher batch yields. They too can provide the ability to perform continuous fluidization. They use a pneumatic pulse design rather than mechanical shaking to reintroduce the product in the process. Their biggest advantage lies in their ease of removal, and they can be designed to provide clean-in-place capability. Their disadvantage may include occlusion, difficulty in cleaning during the process, and the possibility of the product adhering to the outer surface. They too can affect the fluidization pattern during pulse mode.

### Support Equipment and Options

Success in the reproducibility of the film-coating process is dependent on the instrumentation, automation, and control systems of the selected equipment.

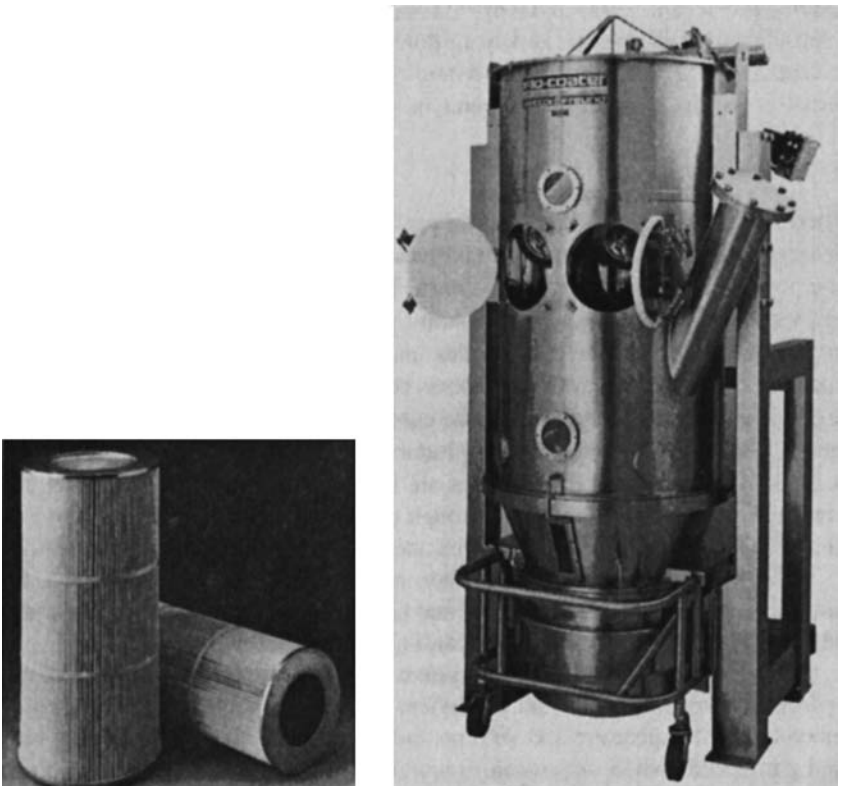

**Figure 25** Fluid-bed equipment showing cartridge filters. *Source*: Courtesy of Vector Corporation, Marion, Iowa, U.S.A.

## Air Handling: Dew Point Control

Holding process variables such as spray rate, inlet temperature, and air volume constant without controlling the process air dew point can lead to problems in all types of coating, both aqueous and solvent. The use of high inlet air temperatures tends to minimize the problem, but some products and coatings have thermal sensitivity, and film formation may be adversely affected by excessive heat.

Since the evaporation rate is a crucial variable, process temperature control is important. Old-style heat exchangers with modulating system valves were at best controllable to ±5°C when calibrated at the given air volume. If the air volume was changed, the response and restabilization of temperature was slow. New heat exchangers use face and bypass, which incorporates a constant-temperature steam heater and a bypass tunnel. As the chosen inlet temperature is approached, air dampers modulate air flow through the heater and bypass to reach and maintain the set point. This system is very responsive and is not nearly as sensitive as older systems to changes in air volume.

## Automation

There are many types of automation packages available, from timers to microprocessing controls. The simplest involves the use of electric or pneumatic timers and product or outlet temperature interlocks to step the process from warm-up to spraying and drying. New installations use control packages consisting of a programmable controller, which handles machine interlocks and digital functions and also communicates with the process controller, which monitors and controls the process variables. The system may be used manually for process development or to run a program automatically for production. For use in rooms designed for hazardous operations, the electronics are installed in a remote control room and are interfaced with the machine through electric/pneumatic switches. Programs are typically stored in the controller's memory and on E-Prom memory chips.

Taking automation a step further, process conditions, including inlet and outlet air dew points, are monitored and altered by a microprocessor system that adjusts the processing variables according to a predetermined hierarchy.

The accuracy of the entire system depends on the compatibility of the sensors, controllers, and control devices (dampers, pumps, etc.). Dew point, incoming air temperature and volume, outlet or product temperature, spray rate, and pan

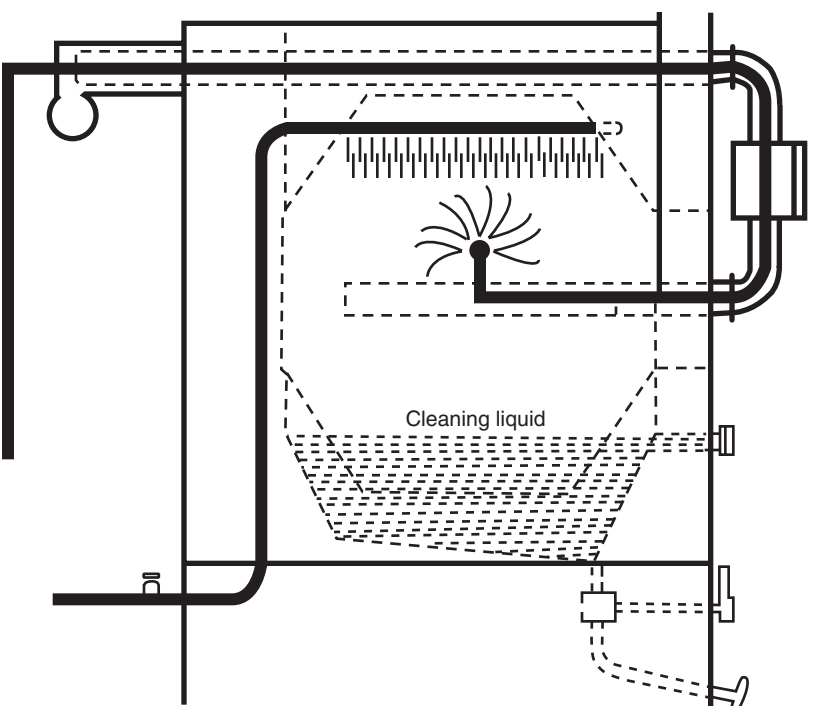


**Figure 26** Clean-in-place system. *Source*: Courtesy of Glatt AG, Pratteln, Switzerland.

speed (where applicable) must be very precisely controlled for alarm tolerances to be of any benefit.

### Material Handling

Several material-handling options are available for both pans and fluidized-bed systems. The fluid bed may be vacuum or gravity fed and discharged by a hoist or a turning bottom. Pans may be rear loaded or front loaded by a bin and unloaded by a scoop attached to the pan or by a flap in the drum that opens and discharges into a storage hopper under the drum.

### Clean-in-Place System

Although the fluidized bed does not lend itself to clean-in-place systems because of the exhaust filter, low-porosity bottom screen, and gaskets, the perforated pan does. Spray nozzles positioned inside the pan housing spray the outside of the drum, and a spray ball cleans the inside (Fig. 26). Detergent solution is injected into the water supply, and drain walls can be kept closed to allow the drum to tumble in a pool of cleaning solution. After draining the soap solution, a clean water rinse is applied and the turbines are engaged to dry the pan and prepare for new product.

## FACTORS AFFECTING EQUIPMENT CHOICE

Many factors affect the choice of process or equipment. The physical characteristics of the product, such as surface area, shape, and friability, all affect final dosage form performance. The surface area of tablets is reproducible because they are compressed to the same size continuously. It is not as easy to achieve uniformity with small particles. Most, if not all, types of equipment that are used to make pellets or granules result in a product that varies from batch to batch. To help reduce surface area variations, a narrow sieve cut is used in products coated for controlled release, but with many materials, it is still not enough. Variation in surface porosity and friability may result in poor reproducibility of release. Attrited particles scuffed from the surface become entrapped in layers of coating, altering the characteristics of the film (Fig. 27). Release that is triggered by other mechanisms (enteric, taste mask) is not so severely affected. Fines may be embedded early enough in the coating process if it is possible to include an overage of coating substance to allow for variation in substrate material. With this in mind, a look at the delivery provided by each type of machine is in order. In coating pans and the top-spray fluidized bed, droplets travel through the drying air before impinging on the product, spreading, and drying. In the Wurster and rotary systems, the nozzle is immersed in the fluidized particles, which are sprayed concurrently with the substrate flow. A scanning electron microscope analysis (3) reveals that the most uniform films are those that are applied wet to the surface but under conditions whereby the solvent or water is evaporated before core penetration becomes

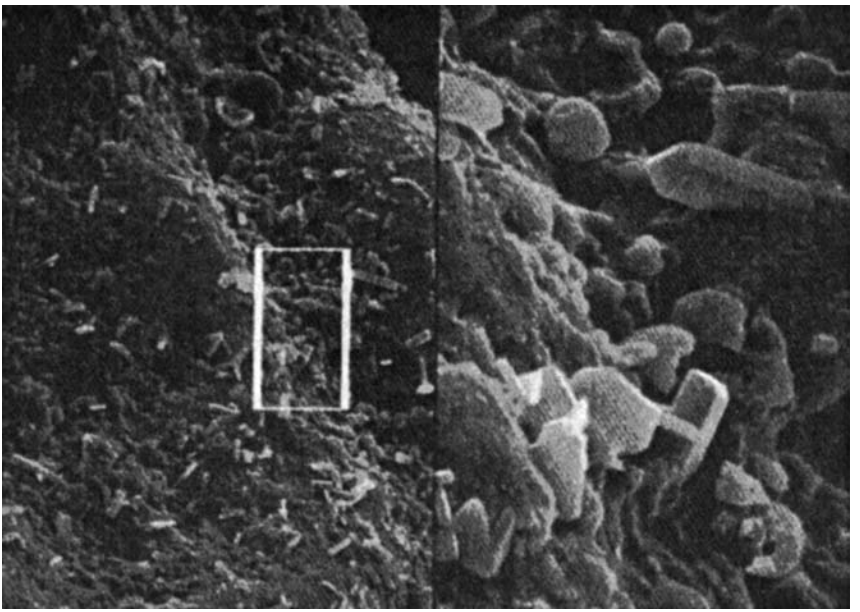

**Figure 27** Scanning electron photomicrograph showing drug particles in the coating; magnification ×250/×1000.

a problem (Figs. 28–31). If droplets are applied after too much of the liquid has evaporated, spreading is inhibited and imperfections in the coating are seen. Additional coating can eventually result in the desired release profile but reproducibility may be difficult to achieve. For this reason, controlled-release coating of small particles from aqueous or solvent systems should be limited to the Wurster or rotary granulator fluid-bed systems. Water-based enteric and taste mask coatings can be applied in top-spray equipment and possibly with perforated pans adapted for coating small particles. For these reasons, it may be worthwhile to evaluate the effect of different spray modes on product performance during the product development phase in an equipment that allows different spray modes such as the one shown in Figure 32.

## PROCESS VARIABLES AND SCALE-UP CONSIDERATIONS

Besides the method of spraying, nearly 20 other variables are involved in the film-coating process. It may be necessary to prioritize these variables in order of significance to avoid the expenditure of an enormous amount of time in the product development phase as well as the scale-up phase. The most significant variables are summarized in Table 2. The significance of these variables and scale-up factors is highly dependent on the type of equipment and process. Often, the scale-up factor selected for a given equipment and process may not be applicable to other

equipment and/or processes. As a result, it is very difficult to generalize and discuss these variables in terms of scale-up. However, scale-up considerations for specific processes are reported in the literature (4–6).

Spray rate is probably the most important consideration in the aqueous film-coating process. As stated earlier, film coating requires both uniform deposition of the film and controlled drying of the coating fluid. These two operations occur simultaneously during the coating process. They occur independently but also are interrelated. The drying rate for this process is determined by the rate of heat transfer from the air to the solvent and the rate of mass transfer of the solvent to the coating surface. Since pharmaceutical coatings are typically quite thin, the rate of heat transfer is critical. The rate of heat transfer not only affects the rate of evaporation of the solvent but also, in the case of latex and pseudolatex systems, regulates the rate and degree of coalescence of the polymeric material. The drying rate is determined by several parameters, including the latent heat of vaporization, the surface area of the material being dried, the relative humidity of the incoming drying air, the velocity and direction of the air stream, and the geometry of the drying chamber. For the most part, these are established by the choice of coating equipment and are therefore not easily varied. It is these parameters that dictate the maximum drying ability of the system. Certainly, it would be impossible to dry more solvent than the drying air can accept or to dry it any

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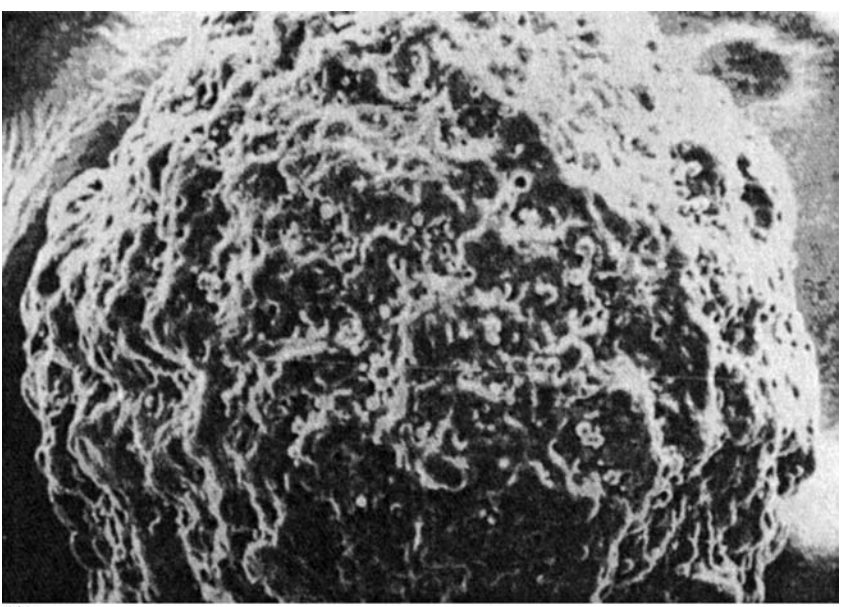
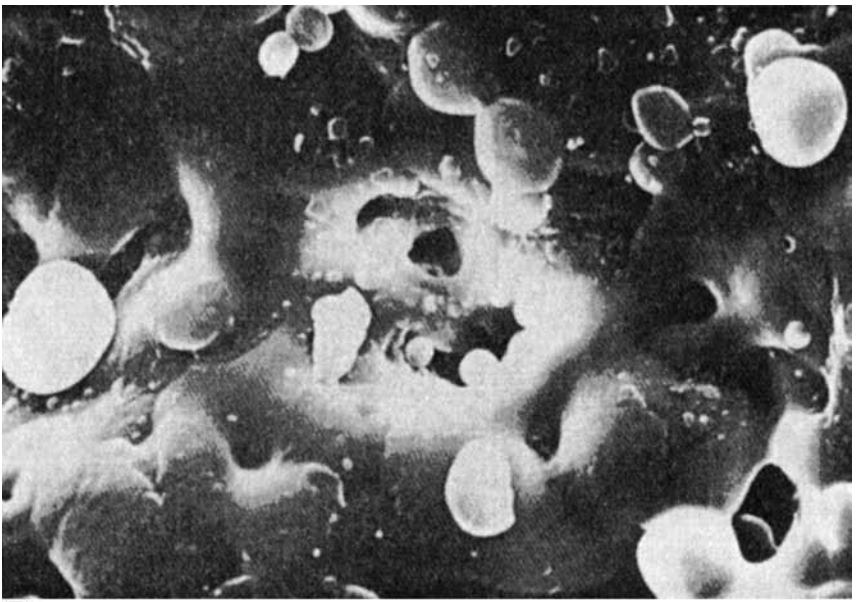


**(A)**

**Figure 28** Pellets coated using an aqueous system in a conventional pan: (**A**) magnification ×100; (**B**) magnification ×1000; (**C**) cross section, magnification ×1000. *Source*: From Ref. 3. (*Continued*)



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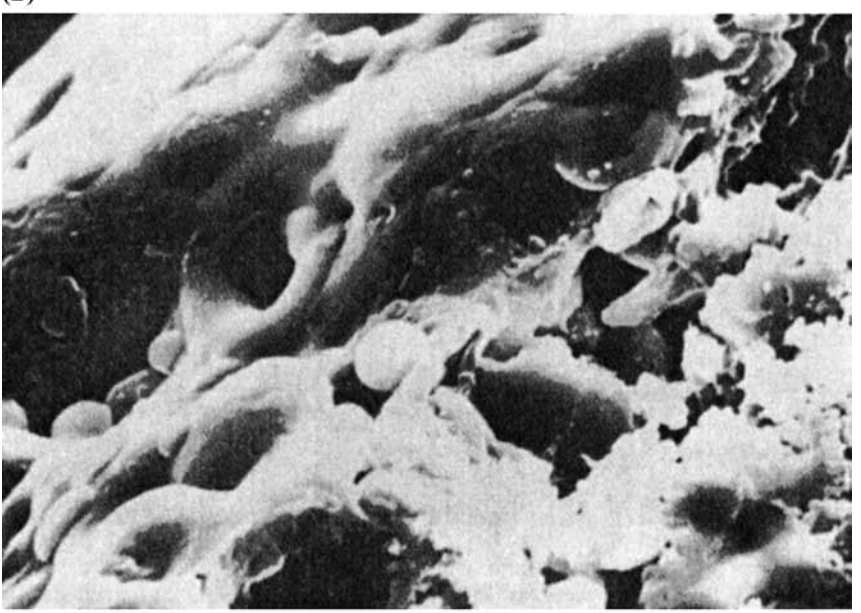

(C)

**Figure 28** Pellets coated using an aqueous system (*Continued*)

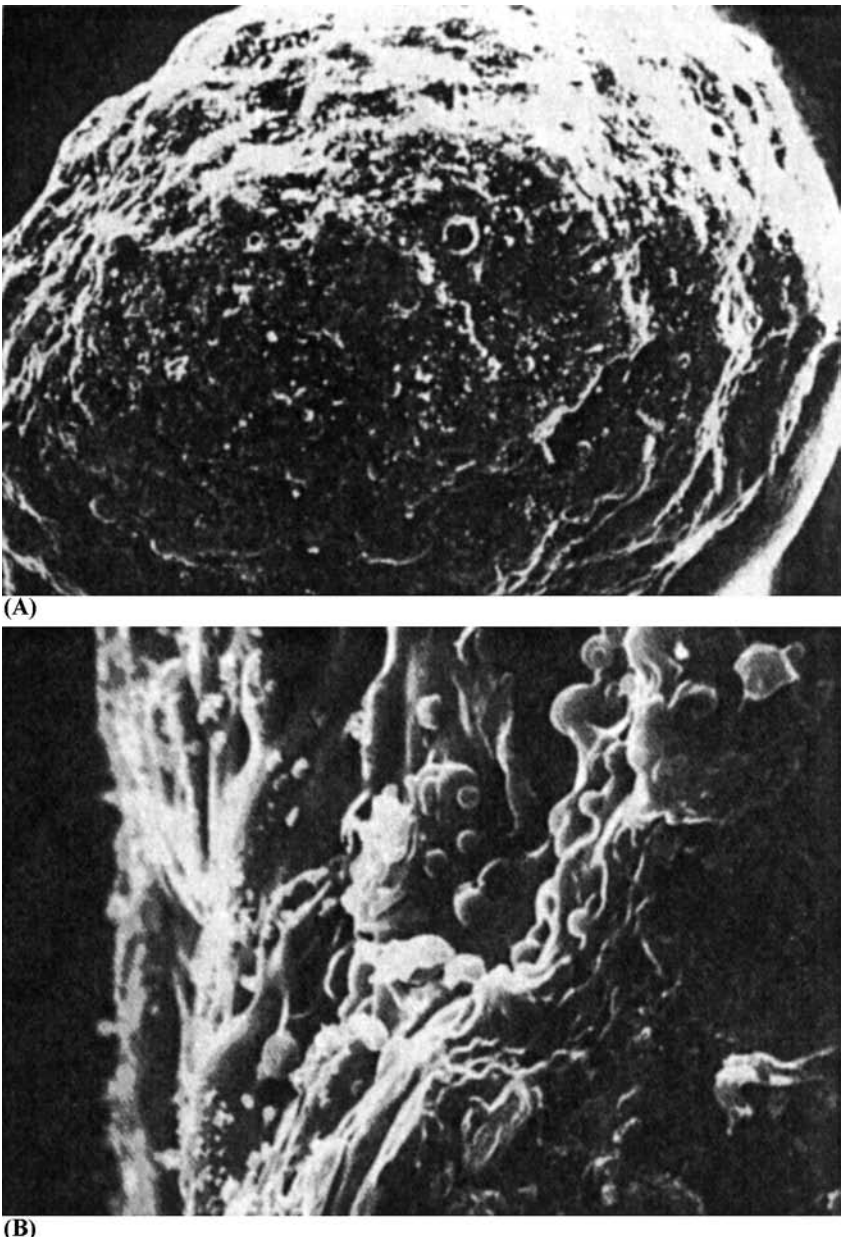


**Figure 29** Pellets coated using an aqueous system in a modified perforated pan: (**A**) magnification ×100; (**B**) cross section, magnification ×1500. *Source*: From Ref. 3.

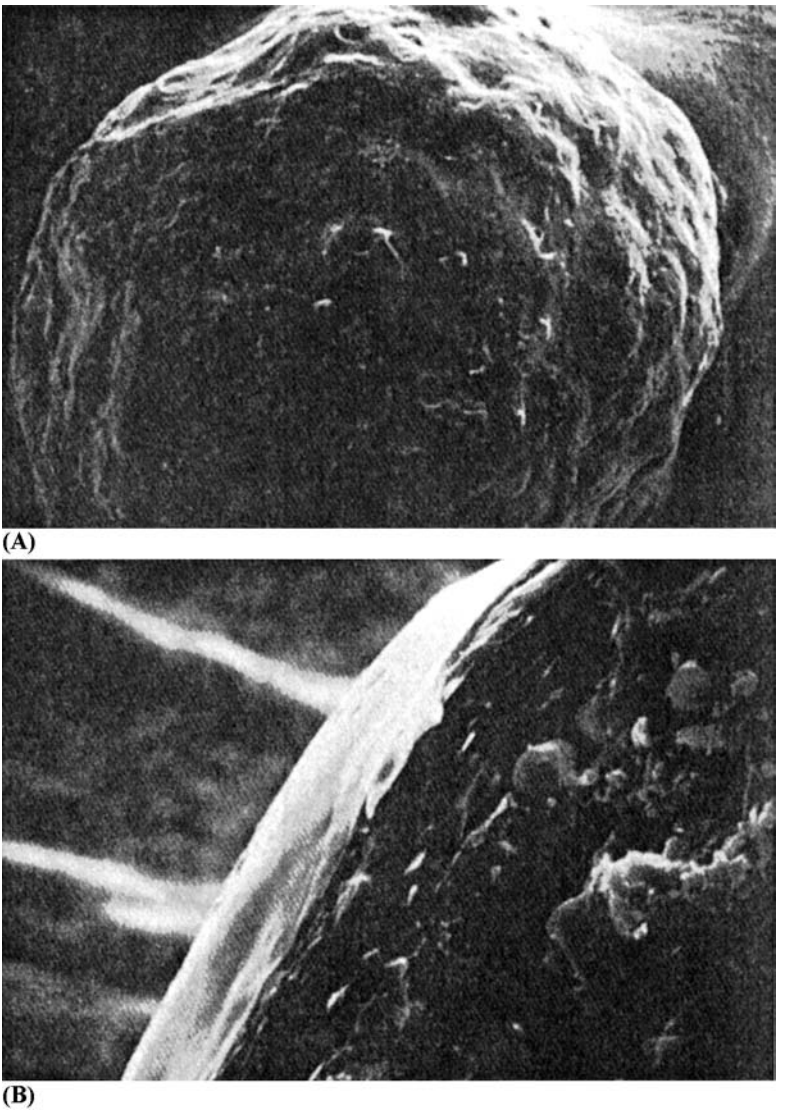


**Figure 30** Pellets coated using an aqueous system in a laboratory-scale fluidized bed using the top-spray method: (**A**) magnification ×100; (**B**) cross section, magnification ×1000. *Source*: From Ref. 3.

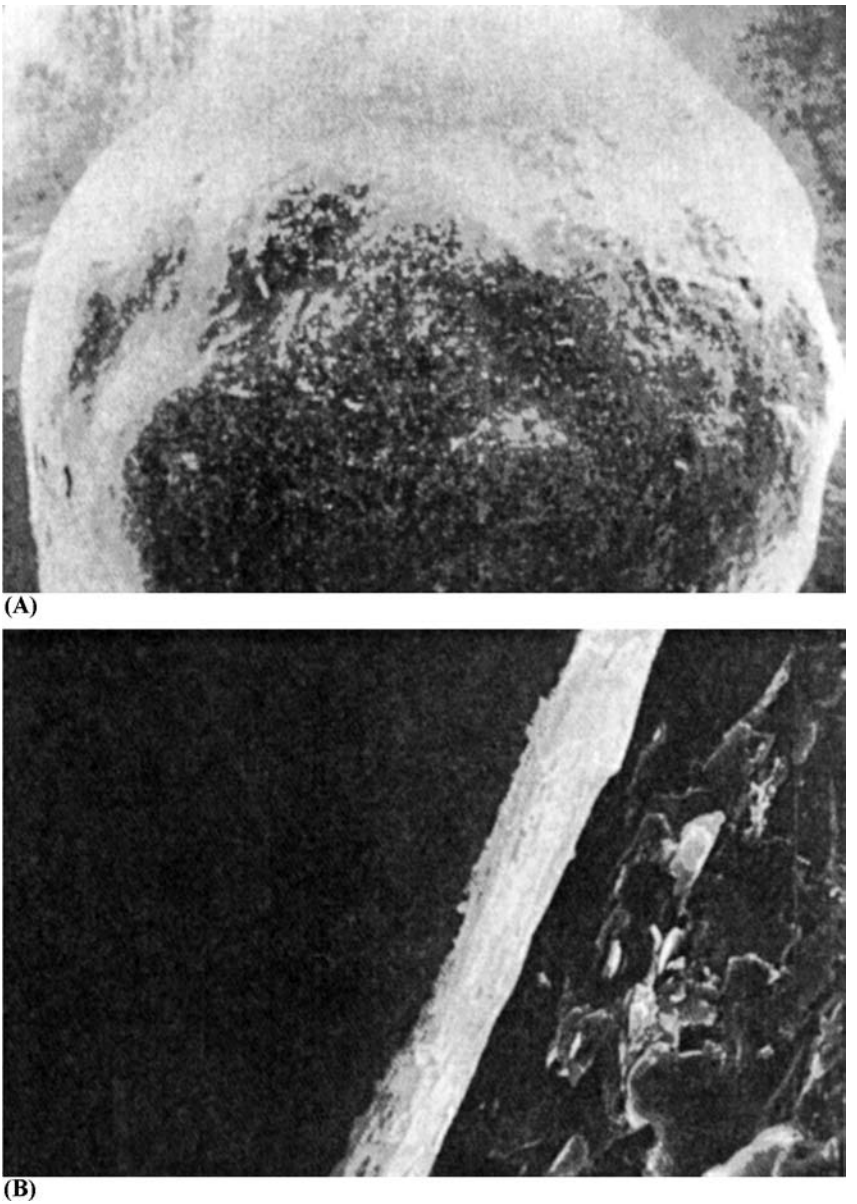


**Figure 31** Pellets coated using an aqueous system in a pilot-scale Wurster coater using the bottom-spray method: (**A**) magnification ×100; (**B**) cross section, magnification ×1000. *Source*: From Ref. 3.

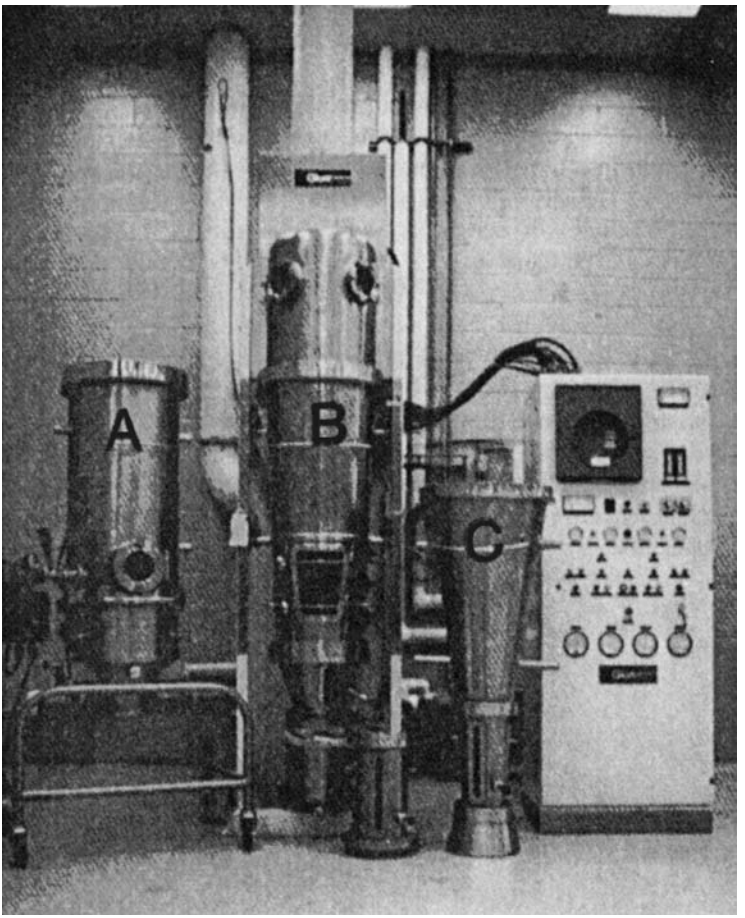


**Figure 32** Fluid-bed processing equipment design for three coating processes: (**A**) rotor coater, (**B**) top-spray coater, (**C**) Wurster coater. *Source*: Courtesy of Glatt Air Techniques, Inc., Ramsey, New Jersey, U.S.A.

faster than it can be heated to its rapid transition temperature. It is important to determine and understand the physical limitations of the coating system that are dictated by these factors and to work within them. It is probably wise to monitor the inlet air temperature, the outlet air temperature, the surface bed temperature, and the spray rate. The outlet temperature will give an indication as to the overall drying conditions, while the bed temperature will indicate drying conditions at the substrate surface.

Problems are often encountered when scaling up the process from one size of equipment to another. The problems are typically a result of either exceeding

**Table 2** Critical Coating Process Variables

| Spray rate | Type of equipment |
|---|---|
| Atomizing air pressure | Method of spraying |
| Inlet air temperature | Nozzle distance |
| Air volume | Drying time |
| Batch size | Effect of moisture |
| Exhaust air temperature | Pan or rotor speed |
| Product temperature | Equipment dimensions |

the stress limitations of the substrate or upsetting the delicate balance between the drying abilities of the equipment and the rate of solvent introduction.

Perhaps one of the more easily overlooked problems is that of exceeding the stress limits of the substrate. As the size of the coating equipment is increased, so, obviously, is the weight of the substrate load. This also results in an increase in the stress applied to the individual substrate particles during the coating cycle. As the bed moves in the equipment—for example, in the pan—tablets tumble onto each other. Depending on the configuration of the equipment, the stress on the tablets can become quite severe. Tablets that survive well in a 150-kg batch size may not survive in a 500-kg load. The manner in which the equipment manufacturer has increased the capacity of the equipment becomes an important consideration. If the diameter of the pan has been increased significantly, particularly if there has not been at least a corresponding increase in the pan depth, the stress on the tablets will be greatly increased. Changes in the geometry of the coating pan affect more than just the stress on the tablets; the geometry is also very important to the drying characteristics. Changes in the dimensions of the coating equipment can also affect the air flow patterns. If the air flow becomes turbulent or nonuniform, serious problems can be expected.

As the size of coating equipment is changed, there is also a change in the equipment's air handling capacity. Changes in air flow volume have dramatic effects on the drying capacity. As the volume of air is increased, so is the drying capacity. The air volume, temperature, and humidity have the greatest impact on the drying capacity and therefore the spray rate. It is tempting to use the maximum possible inlet air temperature in order to more efficiently evaporate water, which has a high heat of vaporization, allowing for a greater spray rate. However, it has been demonstrated in the literature (5) that the dissolution rate of the drug can be affected by the spray rate. The use of a very high inlet temperature can also cause problems such as decreased yield if the product remains too dry, which may subject it to attrition, and with certain thermoplastic polymeric systems, it may cause agglomeration. The most desirable inlet air temperature setting is the one that allows an equilibrium between the application of liquid and subsequent evaporation so that proper film formation occurs. The effect of moisture, also known as the "weather effect," has been discussed in the literature (7). It is a known fact that the heat content of moist air is higher than that of dry air. A thermodynamic model for aqueous film coat-

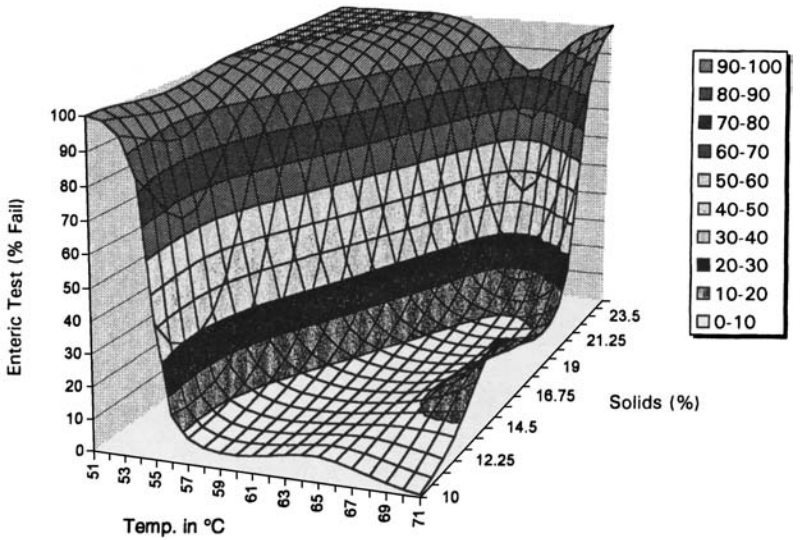


**Figure 33** Enteric test surface response analysis for tablets coated with Sureteric®. *Source*: Courtesy of Colorcon Inc., West Point, Pennsylvania, U.S.A.

ing (8) may enable the prediction of the behavior of a tablet-coating process under different environmental conditions. However, the variation in heat content could result in different release profiles, depending on the solvents and types of polymeric systems used. Residual water in the coating layers may affect the film-formation process. It is therefore recommended that the effect of ambient air dew points be examined as a part of the scale-up program in any coating operation.

The effect of process variables must be examined not only individually but also in combination with the formulation variables. The data in Figure 33 illustrate the predictive value of surface response analysis for optimizing processing parameters. In this case, the influences of inlet air temperature and coating suspension solids [for a study conducted in a laboratory-scale Accela-Cota in which 325-mg aspirin tablets were coated with an 8% w/w enteric coating applied as an aqueous polyvinyl acetate phthalate (PVAP) coating system] on enteric performance are illustrated. These data clearly indicate that for the fixed process conditions shown (spray rate, 70 g/min; atomizing air pressure, 35 psi), the best enteric results are achieved when the suspension solids content is kept below 20% w/w and the inlet air temperature is maintained above 57°C. The optimum results are obtained when the coating solids and drying air are set at 10% w/w and 71°C, respectively.

## SUMMARY

In response to a rapid growth in aqueous film coating, equipment manufacturers have developed new and improved machines to effectively coat materials

ranging from small particles to tablets. Control and automation advancements are resulting in reproducible, well-documented processes. Combined with newly introduced low-viscosity, high-solids latex and pseudolatex materials and process optimization, water-based coating is becoming a safe, economical alternative to organic solvent coating.

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# 4

# Mechanical Properties of Polymeric Films Prepared from Aqueous Dispersions

**Linda A. Felton**

*College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, U.S.A.*

**Patrick B. O'Donnell**

*Neurocrine Biosciences, San Diego, California, U.S.A.*

**James W. McGinity**

*College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*

## INTRODUCTION

Pharmaceutically acceptable polymers used in the film coating of solid dosage forms are primarily based on acrylic or cellulosic polymers. Many of these polymers have been formulated into aqueous colloidal dispersions (e.g., latexes or pseudolatexes) in order to overcome the high costs, potential toxicities, and environmental concerns associated with the use of organic polymer solutions (1–3). Film coating has been successfully utilized to control the release of active ingredients, prevent interaction between ingredients, increase the strength of the dosage form to maintain product integrity during shipping, and protect the dosage form from the environment (2,4–7).

Coating formulations usually contain many additives, in addition to the polymer, that aid in processing, appearance, and product performance. Most formulations contain plasticizers that impart flexibility to the films and reduce the incidence of crack formation (8,9). Pigments may be added to alter the appearance of the final product (10), and lubricants may be required to prevent agglomeration

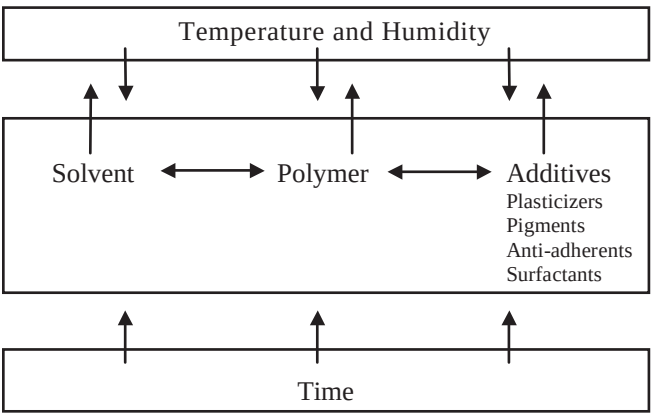


**Figure 1** Factors affecting the mechanical properties of polymeric films.

of the coated substrates (11). Numerous polymer blends for controlled drug release have been investigated (4,5,12), and the release characteristics of these coated dosage forms are strongly dependent on certain properties of the film, e.g., permeability and mechanical strength (13–16). The amount and type of plasticizer in the film and the presence of other additives in the coating can significantly impact the film's mechanical properties (17–21). In addition, factors such as storage conditions and processing temperature will influence coalescence and film formation and thus product performance (22–24). Figure 1 illustrates the relationship between these factors.

## FILM PREPARATION METHODS

Studies to investigate the mechanical properties of polymers may be conducted using free films or films applied to a substrate. Free films can be obtained by the casting method, where a polymeric solution or dispersion is cast onto a nonstick substrate and the solvent is evaporated (25–27). In formulations containing solid particles, however, sedimentation may occur during the drying stages, resulting in nonuniform films. The preparation of multilayered films by the cast method is also difficult because the solvent present when casting secondary layers may dissolve or interact with previous layers (28).

To avoid different film surfaces that may result from casting polymeric dispersions, a spray atomization technique may be employed. This type of spray box apparatus, shown in Figure 2, consists of a rotating drum inset into a box with heat introduced to facilitate solvent evaporation. The polymeric material is then sprayed onto the nonstick surface of the rotating drum (29,30). This technique better simulates coating processes and produces more uniform surfaces (28).

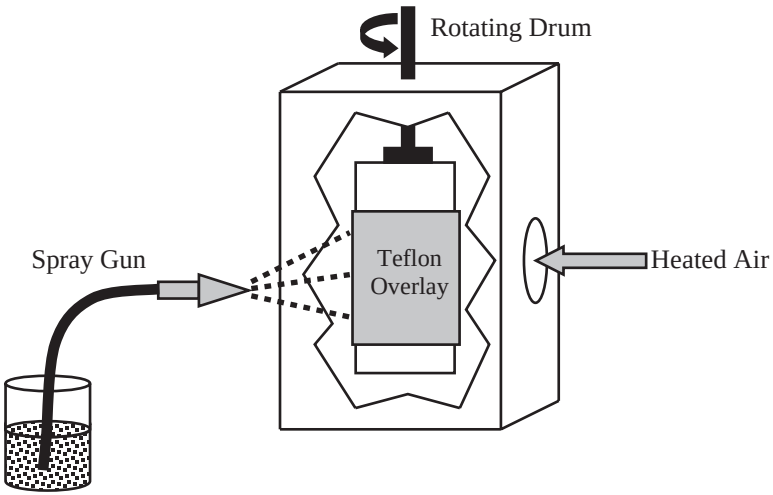


**Figure 2** Schematic of a spray box apparatus used to prepare free films.

In contrast to the study of free films, the evaluation of applied films has recently gained in popularity (31–33). Applied films can be used to investigate substrate variables, processing parameters, storage conditions, and physical aging in addition to coating formulation factors. Since most solid dosage forms are designed to dissolve in water-based biological fluids and the majority of coating systems used today are aqueous-based, the dissolution of the outermost surfaces of the substrate occurs during the coating process, permitting physical mixing at the film–tablet interface, which could lead to migration of drug or excipient into the film (34). This physical mixing and migration of components into the coating can affect the mechanical, adhesive, and drug-release properties of the polymer film (35,36).

## MECHANICAL TESTING TECHNIQUES

### Stress–Strain Testing of Free Films

Stress–strain testing in the tensile mode has been a popular and widely used mechanical test for polymeric films. The tensile test is practical, and analysis of its data is relatively straightforward. The tensile test gives an indication not only of the elasticity and strength, but also of the toughness of the film. In the development of a film coating system, evaluation of the mechanical properties of free films can readily characterize the fundamental properties of the coating (37). However, polymers are viscoelastic, and their mechanical behavior is dependent on many factors, including environmental conditions and experimental testing parameters.

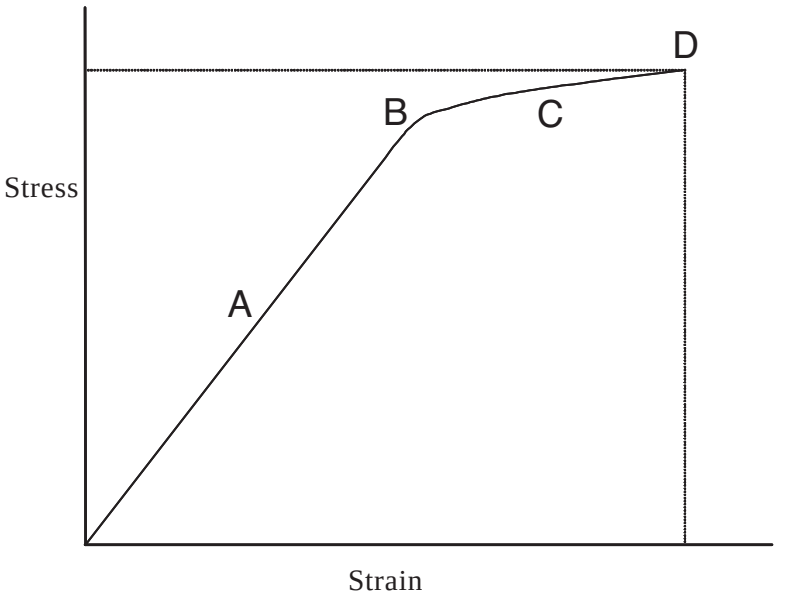


**Figure 3** Example of a stress–strain profile generated from tensile testing of free films. (**A**) Region of elastic deformation, where stress is proportional to strain; (**B**) yield point; (**C**) region of plastic deformation, where polymer chains orient themselves; (**D**) film breaks.

A tensile-testing instrument such as an Instron (Norwood, Maine) or a MTS Systems Corp (Eden Prairie, Minnesota) mounted with a load cell may be used for the measurements. According to the American Society for Testing Materials (ASTM) guidelines, the data for tensile properties may be acquired in the form of a load–time (elapsed) profile or, more typically, a load–displacement or stress–strain profile, as shown in Figure 3. The data collected for a load–time or load–displacement profile can be converted mathematically to a stress–strain curve. Four mechanical properties, namely tensile strength, elongation, work of failure, and Young's modulus, are then computed. The theory behind the computation of these parameters is well documented (21,38). The final equations that define each of these parameters are presented below.

### Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks (Fig. 3D). Tensile strength can be computed as the applied load at rupture divided by the cross-sectional area of the film, as described in Equation 1:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Film thickness} \times \text{Film width}} \quad (1)$$

Tensile strength measurement alone is not useful in predicting the mechanical performance of films; however, higher values of tensile strength are indicative of abrasion resistance (27).

### Strain

A film sample will stretch under applied stress, which is referred to as strain. Strain can be calculated as the deformation in the film divided by the original dimension of the sample. Strain is typically reported as percent elongation at fracture and is calculated using Equation 2:

$$\text{Percent elongation} = \frac{\text{Increase in length of film}}{\text{Initial length of film between the grips}} \times 100 \qquad (2)$$

Elongation of a film will generally increase as the plasticizer level in the coating is increased (19,39).

### Work of Failure

Work of failure is a function of work required to break the film specimen and represents the film toughness. It can be calculated from the area under the curve of the stress–strain diagram, cross-head speed, and the film dimensions, as described in Equation (3):

$$\text{Work of failure} = \frac{\text{Area under curve} \times \text{Cross-head speed}}{\text{Film thickness} \times \text{Film width}} \qquad (3)$$

### Young's Modulus

Young's modulus, sometimes referred to as elastic modulus, is the most basic and structurally important of all mechanical properties and is a measure of the stiffness of the film. It is the ratio of applied stress and corresponding strain in the region of approximately linear elastic deformation and can be computed using Equation 4:

$$\text{Young's modulus} = \frac{\text{Slope}}{\text{Film thickness} \times \text{Cross-head speed}} \qquad (4)$$

Since most amorphous polymers behave as viscoelastic materials, their mechanical properties will depend on the temperature and the application rates of stress and strain. The profile in Figure 4 shows typical changes in polymer chain arrangement that occur during tensile testing of a free film. Initially, there is a linear portion in the stress–strain profile (Fig. 3A), where elongation is directly proportional to applied stress and polymer chains are randomly oriented (Fig. 4A). The slope of this straight line portion of the graph is used to calculate Young's modulus. The greater the slope of the curve, the higher the Young's modulus. As the stiffness and the strength of the film increase, more stress will be required to

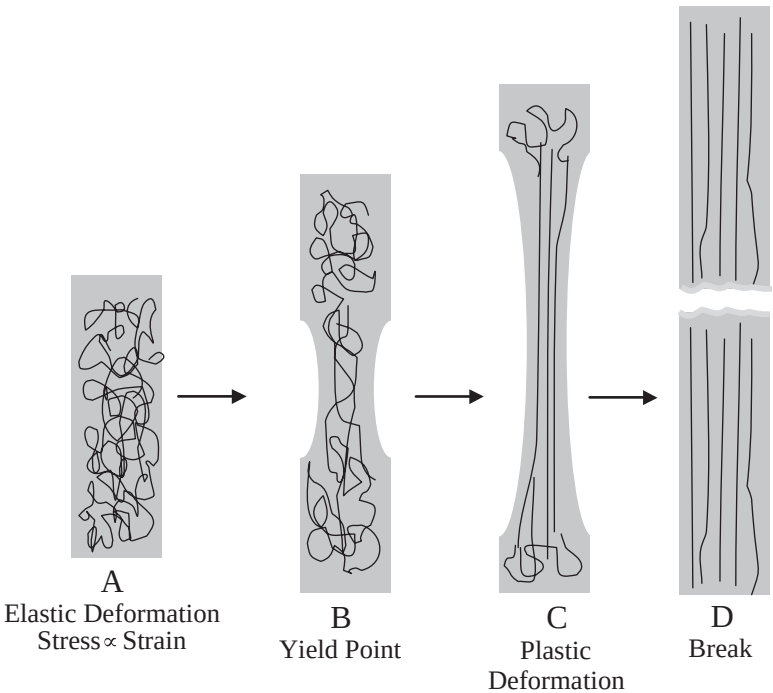


**Figure 4** Schematic of the changes in polymer chain arrangement that occur during tensile testing of a free film.

produce a given amount of deformation. At the yield point (Figs. 3B and 4B), polymer chains begin to orient themselves to the applied stress and are completely aligned during the plastic deformation stage of stress–strain analysis (Figs. 3C and 4C). Finally, the film specimen fractures (Figs. 3D and 4D).

Not all polymers behave in a typical manner, and depending on the mechanical response of the polymer, a family of stress–strain profiles can be obtained to clearly define elasticity, tensile strength, and film elongation at the break of the plasticized polymer. Some examples are illustrated in Figure 5. Hard and brittle films exhibit a high tensile strength and Young's modulus with little elongation. In contrast, a soft and tough film will possess a low tensile strength but much greater elongation and a higher area under the curve (toughness).

## Stress–Strain Testing of Applied Films

Compression testing of applied films is similar to tensile testing of free films in that uniform displacement rates are applied to a sample, and force and displacement values are recorded. The primary difference between the two techniques is in the direction of the applied stress. The substrate has been shown to significantly influence the mechanical strength of applied films (40,41). The affects of process-

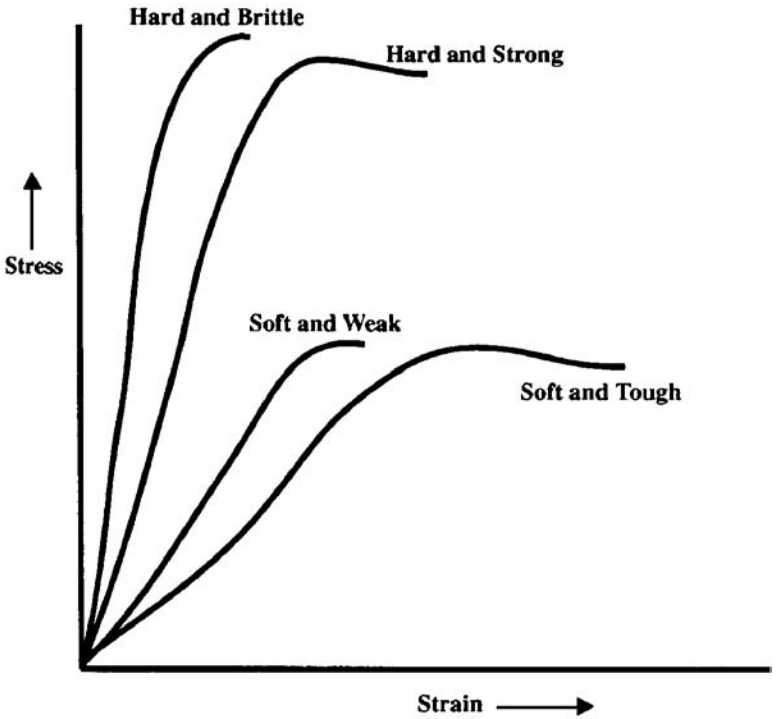


**Figure 5** Examples of characteristic stress–strain profiles obtained from tensile testing of free films.

ing parameters, storage conditions, and physical aging of the applied film can be evaluated using compression testing (22,33). In addition, compression testing of applied films can provide qualitative information on adhesion of the coating to the substrate (6,41), with simultaneous fracture of the substrate and film indicating good adhesion.

Knowledge of the compression properties of applied films is critical if the coated substrate is to be tableted. If the compressional force exceeds the coating strength, the film will fracture and faster dissolution will result (32). The formation of matrix tablets when tableting coated pellets has also been reported, resulting in slower drug release as the polymer coatings fuse during compression (42). To reduce friction during compression and to prevent direct contact of the coating, readily compressible excipients are often blended with the coated pellets prior to tableting (43).

## Glass Transition Temperature

The glass transition temperature ($T_g$) is the temperature at which the mechanical behavior of a film changes. Below this temperature, the polymer exists in a glassy

state that is characterized by a substructure in which there is minimal polymer chain movement. Above the $T_g$, the polymer is in a rubbery state, which is characterized by increased polymer chain movement and polymer elasticity. The $T_g$ is typically measured using a differential scanning calorimeter (DSC), where a sample and reference pan are heated at a programmed rate, and thermal transitions, where more energy is absorbed or emitted, are determined. There are numerous examples in the literature of determining $T_g$ values to evaluate polymer properties and interactions with excipients (44–46). The DSC instrument can also be used to determine melting temperature, detect polymorphism, study polymer miscibility, and investigate oxygen degradation (7,47–49). A number of variations in DSC testing have been developed, including a triple-cell system for more precise measurements of enthalpy, temperature-modulated units to separate reversing and nonreversing transitions, and high-sensitivity models (50,51).

### Dynamic Mechanical Analysis

Dynamic mechanical analysis (DMA) is another type of test used to study the mechanical properties of polymeric films. In DMA testing, a free film is placed between two grips, one stationary and the other oscillatory. The free film is then deformed by torsion oscillation as a function of temperature. The storage modulus, loss modulus (dissipated energy), and damping coefficient (ratio of loss modulus to storage modulus) are determined. Several different modes are available, including fixed frequency, creep relaxation, and stress relaxation. DMA can be used to determine the $T_g$ as well as other smaller, sub-$T_g$ transitions that can provide some indication of polymer structure (52). Modifications to the instrument have permitted the mechanical properties of polymeric films applied to individual pellets to be determined (40).

## EFFECTS OF PLASTICIZERS IN THE COATING FORMULATION ON MECHANICAL PROPERTIES

Many polymers used in film coating of pharmaceutical dosage forms display brittle properties at ambient temperature and humidity conditions, and the addition of a plasticizer is essential to achieve effective coatings without cracks or splitting defects (9). Plasticizers are added to polymeric solutions or dispersions to increase the workability or flexibility of the polymer and reduce brittleness, improve flow, and increase toughness and tear resistance of the films. These effects are the result of the plasticizer's ability to weaken intermolecular attractions and allow the polymeric molecules to move more easily. Several theories have been proposed to explain the mechanism by which the plasticizing agents impart flexibility to polymeric films (53). According to the lubricity theory, the plasticizer functions as an internal lubricant and facilitates movement of the polymer chains. The gel theory proposes that the unplasticized polymer exists as a three-dimensional gel and that the plasticizer functions by cleaving the intermolecular bonds within the gel. Finally, the free

volume theory states that plasticizers increase the free space around the polymer chains, providing a greater area for movement of the polymer molecules.

In addition to enhancing the flexibility of the film, plasticizers influence permeability and drug release (13,14,54). Many compounds can plasticize polymeric films, including water, drugs, and excipients (35,55). The selection of a plasticizer, therefore, is an important decision in the development of controlled-release pharmaceutical dosage forms. Ideally, the plasticizer level in the film should be optimized to reduce the brittle character of the film without adding excess plasticizer. Higher levels of plasticizer can cause sticking or agglomeration of the coated product during storage, which will compromise the release properties of the drug from such dosage forms (56).

The effectiveness of a plasticizing agent is dependent to a large extent on the amount of the plasticizer added to the coating formulation and the extent of polymer–plasticizer interactions. The interaction of a plasticizer with the polymer decreases the $T_g$ of the film and is considered a common measure of plasticizer effectiveness, with the more effective plasticizers producing greater decreases in $T_g$. The influence of water-soluble and water-insoluble plasticizers on the $T_g$ of Eudragit® L 100-55 is shown in Figure 6 (19). The presence of 10% plasticizer in

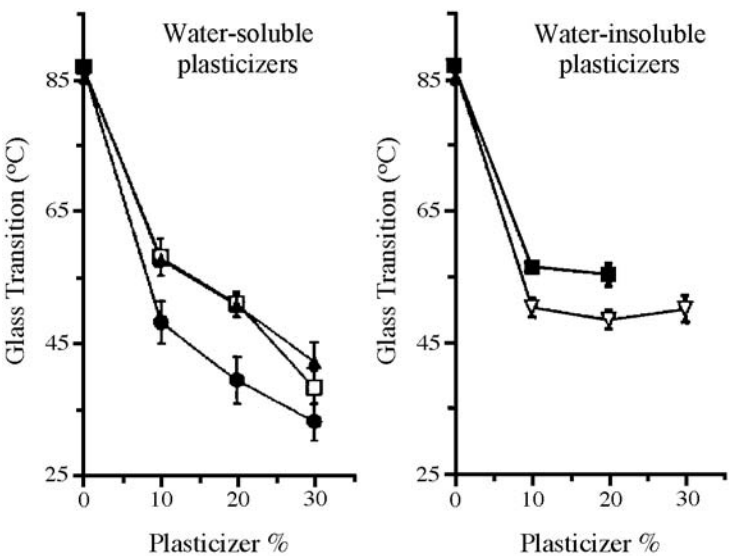


**Figure 6** Effect of different levels of plasticizers on the glass transition temperature of Eudragit® L 100-55 films stored for 60 days at 23°C, 50% RH followed by 30 days at 23°C, 0% RH ($n = 5$). Water-soluble plasticizers: (•) TRI, triacetin (□) TEC, (▲) ATEC; water-insoluble plasticizers: (▽) TBC, (■) ATBC. *Abbreviations*: TRI; TEC, triethyl citrate; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; RH, relative humidity. *Source*: From Ref. 19.

the polymer film caused a dramatic decrease in the $T_g$ for all the plasticizers studied. This decrease continued with the water-soluble plasticizers at levels greater than 10%. For the water-insoluble plasticizers, however, a plateau in the $T_g$ of the polymer was observed due to the immiscibility of the plasticizer with the polymer at the higher levels.

Plasticizers will also influence the elastic modulus of the polymer and, as shown in Figure 7, there was a decrease in the elastic modulus of Eudragit L 100-55 as the level of plasticizer increased for the water-soluble plasticizers (19). The elastic or Young's modulus is a measure of the stiffness of the film or the ability of the film to withstand high stress while undergoing little elastic deformation. The softening effect did not decrease with the insoluble plasticizers at levels greater than 10%, presumably due to the immiscibility of the higher levels of plasticizer with the polymer.

To be effective, a plasticizer must diffuse into the polymer phase and disrupt the intermolecular interactions of the polymer, while having minimal or no tendency for migration or volatilization. Dramatic changes in the mechanical and dissolution properties may result when a plasticizer evaporates or leaches from within a polymeric film (26,57). Plasticizers that are soluble in the solvent phase can be added directly to the mixture or may be dissolved first in the solvent prior to addition of the polymer. Plasticizers that are not water soluble should first be emulsified in water using latex-compatible emulsifiers and then appropriately agi-

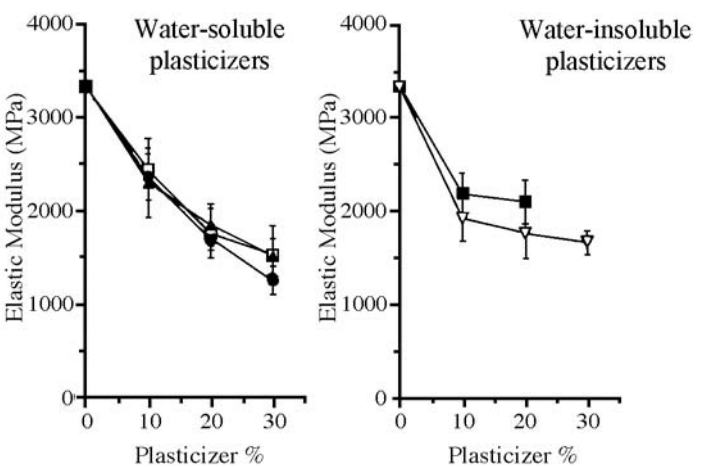


**Figure 7** Effect of different levels of plasticizers on the glass transition temperature of Eudragit® L 100-55 films stored for 60 days at 23°C, 50% RH followed by 30 days at 23°C, 0% RH ($n = 6$). Water-soluble plasticizers: (•) TRI, triacetin (□) TEC, (▲) ATEC; water-insoluble plasticizers: (▽) TBC, (■) ATBC. *Abbreviations*: TRI; TEC, triethyl citrate; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; RH, relative humidity. *Source*: From Ref. 19.

tated with the entire mixture until an equilibrium plasticizer distribution occurs between the water and polymer phases (58,59).

The incorporation of a plasticizer into an aqueous polymeric dispersion is crucial, and sufficient time must be allowed for the plasticizer to partition into the polymer phase prior to initiation of the coating process (60,61). The rate and extent of plasticizer partitioning for an aqueous dispersion is dependent on the solubility of the plasticizer in water and its affinity toward the polymer phase. Equilibration of plasticizer distribution in an aqueous polymeric dispersion for water-soluble plasticizers has been shown to occur rapidly, whereas the time required to achieve equilibrium distribution for water-insoluble agents requires substantially longer mixing times (26,58,59). If insufficient time is allowed for the plasticizer to partition into the polymer phase, the unincorporated plasticizer droplets as well as the plasticized polymer particles will be sprayed onto the substrate during the coating process. Uneven plasticizer distribution within the film could result and potentially cause changes in the mechanical properties of the film during aging.

## EFFECTS OF OTHER ADDITIVES IN THE COATING FORMULATION ON MECHANICAL PROPERTIES

### Pigments

The addition of pigments into a coating formulation may improve the esthetic appearance of the final product (62). Opacifiers, such as titanium dioxide, may be used in coatings to protect photosensitive drugs from exposure to light, thus improving product stability (63). The addition of pigments in the coating will significantly influence the mechanical, adhesive, and drug-release properties of the resulting film (64–66). As the concentration of an insoluble pigment is increased, the amount of polymer necessary to completely surround the particles increases. At a specific concentration, known as the critical pigment volume concentration (CPVC), the polymer present is insufficient to surround all of the insoluble particles, and marked changes in the mechanical properties of the film will occur (67). The CPVC is a characteristic of specific polymer–filler combinations, and theoretic determinations of this value are practically impossible (68).

The tensile properties of hydroxypropyl methylcellulose (HPMC) films as a function of titanium dioxide concentration are shown in Figure 8 (21). The cellulosic films became more brittle as the concentration of the pigment increased, as evidenced by the decrease in elongation and the increase in Young's modulus. More recently, Hsu et al. (69) showed that the addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength.

Felton and McGinity (66) investigated the influence of titanium dioxide concentration on the $T_g$ of Eudragit L 30 D-55 films plasticized with 20% triethyl citrate. Increased concentration of the pigment in the film resulted in a significant increase in the $T_g$ when the polymeric dispersion was applied to hydrophilic tablet

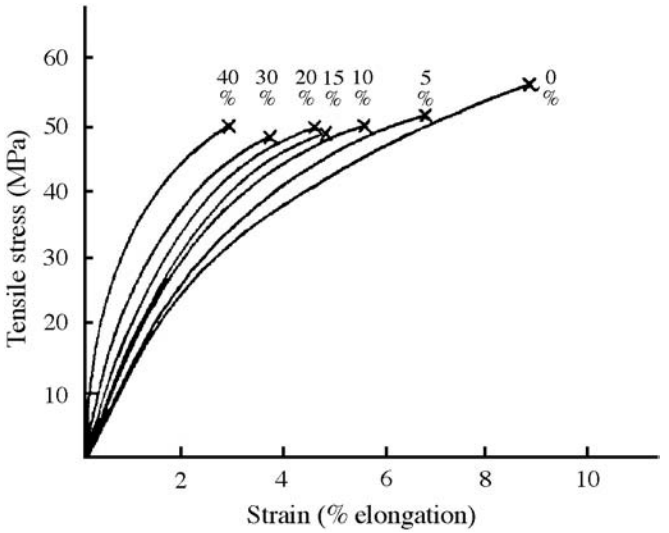


**Figure 8** Influence of titanium dioxide concentration (% w/w) in the dried polymer on the stress–strain curves of HPMC films. *Abbreviation*: HPMC, hydroxypropyl methylcellulose. *Source*: From Ref. 21.

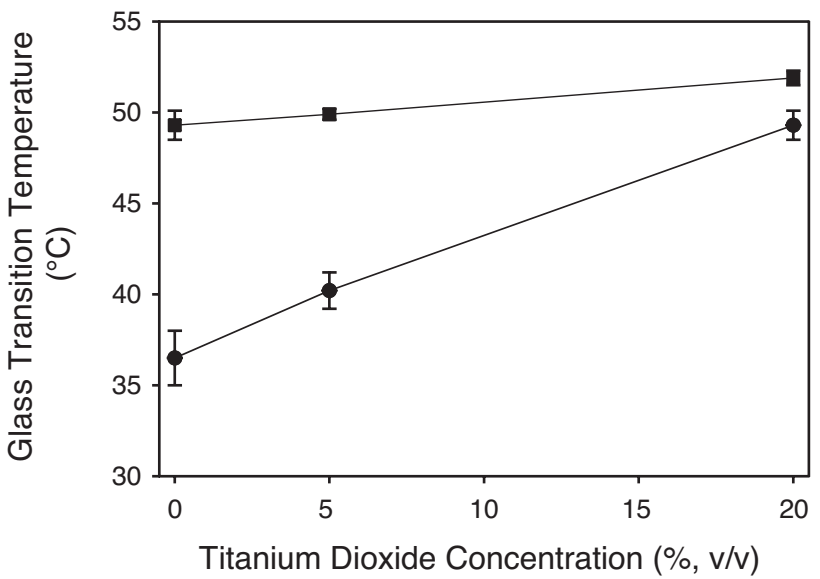


**Figure 9** Influence of titanium dioxide concentration in the coating formulation on the glass transition temperature of applied Eudragit® L 30 D-55 films. (●) 0% wax in the tablet core; (■) 30% wax in the tablet core. *Source*: From Ref. 66.

compacts, as shown in Figure 9. Interestingly, only small, incremental increases in the $T_g$ of the polymeric film with increased titanium dioxide concentration were noted when applied to hydrophobic tablets. These findings demonstrate not only that concentration of a pigment in the coating formulation can influence the mechanical properties of the film, but also that the properties of the substrate also affect the polymer.

### Antiadherents

Stickiness or tackiness of polymeric films is a concern during both the coating process and storage. The extent of product agglomeration may be influenced by processing temperature, curing temperature, plasticizer content, and polymer type (56). To minimize product agglomeration, antiadherents may be incorporated into the coating formulation. Talc and glyceryl monostearate (GMS) are the most commonly employed antiadherents in film coating formulations (70). These fillers, however, are not water soluble, and they have been shown to influence the mechanical and drug-release properties (11,20,71,72).

### Surfactants

As mentioned earlier, incorporation of water-insoluble plasticizers into aqueous polymeric dispersions requires that the plasticizer first be emulsified in water with

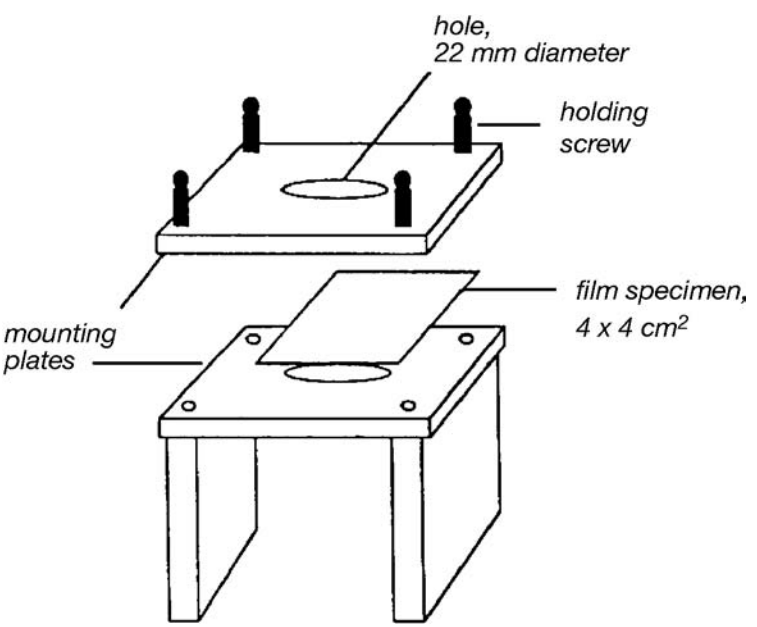


**Figure 10** Schematic of the film holder used in the puncture test device. The holder is submerged in a dissolution bath to hydrate the film. *Source*: From Ref. 75.

an appropriate surfactant. In addition, surfactants have been added to film coating formulations to improve the spreadability of the coating material across tablet surfaces (73) and to modulate drug release (74). The addition of these compounds to film coating formulations has been shown to influence the mechanical properties of the films. Felton et al. (18) showed that increased concentrations of both sorbitan monooleate and polysorbate 80 significantly lowered the $T_g$ of Eudragit L 30 D-55 films plasticized with the hydrophobic tributyl citrate, while no significant changes in $T_g$ were noted when the polymeric dispersion was plasticized with the water-soluble triethyl citrate.

## MECHANICAL PROPERTIES OF WET AND DRY FILMS

Upon ingestion, the polymer coating becomes hydrated, and the mechanical properties of the film may not be the same as in the dry state (44,75). Water may plasticize the film, while plasticizers may leach from the coating upon exposure to biological fluids. To assess the mechanical behavior of films in their hydrated state, a puncture test can be employed (15,76). As shown in Figure 10, the apparatus consists of a platform assembly containing a free film that is submerged in a dissolution bath. A puncture probe attached to a load cell is then driven into the film. Data determined from this experiment include the puncture strength (force at puncture divided by the cross-sectional area of the dry film) and the percent elongation at puncture.

**Table 1** Mechanical Properties of Dry and Wet Films and the Water Content of Wet Films Prepared from Different Polymer Dispersions Plasticized with Triethyl Citrate (20% w/w)

| Polymer dispersion (film thickness, μm) | Puncture strength (MPa) | | Elongation (%) | | Water (g)/ polymer (g) |
|---|---|---|---|---|---|
| | Dry | Wet | Dry | Wet | |
| Aquacoat® (309) | 0.34 (0.11) | 0.10 (0.02) | 1.34 .(0.18) | 0.13 (0.02) | 0.506 (0.032) |
| Surelease® (394) | 0.23 (0.04)[a] | 0.74 (0.10)[a] | 0.62 (0.12) | 4.89 (0.90) | 0.100 (0.006) |
| Eudragit® NE 30 D (314) | 2.16 (0.19) | 1.58 (0.10) | >365.00 | >365.00 | 0.268 (0.014) |
| Eudragit® RD 30 D (309) | 1.99 (0..23) | 0.93 (0.04) | 142.83 (4.32) | 38.41 (4.65) | 0.331 (0.008) |
| Eudragit® RL 30 D (316) | 1.81 (0.11) | 1.60 (0.14) | 126.31 (8.04) | 13.02 (2.45) | 0.807 (0.008) |
| Eudragit® L 30 D (264) | 0.83 (0.05) | 1.78 (0.09) | 0.46 (0.25) | >365.00 | 0.722 (0.023) |

SD in parentheses; $n = 3$.
[a]Films did not rupture.
*Source*: From Ref. 77.

**Table 2** Mechanical Properties of Dry and Wet Eudragit® RS 30 D Films Plasticized with Different Plasticizers (20% w/w)

| Plasticizer + (film thickness) (μm) | Puncture strength (Mpa) | | Elongation (%) | | Plasticizer remaining (% of original) |
|---|---|---|---|---|---|
| | Dry | Wet | Dry | Wet | |
| TEC (309) | 1.99 (0.22) | 0.93 (0.05) | 142.8 (4.3) | 38.4 (4.6) | 56.29 (1.79) |
| Triacetin (302) | 1.82 (0.38) | 0.61 (0.07) | 120.9 (6.0) | 6.8 (0.6) | 35.92 (1.06) |
| ATBC (314) | 4.30 (0.09) | 1.11 (0.13) | 77.8 (7.6) | 85.2 (3.6) | 101.84 (1.67) |
| ATEC (323) | 4.01 (0.18) | 1.01 (0.02) | 86.9 (5.5) | 64.3 (8.5) | 90.38 (0.05) |
| DBP (327) | 3.18 (0.47) | 0.88 (0.19) | 93.2 (12.6) | 106.9 (9.2) | 99.95 (1.88) |
| DBS (324) | 2.37 (0.09) | 0.79 (0.04) | 91.8 (2.0) | 59.7 (3.6) | 88.34 (0.66) |
| DEP (324) | 2.47 (0.40) | 0.91 (0.03) | 91.1 (3.2) | 51.0 (3.8) | 95.27 (1.53) |
| TBC (319) | 2.37 (0.40) | 0.86 (0.03) | 113.5 (1.8) | 86.6 (3.4) | 97.79 (2.06) |

SD in parentheses, $n = 3$.
*Abbreviations*: TEC, triethyl citrate; DBS, dibutyl sebacate; DEP, diethyl phthalate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; ATEC, acetyl triethyl citrate; DBP, dibutyl phthalate.
*Source*: From Ref. 77.

Bodmeier and Paeratakul (77) demonstrated that the mechanical properties of dry and wet films were dependent on the polymeric material used to form the film (Table 1). The ethylcellulose pseudolatexes, Aquacoat® and Surelease®, were found to be brittle in the dry state and weak in the wet state. In contrast, films of Eudragit L 30 D were shown to be brittle in the dry state yet very flexible in the wet state, presumably due to the plasticization effect of water, while Eudragit NE 30 D films were found to be very flexible in both wet and dry states.

The plasticizer used in the polymeric dispersion can also significantly influence the mechanical strength of polymeric films in both dry and wet states (75,77). As shown in Table 2, wet Eudragit RS 30 D polymer films containing water-insoluble plasticizers were significantly more flexible than the corresponding wet films plasticized with water-soluble plasticizers. These results were attributed to the leaching of the water-soluble plasticizers from the films during exposure to the aqueous medium, whereas the water-insoluble plasticizers were almost completely retained within the wet films. Leaching of the plasticizer created pores in the films, with higher concentrations of the water-soluble plasticizers increasing the porosity of the films (75).

## EFFECTS OF ENVIRONMENTAL STORAGE CONDITIONS ON MECHANICAL PROPERTIES

The mechanical behavior of polymeric films is dependent on a number of variables, including the temperature and humidity of the environment. The following

section highlights some of the effects that temperature and humidity can exert on polymer properties during processing, curing, and storage.

During film formation from an aqueous polymeric dispersion, individual polymer particles must coalesce and fuse together to form a continuous film. The degree of coalescence is dependent on the intensity of the primary driving forces, surface tension and capillary forces that are generated upon water evaporation, and the time exposed to such forces. Complete coalescence of latex particles occurs when the polymeric molecules located at the interface between adjacent particles interpenetrate due to viscous flow. Incomplete film coalescence can result in significant changes in polymer properties over time and thus has been extensively studied (1,12,61,78–80).

Temperature may significantly influence the completeness of coalescence (81). Temperatures used during the coating process must be above the minimum film-forming temperature. Processing parameters used during coating, however, must be carefully controlled to ensure an appropriate balance between the rate of water removal, critical for the development of capillary forces, and the bed temperature of the coating apparatus. Low spray rates of aqueous polymeric dispersions, especially when combined with higher bed temperatures, can result in spray drying, where the solvent evaporates before the polymer chains coalesce, and brittle films are produced (29). In contrast, high spray rates can overwet the substrate (82) and cause surface dissolution of the product, with a potential for drug/excipient migration into the resulting film coat (34).

The ratio of tensile strength to elastic modulus of free films has been correlated to their in situ performance, with lower values of this ratio correlating with increased coating defects (83). Since coating with minimal defects is critical to provide and maintain consistent and reproducible drug-release rates from the coated controlled-release dosage forms, a higher value of this ratio is desirable. Figure 11 shows the ratio of tensile strength to elastic modulus plotted as a function of coalescence temperature for films cast from two commercially available aqueous ethylcellulose dispersions (Surelease plasticized with dibutyl sebacate or glycerol tricaprylate/caprate). An increase in the coalescence temperature up to 50°C for both polymeric formulations led to an increase in this ratio, with a slight decrease in the ratio at higher temperatures. Since the highest tensile strength to elastic modulus ratio for the films cast from both Surelease formulations was observed at a drying temperature of 50°C, it may be presumed that films coalesced at or around this temperature are less susceptible to physical defects.

Following the completion of the coating process, the coated dosage forms are often stored at temperatures above the $T_g$ of the polymer to promote further coalescence of the film. Storage at elevated temperatures can also ensure a homogeneous distribution of plasticizer within the film (84). During this storage or curing stage, the microstructure of the polymer is altered (80), and the mechanical properties of the film as well as permeability and drug release are correspondingly affected (5,78). Formulations containing high plasticizer concentrations generally require lower processing temperatures and less time for film coalescence

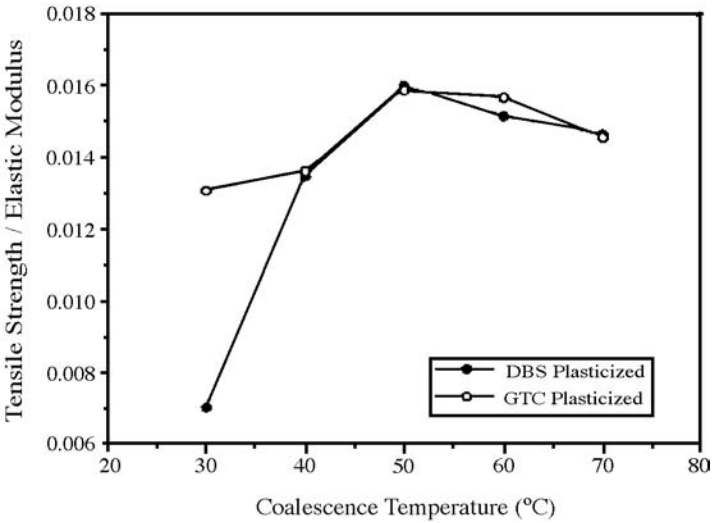


**Figure 11** Tensile strength to elastic modulus ratio of free films of Surelease® plasticized with dibutyl sebacate or glycerol tricaprylate/caprate as a function of coalescence temperature. *Source*: From Ref. 27.

and curing (14,61,85). Drying air volume and humidity used during film coating processes have also been shown to influence film formation and hence polymer properties (24,86,87).

Chemical, mechanical, and dissolution profiles of drug products are determined within a short time after manufacturing. Products may be placed under stress conditions of high temperature and/or relative humidity, and the data extrapolated to predict shelf life. Pharmaceutical products, however, may be exposed to a number of different environmental conditions during normal shelf life, and these changes in storage conditions can affect the mechanical properties of polymeric films, ultimately affecting drug release. Wu and McGinity (22) showed that the mechanical properties of Eudragit RS 30 D/RL 30 D polymer blends containing methyl paraben as a nontraditional plasticizer were dependent on the humidity of the storage environment. A decrease in tensile strength and Young's modulus was noted when coated beads were stored at 84% relative humidity, which was attributed to the absorbed water further plasticizing the film. In contrast, coated beads stored at 0% relative humidity exhibited brittle fracture failure during compression testing.

There are two major issues involved in changes that occur in polymer properties over time. The first and obvious one, based on the previous discussion, is that incomplete coalescence of the film will exert a significant affect on film properties during storage. The other major concern is physical aging. Most polymers used in pharmaceutical products are amorphous and are not at thermodynamic

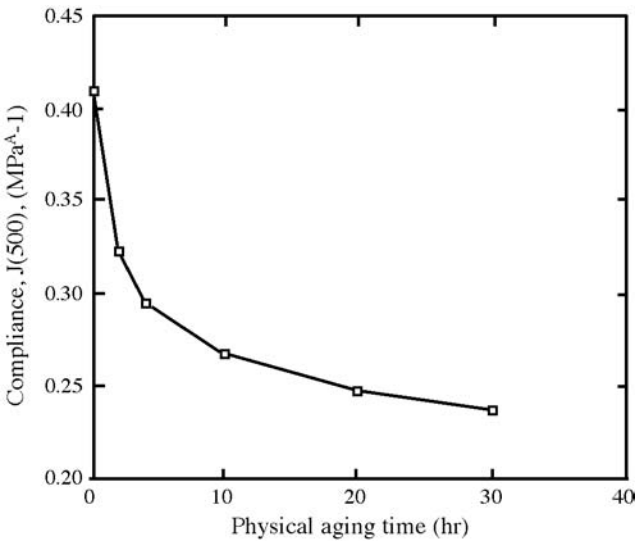


**Figure 12** Effect of physical aging on the 500-s creep compliance of Aquacoat®-free films plasticized with 15% diethyl phthalate. *Source*: From Ref. 88.

equilibrium at temperatures below their $T_g$. Over time, amorphous polymers undergo a slow transformation toward a thermodynamic equilibrium. As temperatures are cooled to below the $T_g$, the free volume of the polymer will slowly relax toward a lower free energy state, a process referred to as physical aging. Although this equilibration process is slow at ambient conditions, physical aging may produce significant changes in polymer properties. Guo et al. (88) used DMA to demonstrate that creep compliance (ratio of the relative creep extension to the applied stress) of Aquacoat films decreased over time, as shown in Figure 12. For these experiments, Aquacoat films were equilibrated at 5°C above the $T_g$s for 15 minutes, quenched to 25°C, then annealed at this temperature for up to 30 hours. The observed changes in creep compliance were attributed to a decrease in free volume and the further gradual coalescence of latex particles in the films. Physical aging and approaches to reduce or eliminate these problems (5,12,14,72,89) are discussed in more detail in another chapter.

## CONCLUSIONS

The mechanical properties of free films and applied films prepared from aqueous polymeric dispersions provide valuable information to help the pharmaceutical scientist predict the stability and drug-release properties of film-coated solid dosage forms. The plasticizers in the film coating enhance flexibility, lower the $T_g$, enhance the coalescence of the colloidal polymeric particles, and minimize the formation of cracks or defects. Thus, plasticizers are essential additives for most

polymers of pharmaceutical interest. Sufficient mixing time is required for the plasticizer to partition into the polymer phase, with longer equilibration times needed for water-insoluble plasticizers. The permanence of plasticizers in both the dry and the wet state is an important consideration, and leaching of a plasticizer from a film-coated dosage form leads to a porous membrane, which will impact drug release. The addition of other excipients in film coating formulations, such as pigments to enhance product appearance and talc to reduce tackiness of the coating, will influence the mechanical properties of polymeric films. Temperature, humidity, and processing parameters as well as physical aging can also have a significant effect on the mechanical properties of polymer films, ultimately affecting drug release from coated dosage forms.

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# 5

# Defects in Aqueous Film-Coated Tablets

**Ray C. Rowe**
*School of Pharmacy, University of Bradford, Bradford, U.K.*

## INTRODUCTION

Film coating is a process that involves the deposition of a membrane—consisting of polymer, plasticizer, colorant, and possibly other additives—onto the surface of a pharmaceutical dosage form, typically a tablet or a granule. Compared to the conventional sugar coat, the film coat is relatively thin, i.e., typically 10 to 100 μm. Although the technology involved in the application of such a thin coating to a substance is not new, having precedents in both the paints and adhesive technologies, problems do occur, resulting in a number of film defects. These can either affect the visual appearance of the coated tablet or, more importantly, result in the loss of continuity of the film and thus affect the release of the active ingredient from the preparation. Over the past two decades, with the increasing use of aqueous film coating, the number of defects reported has increased dramatically.

In this chapter, the various defects commonly found on aqueous film-coated tablets are discussed, with particular reference to their identification, diagnosis, and possible solutions.

## IDENTIFICATION AND SOLUTIONS

Film-coating defects can generally be divided into three groups depending on the complexity of the solution.

## Group 1

Group 1 consists of defects that can be easily remedied by changing one or more of the process conditions, e.g., inlet air temperature and spray rate. This group includes blistering (wrinkling), chipping, cratering, picking, and pitting.

### Blistering (Wrinkling)

With blistering, the film becomes locally detached from the substrate, forming a blister. It is not very common in tablet film coating, since in most cases the blister collapses under the attrition occurring in the coating process, leaving a film with a wrinkled appearance (wrinkling).

Blistering is caused by gases trapped in or underneath the film due to overheating either during spraying or at the end of the coating run. It is exacerbated by poor film substrate adhesion and usually occurs on tablet core formulations containing a high proportion of inorganic excipient. This is not surprising since inorganic substrates generally exhibit low film/tablet adhesion (1).

The solution to this defect is relatively simple. It involves the reduction of inlet (drying) air temperature and the cessation of the use of hot air to dry the tablets at the end of the coating run.

### Chipping

With chipping, the film becomes chipped and dented, usually at the edges of the tablet. It generally occurs where there is a high degree of attrition associated with the coating process as in the case of fluidized bed coating of large tablets. Decreasing the fluidizing air or the speed of rotation of the drum in pan coating often alleviates the problem. If there is excessive chipping, then it may be necessary to increase the hardness of the film by increasing the molecular weight grade of polymer (2).

### Cratering

Cratering is a defect whereby volcano-like craters appear in the film coating, exposing the tablet surface (Fig. 1a). Generally, it occurs during the initial stages of the coating process and becomes partially obscured as more film is deposited during coating.

Cratering occurs where drying is inefficient or where the rate of application of the coating solution is too high. The coating solution penetrates the surface of the tablet, often at the crown where the surface is more porous, causing localized disintegration of the core and disruption of the coating. The defect is often alleviated by increasing the drying (inlet air) temperature and decreasing the spray application rate, although in a minority of cases, increasing the viscosity of the coating solution by increasing the polymer concentration may be necessary to slow the rate of penetration of the solution into the tablet surface.

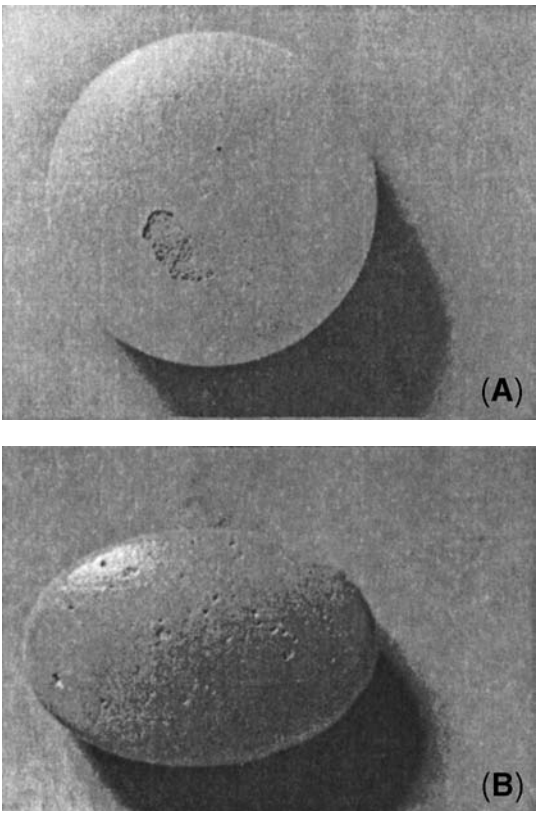


**Figure 1** Examples of group 1 defects that can be easily remedied by changing the process conditions: (**A**) cratering; (**B**) pitting.

### Picking

With picking, isolated areas of film pull away from the surface when the tablets stick together and then part. The areas may be large or small and, depending on whether the defect occurs early or late in the coating process, may be partially obscured as further polymer is deposited.

Picking occurs under the same conditions as cratering, i.e., any condition that produces an overly wet tablet bed (3) where adjacent tablets can stick together and then break apart. Corrective measures involve decreasing the spray application rate and increasing the inlet air temperature. If the defect occurs early on in the coating process and if corrective measures are taken, then it may be possible to recover the tablets since the defect can be obliterated by subsequent application of more polymer. However, if the defect is extensive and the film coating relatively thin, then this may not be possible.

### Pitting

Pitting was first described by Rowe and Forse (4) on tablet cores containing stearic acid. It is a defect whereby pits occur on the surface of a tablet core without any visible disruption of the film coating (Fig. 1b). It only occurs when the temperature of the tablet core exceeds the melting point of the stearic acid, implying that it is the melting point of the particles/aggregates of the stearic acid in the surface of the tablet that causes the pitting to occur. It is likely that this defect could also occur with other materials used in tablet formation, e.g., polyethylene glycol 6000 and vegetable stearin with melting points of 60°C and 62°C, respectively.

In all cases, the defect can be eliminated by dispensing with preheating procedures at the initiation of coating (especially those involving temperatures in excess of 60°C) and modifying the drying (inlet air) temperature such that the temperature of the tablet core does not exceed the melting point of the batch of additive used.

Other than a visual effect, this defect has no detrimental effect on film continuity and hence on the release rate of an active ingredient. This is in contrast to "pinholing," whereby the film contains minute holes, resulting in a loss of film integrity.

## Group 2

Group 2 includes defects that can only be remedied by changing a combination of both process conditions and film-coating formulation. This group includes blooming, blushing, color variation, infilling, mottling, and orange peel (roughness).

### Blooming

Blooming is best described as the dulling of the coating (5). It can occur directly after coating but is more commonly seen on coated tablets upon prolonged storage at high temperatures.

The dulling of the coating is thought to be due to the collection on the surface of low-molecular-weight ingredients included in the coating formulation (5). In most circumstances, the ingredient will be the plasticizer, although it is not inconceivable that it could also be a surfactant included in the coating formulation to lower surface tension. Since the amount present on the film surface will be governed by the laws of diffusion, i.e., the concentration of the plasticizer and its effective diffusion coefficient, any parameter that will affect the latter will have an effect on the incidence of the defect. Effective solutions involve not using hot air to dry the tablets at the end of the coating run, the decrease in plasticizer concentration, and the increase in the plasticizer molecular weight.

### Blushing

Blushing is generally seen in nonpigmented film since it is best described as whitish specks or haziness in the film.

Blushing is not a very common defect in film-coated tablets, and in the author's experience, it has only been seen in systems involving aqueous coating with the cellulose ethers, methylcellulose, hydroxypropylcellulose, and hydroxypropyl methylcellulose. The white specks or haziness in the film is thought to be due to precipitated polymer exacerbated by the use of high coating temperatures at or above the thermal gelation temperature of the polymers. Because the addition of the plasticizers, polyethylene glycol, and propylene glycol tends to cause an increase in the thermal gelation temperature but addition of glycerol or sorbitol causes a decrease, the formulation most likely to cause the defect would be one containing sorbitol, as this additive causes the largest fall in the thermal gelation temperature. Provided the polymer is used alone or admixed with polyethylene glycol or propylene glycol as plasticizers, there will be little incidence of this defect. If it does occur with such a formulation, then it may be eliminated by decreasing the drying air temperature.

### Color Variation

Color variation is self-explanatory, but it is very important if found intrabatch, because it indicates a variation in the deposition and therefore the thickness of the polymer film. Variations in film thickness can affect both the release rate of an active ingredient and the incidence of such defects as bridging (6).

Color variation is essentially a mixing problem involving the distribution of a coating formulation over a large surface area of tablets continuously moving in and out of a relatively small zone—the so-called spray zone. Hence any process or formulation variable that affects the frequency and duration of appearance of tablets in the spray zone or the size/shape of the spray zone itself will have an effect on color variation.

In coating drums, both Rowe (7) and Porter and Saracini (8) have found a decrease in color variation with drum speed, whereas more recent work has demonstrated an effect with change in baffle design. An increase in the number of spray guns and hence an increase in the effective areas of the spray zone also decreased color variation (8).

Significant effects can also be obtained by decreasing the solids content of the coating formulation with the application of more dilute coating formulations, thus improving product quality to the detriment of processing time (8).

### Infilling

Infilling, a defect that was first described by Down (9), has the same end effect as bridging, i.e., that of rendering the intagliations (logos, monograms) indistinct and illegible. However, in this case, the intagliation is filled with a solidified foam structure that cannot be deformed or pushed back into the intagliation.

The primary cause for this defect has been postulated (9) as being the inability of a foam, formed by air spraying of a polymer solution, to break. The foam droplets on the surface of the tablet breakdown readily due to attrition, but

the intagliations form a protected area, allowing the foam to accumulate and "set." Once the foam has accumulated to a level approaching the outer contour of the tablet surface, normal attrition can occur, allowing the structure to be covered with a continuous film.

It is interesting to note that the addition of conventional antifoam agents does not decrease the incidence of this defect. However, the addition of alcohol and the use of spray nozzles capable of finer atomization have both been found to be effective (9).

In a more recent paper (10), it was postulated that the collapse of the bubbles in the foam structure can cause pinholes to develop (pinholing).

### Mottling

Mottling, as the name suggests, is the perception of an uneven distribution of color within the film coating. It can occur in all film-coating formulations—pigmented or nonpigmented, with the latter arising from mottling within the tablet substrate due to poor opacity of the film coating. Mottling is a complex defect with many origins.

**Inadequate pigment dispersion:** Typical pigment particle sizes lie in the submicrometer range (11), but the presence of agglomerates (>10 μm) is not uncommon. If these agglomerates are not broken down and dispersed effectively in the coating formulation, mottling will occur due to the differences in the absorption (color strength) of the differing sizes of the agglomerates of the pigment particles.

**Color migration:** Color migration occurs either by evolution of residual solvent in the film or by migration of the plasticizer in which the colorant may be soluble (3). It is exacerbated by the use of soluble dyes as colorants but can occur with specific lake pigments with a low "bleed" threshold, especially in the presence of polyethylene glycols (a common plasticizer in film coating). In this case, the dye becomes desorbed from the alumina substrate dissolving in the polyethylene glycol, which then migrates, producing a mottled film with areas of high dye concentration. Elimination of dyes or aluminum lakes as colorants would be the best means of alleviating this defect.

**Mottling of the tablet core:** Mottling of the tablet core can be due to either poor mixing of the ingredients (especially if the active ingredients are colored) prior to tableting or selective light degradation of one or another ingredient (usually the active ingredient) resulting from poor film opacity. In both cases, especially if the film is transparent or lacking in opacity, the resultant preparation will appear mottled.

The quantification of the opacity of tablet film coatings has been the subject of much detailed research (12–16). It can be simply and rapidly assessed by means of a contrast ratio, which is defined as the ratio of the measured reflectance when the film is placed as a black substrate to that when the film is placed on a white substrate, with magnitudes of greater than 98% being taken to define com-

plete opacity for the human eye. Although opacity is generally associated with the inclusion of titanium dioxide, due to its high refractive index, the color of a pigment can play an important role. Table 1 shows the contrast ratios for a film formulation containing a wide variety of pigments and fillers where it can be seen that, although pigments with high refractive indices generally exhibit a high opacity, a similar effect can be obtained by the use of blue pigments with a much lower refractive index. Increasing the pigment concentration also increases the contrast ratio as does increasing film thickness (12).

It is therefore possible, by applying these concepts, to decrease the incidence of mottling of the tablet core. However, it has been shown that light degradation of an active ingredient can still occur under a white film with a very high contrast ratio (7,16), and in these cases, it may be necessary to add other colored pigments (15,17) to alleviate the problem.

### Orange Peel/Roughness

Orange peel (roughness) is purely a surface effect that results in the film being rough and nonglossy, with a surface appearance similar to that of an orange (Fig. 2). An interesting consequence of this defect is in the visual perception of color of tablets with rough surfaces—a colored film with a smooth glossy surface will always appear darker and more saturated in color than the same film with a rough, less glossy surface. Film-coated tablets with very rough surfaces can also be more difficult to package on high-speed packing lines due to the increased friction on the chute mechanisms.

In the majority of the film-coating processes, film-coating formulations are applied using spray techniques. In flight, the droplets of spray lose solvent and become more viscous and in some cases dry. If the droplets are dry or too

**Table 1** Contrast Ratios for Tablet Film Coatings Based on Hydroxypropylmethylcellulose Containing a Number of Pigments/Fillers/Colorants at a Fixed Concentration of 16% w/w

| Pigment/filler | Refractive index | Contrast ratio (%) |
|---|---|---|
| None | 1.48 | 33.3 |
| Talc | 1.54–1.59 | 46.3 |
| Calcium carbonate | 1.51–1.64 | 46.7 |
| Titanium dioxide | 2.49–2.55 | 91.6 |
| Red iron oxide | 2.94–3.22 | 99.5 |
| Yellow iron oxide | 1.90–2.50 | 98.4 |
| Black iron oxide | 2.40 | 99.6 |
| FD&C Blue 2 Lake | 1.50–1.54 | 97.5 |
| FD&C Red 3 Lake | 1.50–1.54 | 70.1 |
| FD&C Yellow 6 Lake | 1.50–1.54 | 73.2 |
| FD&C Yellow 5 Lake | 1.50–1.54 | 62.9 |

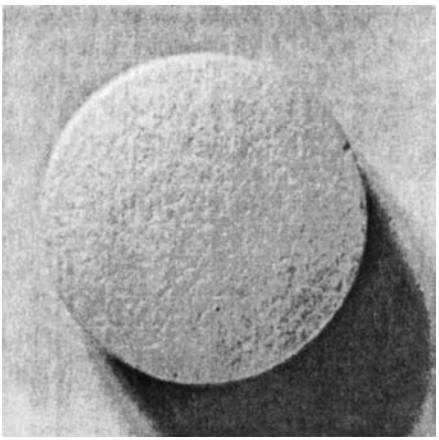

**Figure 2** Roughness/orange peel. Example of a group 2 defect that can only be remedied by changing both process conditions and film-coating formulation.

viscous to spread when they reach the tablet surface, a rough film results. Both extremes of viscosity of a coating formulation will result in poor spreading and hence rough surfaces—the low-viscosity solutions because of the small droplet sizes and high evaporation rates causing spray drying; the high-viscosity solution because of large droplet sizes with low surface area for evaporation and high internal viscosity and hence poor spreading. Very rough surfaces with low gloss are always found when tablets are coated with solutions with high polymer concentrations.

Spray properties are not the only factor that can affect the roughness and gloss on film-coated tablets. The roughness of a coated surface can be regarded as the sum of three components: one due to coating formulation, one due to method of application/process conditions, and one due to the inherent surface roughness of the substrate. Factors of relevance in the first are the concentration and size of any added pigment or fillers (18–20), especially because increasing both can have a significant effect on increasing the roughness and decreasing the gloss. Factors of relevance in the second are the thickness of the film itself (18) and the extent of mutual rubbing, which is dominant in film coating in drums (21) and is a process that is activated when so-called glossing solutions are applied at the end of a coating run (22). Factors of relevance in the third are the compaction pressure and porosity of the tablet core (18). Unfortunately, the extent to which each will affect the final appearance of the coating will be dependent on individual cases and there are no hard and fast rules. This is illustrated by the data given by Rowe (18), where it was found that film coating a core with a very rough surface produced a coated tablet with a smoother finish and vice versa.

## Group 3

Defects that require a more fundamental approach may also include reformulation of the tablet core in addition to changes in the film formulation and process conditions. Group 3 includes bridging, cracking, flaking, peeling, and splitting—defects associated with high internal stresses within the film coating.

### Bridging

Bridging of the intagliations is a defect whereby the film pulls out of the intagliation or monogram in the tablet core, forming a bridge across the edges of the mark (6). This renders the intagliations indistinct and illegible, thus losing the advantage of using intagliated tablets for product identification (Fig. 3A). A scanning electron photomicrograph (Fig. 4) of a typical bridged intagliation shows that film has a normal structure (23). However, there is evidence of small amounts of

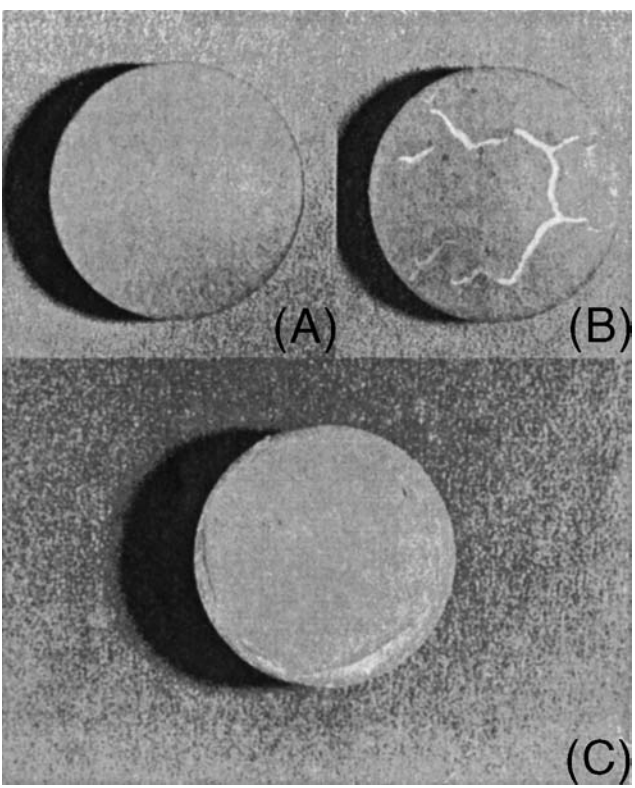


**Figure 3** Examples of group 3 defects that are associated with high internal stresses within the film coating: (**A**) bridging of the intagliations (logos monograms); (**B**) cracking; (**C**) edge splitting and peeling.

**Figure 4** Scanning electron photomicrograph of a bridged intagliation.

tablet substrate still adhering to the underside of the film, indicating that at some time during the coating process, the film has actually followed the contours of the intagliation. The bridged film can be easily deformed and pushed back into the intagliation by means of a round pinhead, thus providing a simple confirmatory test to distinguish this defect (23) from infilling.

### Cracking/Splitting

In this defect, the film either cracks across the crown of the tablet (cracking, Fig. 3B) or splits around the edges of the tablet (splitting, Fig. 3C). In some cases, the film either flakes off, exposing the tablet surface (flaking), or peels back, exposing the tablet surface (peeling). Conventionally, peeling has been associated specifically with edge splitting (24).

Cracking can also occur at the microscopic scale both in nonpigmented films (25) and in pigmented films, where it is usually localized around individual pigment particles or aggregates (3). These cracks can have a profound effect on the release of an active ingredient.

### Peeling/Flaking

Both of these defects describe the situation in which there is exposure of the tablet surface due to the film either peeling back (peeling) or flaking off (flaking). Both are associated with cracking or splitting of the film: conventionally, flaking with cracking and peeling with edge splitting. Unfortunately, Porter (3) mistakenly defined peeling as an extension of picking, and this definition has been perpetuated and in some cases extended to flaking by others (26,27).

## ORIGINS AND THEORY OF INTERNAL STRESSES

In order to understand how internal stresses are caused in polymer films, it is first necessary to consider the physical changes that occur in the formation of a film from a coating formulation. First, the solvent evaporates until, at a certain polymer concentration, a gel consisting of solvent dispersed in an open polymer network is formed. The gel structure then contracts as further solvent is lost until a viscoelastic film is produced. As the film solidifies, only the thickness can contract, with movement in the other dimensions being constrained by the adhesion of the film to the tablet substrate, thus producing an internal stress in the film. Additionally, if there is a large difference between the expansion coefficients of the coating and the substrate, then similar stresses can be created during the coating process due to the temperature changes that inevitably occur. Stresses due to a volume change in the substrate (e.g., swelling of a tablet during storage at high humidity) can also be a problem. Since these stresses are present in the plane of the coating (Fig. 5), failure can occur either at the film/tablet interface, resulting in bridging, or within the film itself, resulting in cracking, splitting, peeling, and flaking. In some severe cases, all defects can occur at the same time.

Recently, it has become possible to quantify these stresses. If $P_s$ is the internal stress due to shrinkage of the film on evaporation of the solvent, $P_t$ the thermal stress due to differences in the thermal expansion of the film coating and tablet substrate, and $P_v$ the stress induced by volume changes in the tablet substrate

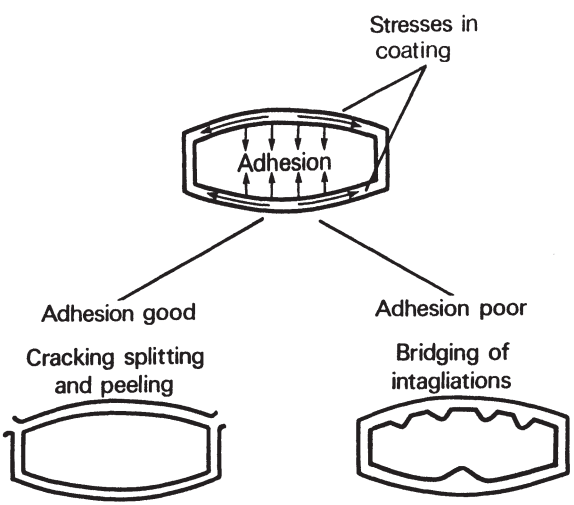


**Figure 5** Schematic diagram of the stresses in a film coating applied to a tablet and the causes of cracking/splitting and bridging of the intagliations.

in storage, then by analogy with the equations derived for the stress in lacquers (28–30), it has been possible to show (25,31) that

$$P_s = \frac{E}{1-v} \cdot \frac{\phi_s - \phi_r}{3(1-\phi_r)}$$

$$P_t = \frac{E}{1-v} \cdot \frac{\Delta\alpha\,\Delta T}{3}$$

$$P_v = \frac{E}{1-v} \cdot \frac{\Delta V}{3V}$$

where $E$ is the Young's modulus of elasticity of the film coating, $v$ is Poisson's ratio of the film coating, $\phi_s$ is the volume fraction of the solvent in the film at its solidification point (i.e., when the coating solution first behaves as a solid rather than a viscous liquid), $\phi_r$ is the volume fraction of the solvent remaining in the dry film at ambient conditions, $\Delta\alpha$ is the difference between the cubical thermal expansion coefficient of the tablet substrate and the film coating, $\Delta T$ is the difference in temperature between either the glass transition temperature of the film coating $T_g$ or the process temperature and the ambient temperature, whichever is the smaller, $\Delta V$ is volume change, and $V$ is the volume before the storage of the tablet substrate.

It is assumed that before solidification and/or above the glass transition temperature of the film, the polymer chains are mobile such that they can effectively minimize the stresses created, but that after solidification and/or below the glass transition temperature, polymer chain mobility is restricted and the stresses become "frozen in." These equations are particularly important in that they highlight those factors in the formulation and process that will affect the incidence of these defects and provide options for alleviating them.

## TABLET CORE FORMULATION

The only factor in the equations directly affected by the tablet core formulation is $\Delta\alpha$. Unfortunately, data on thermal expansion coefficients of materials relevant to tableting and film coating are not generally available. Rowe (32) compiled a list of data for some representative materials, showing the distinct differences between inorganic tablet fillers (i.e., calcium carbonate, magnesium carbonate) and the organic tablet fillers (i.e., the sugars). The former have very low values compared to the polymeric film formers whereas the latter have values comparable with the polymer film formers. This is in accordance with what is found in practice, with tablet cores based on the inorganic fillers having a higher incidence of cracking than those based on the organic fillers (32). Data (33) from direct expansion measurements on granules of tablet formulation have shown similar trends; i.e., those formulations with a large $\Delta\alpha$ compared to hydroxypropylmethylcellulose causing most problems on coating.

Recent measurements on the dimensional changes occurring with various tablet core formulations under simulated temperature/humidity variations experienced during a typical film-coating process have shown significant effects (34,35). Tablets of microcrystalline cellulose and starch decreased significantly in size during heating and expanded during cooling, whereas tablets of dicalcium phosphate exhibited the opposite behavior but to a smaller extent. The results were evaluated in terms of the changes in moisture content of the tablets, especially the uptake of moisture at the end of the coating process (35).

Tablet core formulations are also known to swell on storage specifically at a high relative humidity (36). Problems with bridging of the intagliation can occur at this stage especially with tablets having a high proportion of specific direct compression excipients (31).

## POLYMER GRADE

It follows from the equations that if the mechanism of film cracking is as stated, the incidence of this defect will be dependent on the strength/mechanical properties of the polymer used in the coating formulation. A particularly easy way of increasing the effective strength of a polymer is by increasing its molecular weight and hence its viscosity grade. The rationale behind this approach is based on the fact that the relationship between the mechanical properties of a polymer and its molecular weight is qualitatively the same for all polymers. Low-molecular-weight polymers are usually relatively weak, but as their molecular weight is increased, their mechanical properties also increase until at some critical molecular weight, there is no further increase. This rationale has now been successfully applied in the cases of splitting and microcracks in films prepared from hydroxypropylmethylcellulose (24).

It is also known that the addition of high-molecular-weight components to a distribution as a result of blending high- and low-molecular-weight grades of a polymer can increase its effective strength. This has also been shown to be beneficial for tablets coated with hydroxypropylmethylcellulose (24).

## PLASTICIZER TYPE AND CONCENTRATION

Plasticizers are often added to polymers in order to enhance their film-forming characteristics. Plasticizers act by interposing themselves between the polymer chains, thereby extending and softening the matrix, lowering the glass transition temperature of the polymer, and decreasing internal stress. However, the extent to which this happens is dependent on the compatibility of the plasticizer with the polymer, with the most compatible plasticizers being the most efficient.

The beneficial effect of plasticizers on the incidence of bridging of the intagliations has been demonstrated (37). In this respect, the curves are similar in shape to those showing the effect of the same plasticizer on the glass transition

temperature of hydroxypropylmethylcellulose, with those plasticizers that cause a significant lowering in the glass transition temperature (i.e., the most compatible) being the most efficient in reducing the incidence of the defect.

## PIGMENT/COLORANT TYPE AND CONCENTRATION

Extensive work has been done on the effect of pigments and fillers on the incidence of film cracking/splitting (38–41). In general, the addition of most pigments exacerbates the problem proportional to their concentration. However, it has been found that the addition of materials such as calcium carbonate, magnesium carbonate, and talc (the so-called extender pigments) had either little or no effect or was beneficial in reducing the incidence of the defect. In fact, the addition of talc has been shown to eliminate the problem in once case, while in another, where it was added to a film already colored with an aluminum lake pigment, it reduced the incidence of the defect in proportion to its concentration in the film (40). These effects have generally been interpreted in terms of the differences in morphology of the various pigment particles (41).

A further factor to be considered is the magnitude of the localized stress at the pigment/polymer interface ($P_L$) caused by differences in the thermal expansion of the pigment particle and the polymer film ($\Delta\alpha$) over the temperature range $\Delta T$, given by

$$P_L = \frac{\Delta T \Delta \alpha}{(1+v)2E + (1-2v_p)E_p}$$

where $E_p$ and $v_p$ are Young's modulus of elasticity and Poisson's ratio of the pigment, respectively.

In the case where the thermal expansion coefficient of the polymer film is higher than that of the pigment as in tablet film coating, this equation predicts that cracking, if it occurs, will always proceed radially from the pigment—a fact seen in photomicrographs of cracked film coatings (3). Recently, this approach has been extended using computer modeling and simulation (42–44). Using the simulation (Fig. 6), the authors have investigated specific formulation variables hitherto difficult to investigate experimentally, such as pigment particle size/distribution and the addition of a second pigment on cracking. An interesting feature of the work is the finding that the addition of a second population of a pigment of a larger particle size and the broadening of the size distribution of the pigment both result in a decrease in crack velocity, thus providing an alternative, although as yet unproven, method for alleviating cracking.

## FILM THICKNESS/INTAGLIATION SHAPE

Two factors that have been shown to have a dramatic effect on bridging of the intagliation are film thickness, where the incidence of the defect increases with

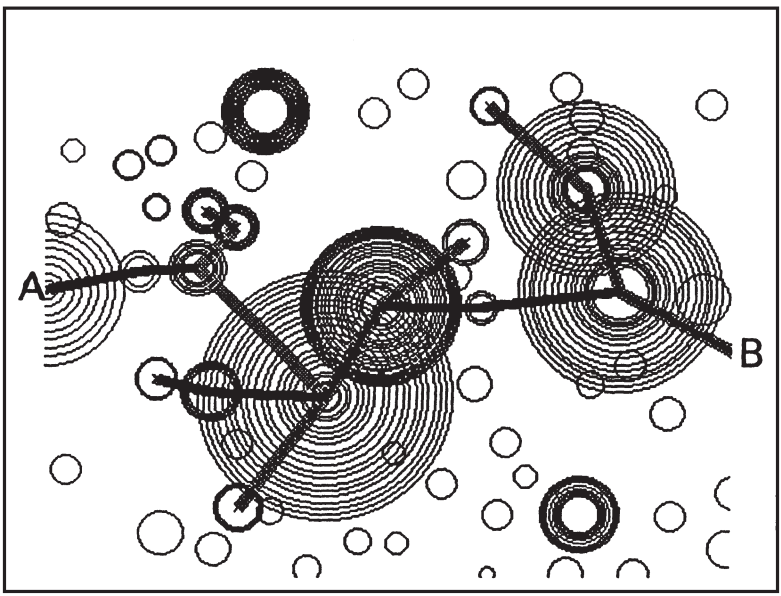


**Figure 6** Example of a computer simulation of cracking on a pigmented film coating. Small circles represent pigment particles, concentric circles represent the new periphery for each step in growth, straight lines between the circles represent the crack emanating radially from the pigment particles starting at point A and finishing at point B. *Source*: From Refs. 42 and 43.

increasing film thickness (6,45), and intagliation shape, where the incidence of the defect can be minimized by the use of an intagliation with a large, deep profile as opposed to a small, shallow profile (46). Both effects are thought to be related to the magnitude of the adhesion between the film and the tablet substrate.

## PROCESS CONDITIONS

In the stress equations, the factor of most relevance with respect to processing is $\Delta T$, and hence any factors that are known to have any effect on the tablet bed temperature, i.e., spray rate and inlet air temperature, will have an effect on the incidence of both bridging of the intagliations and film cracking/splitting (45,47). Table 2 shows data for two tablet formulations, one known to be prone to bridging of the intagliation and the other known to be prone to edge splitting.

It can be seen that at higher tablet bed temperatures, bridging of the intagliations was reduced but edge splitting was increased. This discrepancy can be explained by reference to the stress equations. It is known that films prepared under spray conditions where evaporation of the solvent is increased (i.e., analogous to

**Table 2** Effect of Process Conditions on the Incidence of Bridging of the Intagliations and the Incidence of Edge Splitting

| Inlet air temperature (°C) | Stray rate (mL/min) | Tablet bed temperature (°C) | Incidence of defect (%) | |
|---|---|---|---|---|
| | | | Splitting | Bridging |
| 50 | 50 | 33 | 1.9 | – |
| 60 | 60 | 38.5 | 8.5 | – |
| 60 | 50 | 42 | 14.3 | 49.3 |
| 60 | 40 | 54 | – | 38.5 |
| 70 | 50 | 50 | 70.0 | 21.2 |

*Source*: Ref. 47.

conditions of high tablet bed temperature in Table 2) tend to show a progressive decrease in Young's modulus of elasticity. This will result in a lower induced stress and hence less bridging. However, the same conditions can cause a decrease in the tensile strength of the film, and if this is the dominant effect, then film cracking/spitting will be exacerbated.

## EXPERT SYSTEM DEVELOPMENT

It can be seen that it is now possible to utilize a rational scientific approach to the solution of a number of defects found on aqueous film-coated tablets. It is obvious that in solving problems, compromises have to be made and that these may result in imbalances in the process/formulation, which themselves can create more problems (26). Judging the overall effect of any compromise is the field of the expert and requires specific knowledge and vast experience. Expertise and knowledge of this form are not easily documented and are generally passed on by word of mouth; thus experts often spend considerable time training new personnel. In addition, early retirement can lead to loss of irreplaceable knowledge, and personal preferences often result in inconsistencies of approach.

Expert systems technology provides an affordable means of capturing this knowledge and expertise in a documented form that is available to all. Furthermore, expert systems can combine the expertise of more than one expert or make use of supplementary theory or data, leading to a heightened consistency of the decision-making process, which in turn can be queried, examined, and easily updated.

Recently, this concept has been applied to the identification and solution of defects in film-coated tablets (48). The expert system is based on a commercially available shell on a PC microcomputer. A flow diagram of the complete system is shown in Figure 7. Basically the system is divided into three stages: identification, solution, and information/references.

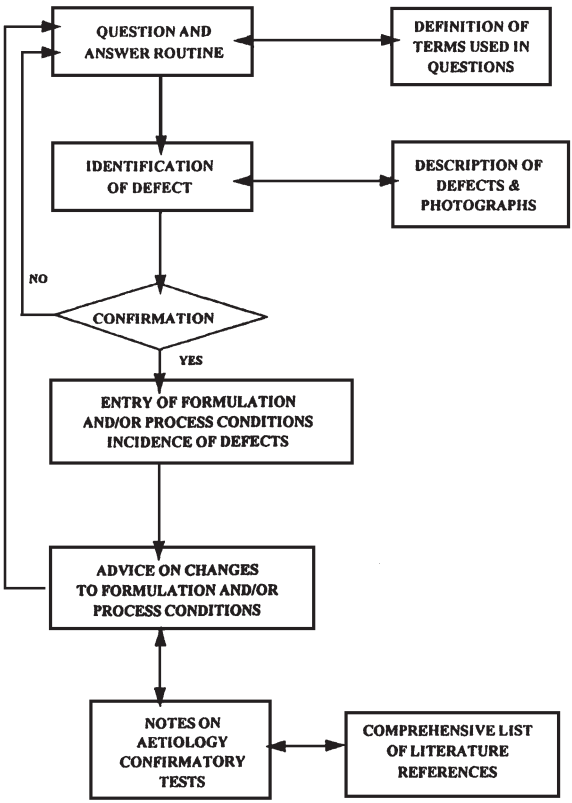


**Figure 7** Flow diagram of the expert system for the identification and solution of film-coating defects.

## Stage I: Identification and Confirmation of the Defect

Correct identification of the defect is essential, and in this part of the system, a question-and-answer routine is used. The questions are displayed on the screen in a simple format and the user is asked to select an appropriate answer. If the user is uncertain of the terminology, a hypertext system is used to define and amplify the terms. The routine is repeated until there are sufficient data for a decision to be made via the decision tree (Fig. 8). At this point, the decision is displayed with a brief description of the defect identified. In addition, the user is asked to confirm the decision by comparing the defect with pictures and photographs stored in the database. If the answer is negative, the question-and-answer routine is rerun, as it is assumed that an incorrect answer was given at some stage. If the answer is positive, the system proceeds to the next stage.

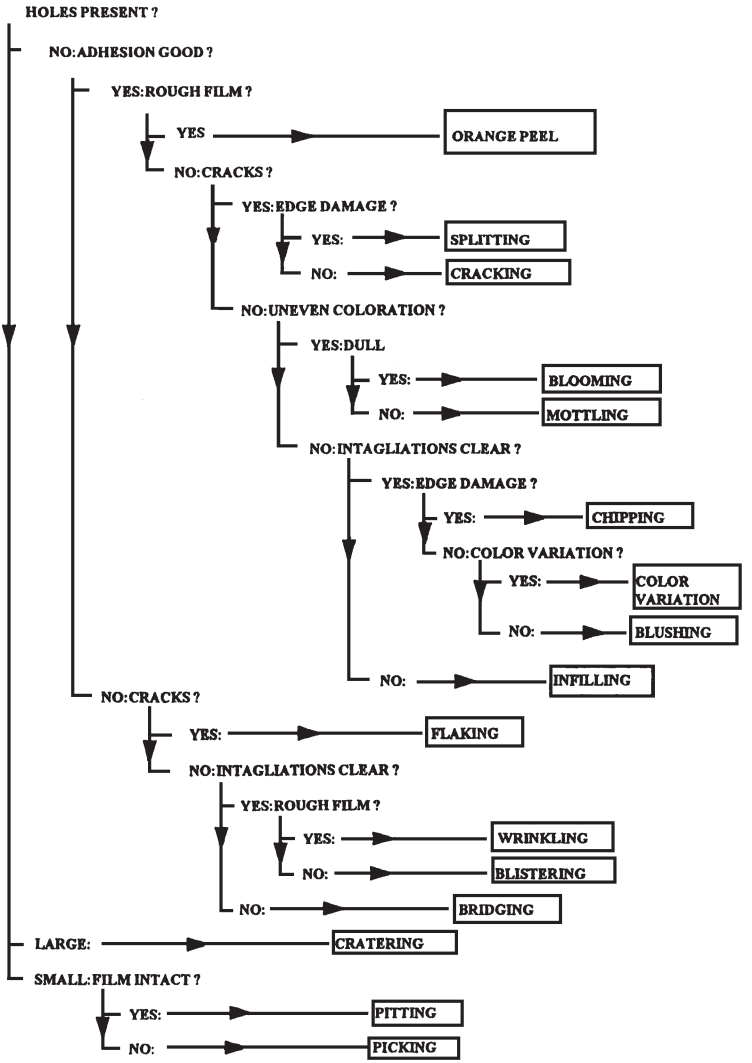


**Figure 8** Decision tree for the identification of film-coating defects.

## Stage II: Solution of the Defect

In stage II, the user is asked to enter relevant process conditions used in the coating machine, formulation details, and incidence of the defect. As in stage I, hypertext is used to amplify or define terms. The system allows for two cases: first, solution by changing only process conditions, as in the case of defects occurring

with an already registered formulation, and second, by changing either or both process conditions and formulation, as in the case of defects occurring at a development stage. This is indicated by the selection of the answer to the question "Change Formulation?" which occurs where necessary.

After all of the data have been entered, the relevant advice is displayed. At this stage, the user can enter the third stage of the system, which gives advice, information, and references.

### Stage III: Information and References

The system contains comprehensive information on each effect in the form of notes, additional pictures/photographs, and literature references. In addition, hypertext can be used to link to other associated defects.

The system is easy and rapid in use, combining all of the knowledge in the area in a permanent and readily accessible format. It is obvious that such a system could easily be combined with the computer program for simulating crack propagation in pigmented films (44), as mentioned above, to run within a more advanced expert system shell such as the Product Formulation Expert System (PFES, Logica, Cambridge, U.K.) as described by Skingle (49) and Turner (50). This would provide a comprehensive formulation/process development expert system for tablet film coatings comparable with that already described for tablet cores (51).

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# 6

# Adhesion of Polymeric Films

**Linda A. Felton**

*College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, U.S.A.*

**James W. McGinity**

*College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*

## INTRODUCTION

Adhesion between a polymer and the surface of a solid is a major prerequisite for the film coating of pharmaceutical dosage forms (1–3). Loss of adhesion may lead to an accumulation of moisture at the film–tablet interface, potentially affecting the stability of drugs susceptible to hydrolytic degradation (4). Poor adhesion may also compromise the mechanical protection that the coating provides to the substrate (5). In addition, experiments on adhesion are useful to the pharmaceutical scientist during formulation development to investigate the relationship between tablet excipients and polymeric film-coating formulations (6).

## MAJOR FORCES AFFECTING FILM–TABLET ADHESION

The two major forces that have been found to affect polymer–tablet adhesion are (*i*) the strength of the interfacial bonds and (*ii*) the internal stresses in the film. Hydrogen bond formation is the primary type of interfacial bonding between the tablet surface and polymer for pharmaceutical products (7). To a lesser extent, dipole–dipole and dipole-induced dipole interactions also occur. Factors that affect either the type or the number of bonds formed between the polymer and the solid surface will influence film adhesion.

When a polymeric solution or dispersion is applied to a substrate, internal stresses inevitably develop within the film (8). These stresses include stress due to shrinkage of the film as the solvent evaporates, thermal stress due to the difference in thermal expansion of the film and the substrate, and volumetric stress due to the change in volume when the substrate swells during storage. The total stress within a film is the sum of all the stresses acting on the polymer, and several researchers have developed equations to estimate total stress (8–11). Equation 1, developed by Okutgen et al. (12), includes contributions of volumetric changes of the tablet core in addition to the other well-established mechanisms:

$$P = \frac{E}{3(1-v)}\left[\frac{\Phi_s - \Phi_r}{1-\Phi_r} + \Delta\alpha_{(cubic)}\Delta T + \frac{\Delta V}{V}\right] \quad (1)$$

where $P$ is the total internal stress in the film, $E$ is the elastic modulus of the film, $v$ is the Poisson's ratio of the polymer, $\Phi_s$ represents the volume fraction of the solvent at the solidification point of the film, $\Phi_r$ is the volume fraction of solvent remaining in the dry film at ambient conditions, $\Delta\alpha_{(cubic)}$ is the difference between the cubical coefficient of thermal expansion of the film coat and the substrate, $\Delta T$ represents the difference between the glass transition temperature of the polymer and the temperature of the film during manufacturing and storage, $\Delta V$ is the volumetric change of the tablet core, and $V$ denotes the original volume of the tablet core. Although this equation has been derived for polymeric solutions, the theory is applicable to polymeric dispersions as well. It is apparent from Equation 1 that the total stress within a film is directly proportional to the elasticity of the polymer. Factors that influence the elastic modulus of the polymer will, therefore, affect internal stress and film–tablet adhesion.

## METHODS USED TO ASSESS POLYMER ADHESION

A distinction must be made between "fundamental" and "practical" adhesion. Fundamental or "true" adhesion refers to the intermolecular interactions between the polymer and the substrate (13). Practical or "measured" adhesion refers to the numerical value that results from a variety of testing methods, including shear and tensile tests. In addition to the interfacial interactions, other factors such as stresses in the film and the adhesion measurement technique will influence measured adhesion (11). No methods used to quantify polymer adhesion, however, can be directly used to measure fundamental adhesion.

The small size of the tablet and the nonuniform surface roughness of the substrate have presented significant challenges to the pharmaceutical scientist in determining the adhesive properties of a polymer (14,15). The earliest method for assessing adhesion of thin polymeric films to surfaces was the "Scotch tape" test (16), where a piece of adhesive tape was applied to the film surface and then peeled off. The film either adhered to the solid surface or was removed with the adhesive tape. This method was obviously qualitative in nature and did not provide an accurate measurement of polymer adhesion.

Another method that has been used to provide qualitative information regarding adhesion of polymers to pharmaceutical solids is diametral compression of coated substrates (17). During compression experiments, the total load will be distributed between the film coating and the solid substrate (5). The simultaneous fracture of the coating and the substrate is indicative of good adhesion between the polymer and the solid (17,18).

The first quantitative adhesion test was developed by Heavens in 1950 and was known as the "scratch test" (19). In this technique, the tip of a hard stylus is drawn across the surface of the film. The critical load required to completely detach the film from the substrate along the track of the scratch is determined and related to polymer adhesion. Although it is used extensively to study the adhesion of films cast onto metal surfaces, this method is unsuitable for pharmaceutical systems due to the relative rough surface of tablet compacts (20).

In the 1970s, the peel test was a popular method for the determination of film adhesion to tablets. The peel test uses a modified tensile tester to peel the film from the surface of the tablet at a 90° angle (21). The primary deficiency of this method is that the peel angle measured at the tablet surface is dependent on the elasticity of the film and the uniformity of adhesion, both of which can produce significant deviations in the data (15).

Several variations of the butt adhesion technique have been reported in the pharmaceutical literature over the past 20 years (22–26). This method is similar to the peel test. However, the entire film is removed normal to the surface of the tablet, rather than sections of the film being peeled. The butt adhesion technique eliminates variations due to the elasticity of the film and is less influenced by the uniformity of adhesion. The experimental set-up requires that the film coating around the edge of the tablet be removed using a scalpel. Next, the tablet is affixed to a lower, stationary platen. Double-sided adhesive tape is placed between the tablet surface and the upper platen. Rubber backing may be used to ensure adequate contact. A uniform displacement rate should be used to remove the film from the substrate (27). In 1980, Rowe (27) investigated the rate effects on measured adhesion of film coatings. Small increases in measured adhesion were found when the crosshead speed was increased from 0.1 to 1.5 mm/sec, whereas decreased adhesion resulted when the deformation rates were increased above 1.5 mm/sec, as shown in Figure 1.

The rates of deformation influence the rheological behavior of different components in the system, including the adhesive tape as well as the polymer itself, and, therefore, they affect how the applied stress is transmitted and distributed at the film–tablet interface (27). Higher rates of deformation resulted in an uneven stress distribution, thus lowering the measured adhesion.

Felton and McGinity (23) used a Chatillon digital force gauge and motorized test stand to conduct butt adhesion experiments. The apparatus was connected to a personal computer and force–deflection diagrams were constructed from the data, which permitted the visualization of the development of the force within the sample during the adhesion experiments. An example of a force–deflection diagram generated from this equipment is shown in Figure 2.

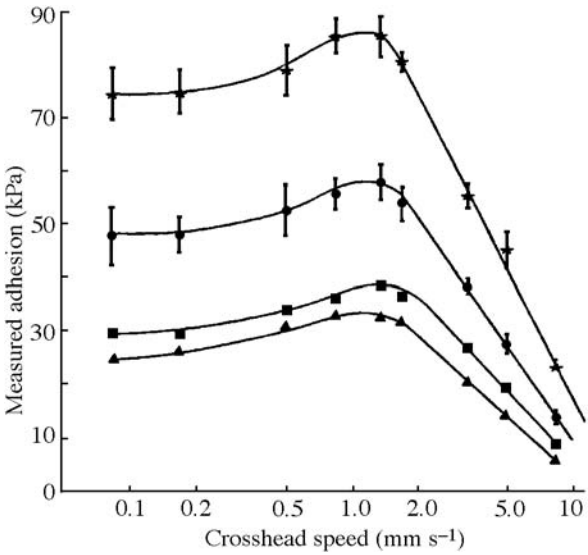


**Figure 1** The effect of crosshead speed on measured adhesion of an organic-based cellulosic film. (★) Microcrystalline cellulose tablet core, 18 μm film thickness (Pharmacoat® 606); (●) microcrystalline cellulose tablet core, 70 μm film thickness (Pharmacoat 606); (■) lactose tablet core, 35 μm film thickness (Pharmacoat 606); (▲) lactose tablet core, 35 μm film thickness (Methocel® E 50). *Source*: From Ref. 27.

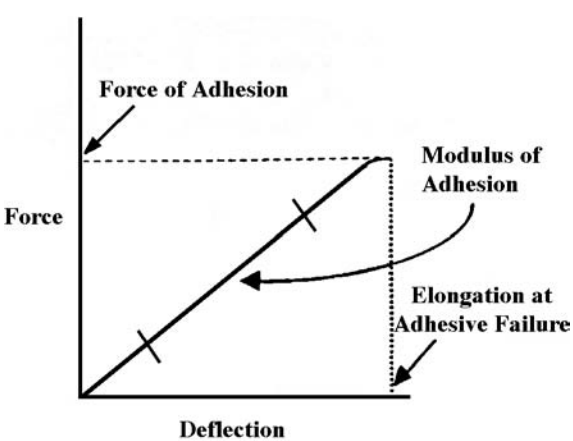


**Figure 2** Example of a force–deflection profile generated using a Chatillon digital force gauge and motorized test stand to quantitate polymer adhesion by employing a butt adhesion technique. *Source*: From Ref. 23.

The profile is similar to the stress–strain diagram commonly generated in the tensile testing of free films. From the force–deflection diagrams, the elongation at adhesive failure, the modulus of adhesion, and the adhesive toughness of the polymer, in addition to the force of adhesion, can be determined. The elongation at adhesive failure, analogous to the elongation at break obtained from tensile testing of free films, reflects the ductility of the polymer. The adhesive toughness is calculated as the area under the force–deflection diagram and is equal to the work required to remove the film from the surface of the solid.

An important factor to consider in the experimental design for investigating polymer adhesion is the shape of the tablet. In 1977, Rowe (28) compared the adhesive force between organic-based cellulosic films and either flat-faced or biconvex tablets. The force required to remove the film from the surface of the biconvex tablets was lower than the same films coated onto flat-faced tablets. A direct relationship between the force of adhesion and the square of the diameter of flat-faced tablets was found, whereas a maximum force was reached with biconvex table and no such correlation occurred. Interestingly, a direct relationship between the work required to remove the film from the tablet surface and the square of the diameter of the tablet was found for both flat-faced and biconvexed tablets. These findings suggest that the work done to remove the film from the tablet surface provides a more accurate and quantitative measure of film–tablet adhesion for biconvex tablets than the direct force measurement, whereas investigation of either the adhesive force or the adhesive toughness would be useful in the study of adhesion involving flat-faced tablets.

The majority of published studies investigating adhesion of polymeric films to pharmaceutical solids involve flat-faced tablets (15,22,23). Flat-faced tablets, however, may agglomerate in the coating pan apparatus during the coating process. Nonuniform adhesion of the polymer at the edge of the tablets has also been reported due to the high internal stresses within the film at the tablet edge (11,29). In a study conducted by Felton and McGinity (23), flat-faced punches with a beveled edge were used to achieve a more uniform adhesion of the polymeric film. The bevel decreased the sharp angle at the edge of the tablet and lowered the internal stresses within the film.

## Film Thickness

Theoretically, film thickness should not affect the intrinsic adhesion at the film–tablet interface, with no influence on adhesion expected after the initial coverage of the substrate. Researchers, however, have found that polymeric film thickness will influence the measured force of adhesion. Rowe (14), for example, showed that for films up to a thickness of 35 μm, increased film thickness resulted in decreased adhesion of an organic-based cellulosic polymer, while films greater than 35 μm in thickness exhibited increased adhesion with increased film thickness. Similar results were reported for aqueous- and organic-based hydroxypropyl cellulose (HPC) (24) and aqueous-based acrylic polymeric films (23).

The effect of film thickness on measured adhesion is thought to be a property of the test method and associated with changes in the stress distribution within the film during the adhesion experiment (14). During the adhesion test, these stresses will either augment or oppose the applied stress and, therefore, influence measured adhesion. Extrapolation of the force of adhesion to a zero film thickness has been suggested by Reegen and Ilkka (30) as a method of minimizing the effects of residual stresses within a film. In most cases, however, a linear relationship between polymer adhesion and film thickness does not occur, and extrapolation of the force of adhesion to zero film thickness, therefore, would be difficult (14,24). Furthermore, measured film thickness is a mean value and does not account for variations in thickness that occur when the polymer is applied to the tablet (14).

## SUBSTRATE VARIABLES

The physical and chemical characteristics of the substrate can significantly influence the adhesive properties of polymeric films. For example, the measured force of adhesion has been shown to be directly related to the square of the diameter of the tablet for flat-faced tablet compacts (15). In addition, the size of the substrate may also affect the error in the data, with higher coefficients of variation in the adhesive force occurring when testing small tablets, due to the difficulties involved in removing the film from the edge of the tablets (15). The following section describes some of the major substrate variables that impact polymer adhesion.

### Surface Roughness

Surface roughness of a tablet and the force of compression used during the tableting process will affect polymer adhesion by altering the effective area of contact between the film coating and the surface of the solid. Above a critical compression force, increased compression pressure during tableting generally results in decreased adhesion, as a smoother tablet is produced. Below a critical compression pressure, cohesive failure of the tablet will occur, where the tablet laminates rather than the film being separated from the tablet surface. This type of failure occurs when the intermolecular bonding forces between the film and the tablet surface are stronger than the bonds between the powdered particles within the tablet (23). In contrast, adhesive failure of film-coated tablets will result in the coating being completely removed from the tablet surface with a minimal amount of powdered particles attached. In order to study film–tablet adhesion, the experimental parameters should be designed such that failure of the film is adhesive in nature (15,23). Data from cohesive failure should not be compared to data from adhesive failure, due to the different forces that are involved in these processes.

In a study involving an aqueous-based acrylic polymeric dispersion, Felton and McGinity (23) demonstrated a relationship between tablet hardness and polymer adhesion. Force–deflection profiles, as seen in Figure 3, show that as the tab-

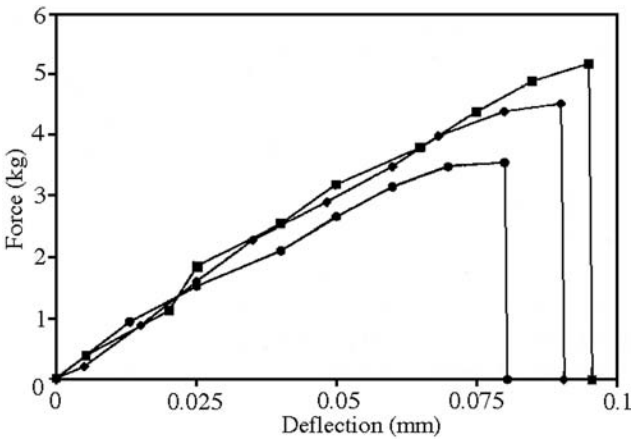


**Figure 3** Force–deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of tablet hardness: (■) 7 kg; (♦) 10 kg; (●) 14 kg. *Source*: From Ref. 23.

let hardness was increased, the force of adhesion, elongation at adhesive failure, and the adhesive toughness of the acrylic polymer decreased.

The softer tablets possessed a relatively rougher surface, as evidenced by a higher arithmetic mean and root-mean-square roughness. The rougher surfaces of the tablet provided greater interfacial contact with the polymeric film, thus resulting in stronger polymer adhesion. Using a peel test, Nadkarni et al. (1) also found that the compressional force used during tableting influenced the adhesion of poly(methyl vinyl ether/maleic anhydride). Using contact angles between the polymeric solution and the tablet surface, these researchers showed that rougher tablets were more readily wetted by the polymeric solution.

In addition to surface roughness, tablet porosity can influence polymer adhesion. Polymeric films are generally applied to solid dosage forms using a spray atomization technique, and the water in the atomized droplets causes dissolution of the outermost surface of the tablet (26,31). The rate and depth of polymer solution/dispersion penetration will influence the interfacial contact between the polymer and the tablet, with the more porous tablet allowing faster penetration of the polymeric solution (15). Moreover, drugs and excipients from the tablet can physically mix with the coating (26,31) and affect the adhesive, mechanical, and drug-release properties of the polymer (23,32,33).

## Tablet Excipients

Adhesion between a polymer and a substrate is due to the intermolecular bonding forces. For pharmaceutical products, hydrogen bond formation is the primary type of interfacial contact between the film and the tablet surface (7). Excipients used

in tablet formulations can alter the chemical properties of the tablet surface, thus influencing polymer adhesion. Sustained-release wax matrix tablets, for example, are generally difficult to coat with aqueous polymeric dispersions due to the poor wettability of the hydrophobic tablet surface (34).

The influence of direct-compression filler excipients on adhesion of organic-based hydroxypropyl methylcellulose (HPMC) films was investigated by Rowe (2). Polymer adhesion was found to be strongest when microcrystalline cellulose (MCC) was used in the tablet compacts. The interaction between the primary and secondary hydroxyl groups of HPMC and MCC was greater than with other excipients studied, including sucrose, lactose, and dextrose, due to the saturation of the tablet surface with hydroxyl groups (35). Lehtola et al. (22) found similar results with aqueous-based HPMC. HPMC phthalate was also found to adhere more strongly to MCC tablet compacts than tablets containing lactose or calcium phosphate (26).

Lubricating agents used in tablet formulations may influence polymer adhesion by presenting surfaces consisting of mainly nonpolar hydrocarbon groups, and the extent of the effect is dependent on the nature and concentration of the lubricant. Rowe (2) showed that increased concentrations of stearic acid, a commonly used lubricating agent that has a free polar carboxyl group, improved adhesion of an organic-based cellulosic polymeric film, as shown in Figure 4A.

When this group was combined with glycerol to form the glyceryl esters present in hydrogenated castor oil and vegetable stearin, polymer adhesion decreased, as seen in Figure 4B. Similar results were reported by Lehtola et al. for aqueous-based HPMC films (22). More recently, Felton and McGinity (23), investigating an aqueous-based acrylic polymer, found that adhesion decreased

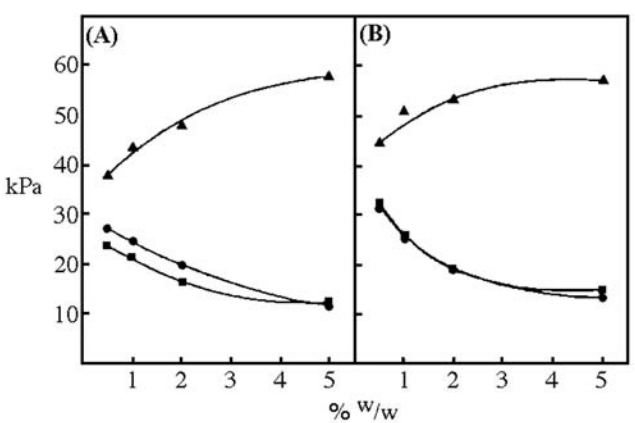


**Figure 4** The effect of lubricant concentration (% w/w) on the measured adhesion (kPa) of hydroxypropyl methylcellulose films: (**A**) Pharmacoat® 606; (**B**) Methocel® 60HG viscosity 50; (▲) stearic acid; (●) magnesium stearate; (■) calcium stearate. Source: From Ref. 2.

when the concentration of the hydrophobic filler hydrogenated castor oil was increased in tablet compacts.

### Adhesion to Capsules

Difficulties reported in the film coating of hard gelatin capsules have been attributed to the physical properties of the gelatin and the dosage form itself (36). In addition to the capsule shell softening and becoming sticky during the coating process due to solubilization of the gelatin, poor adhesion of the polymer to the walls of the hard gelatin capsule may occur. Insufficient adhesion may result in splintering of the film coating. The capsule shell is relatively smooth and generally provides less surface area for interfacial contact between the polymer and the surface of the gelatin than tablet compacts (37,38). The addition of polyethylene glycol (PEG) 400 and PEG 6000 to the coating formulation has been used to improve adhesion of polymeric films to the gelatin shell (36). An aqueous–alcoholic solution has also been shown to enhance polymer adhesion to capsule shells (38). Several studies suggest that hard-shell cellulosic capsules have a relatively rougher surface than the gelatin capsule and thus can provide better film adhesion (39,40).

Felton et al. (17) conducted diametral compression experiments on film-coated soft gelatin capsules and found that adhesion of an aqueous-based acrylic polymer was dependent on the fill liquid of the capsule in conjunction with the plasticizer used in the coating formulation. Good polymer adhesion resulted, as evidenced by single-point failure during compression of the coated capsules (5,18), when triethyl citrate (TEC) was incorporated into the coating formulation, regardless of the fill liquid. When the more hydrophobic plasticizer tributyl citrate (TBC) was added to the coating formulation, polymer adhesion was dependent on the fill liquid of the soft gelatin capsule, with better adhesion occurring with the hydrophobic Miglyol® 812 (Sasol GermanyGmbH, Witten, Germany) fill liquid compared to the hydrophilic PEG 400.

## COATING VARIABLES

Since the strength of adhesion between the film and substrate surface is dependent on the number and type of interfacial interactions, different polymers will exhibit different adhesive properties, depending on their chemical structures. In addition to the polymer itself, film-coating formulations generally include a solvent, a plasticizing agent, an antiadherent, and pigments, all of which may also influence polymer adhesion. The following section describes some of the major coating formulation components that impact polymer adhesion.

### Solvents

The solvent used in a film-coating formulation will interact with the polymer and affect the random coil structure of the polymer chains. It is generally accepted that

the greater the polymer–solvent interaction, the greater the end-to-end distance, thus exposing more of the polymer which is capable of interacting with and binding to the surface of the solid. Nadkarni et al. (1) suggested that the solubility parameter of the solvent be used as a qualitative measure of the extent of polymer solvation, with greater polymer solvation resulting in greater film–tablet adhesion. A good correlation between the cohesive energy density of the solvent and the peel strength of methyl methacrylate films coated on a tin substrate was found by Engel and Fitzwater (41). In 1988, Rowe (42) developed equations using solubility parameters of tablet excipients and polymers to predict trends in film–tablet adhesion.

Early research on film–tablet adhesion focused primarily on organic-based cellulosic films, and several studies have been published on the effects of solvent systems used in the coating formulation on polymer adhesion. Wood and Harder (21) used contact angle measurements, as an indication of surface wettability, to predict polymer adhesion. Fung and Parrott (6) compared the force of adhesion of HPC films prepared from several solvent systems and found that the force of adhesion varied twofold. Adhesion of films prepared from an aqueous-based system was one-fourth to one-half that of the organic-based films. These results further emphasize the importance of polymer–solvent interaction, since it is the polymer that must interact with and bind to the substrate.

## Additives in the Coating Formulation

### Plasticizers

Plasticizers are included in film-coating formulations to improve the mechanical and film-forming properties of the polymers (43–45). Several studies have focused on the effects of plasticizing agents on the adhesive properties of polymers. Felton and McGinity (46) investigated the influence of plasticizers on the adhesive properties of an acrylic resin copolymer to both hydrophilic and hydrophobic tablet compacts. Increasing the concentration of the hydrophilic plasticizer TEC in the coating formulation from 20% to 30% caused a slight, insignificant decrease in the force of adhesion. These results are in agreement with those of Fisher and Rowe (15), who found only slight, insignificant decreases in the measured force of adhesion between organic-based HPMC films and tablet compacts when the concentration of propylene glycol was increased from 10% to 20%. Felton and McGinity (46) showed that the plasticizer concentration also influences the elongation at adhesive failure. Moreover, these researchers demonstrated a relationship between the adhesive and mechanical properties of the acrylic polymer and suggested that the elongation at adhesive failure and the adhesive toughness of the polymer in conjunction with the force of adhesion provided a more complete understanding of the mechanisms involved in polymer adhesion.

Felton and McGinity (46) further investigated the effects of hydrophilic and hydrophobic plasticizers on polymer adhesion and found a relationship between adhesion and the glass transition temperature ($T_g$) of the film, with stronger adhesion occurring when the $T_g$ of the film was lower, as shown in Table 1.

**Table 1** Influence of the Plasticizer in the Coating Formulation on the Force of Adhesion and the Glass Transition Temperature ($T_g$) of an Acrylic Resin Copolymer to Lactose-Containing Tablets

| Plasticizer | Force of adhesion (S.D.) | $T_g$ (S.D.) |
|---|---|---|
| Triethyl citrate | 4.85 kg (0.27) | 36.5°C (1.1) |
| Polyethylene glycol 6000 | 4.32 kg (0.25) | 38.6°C (2.5) |
| Tributyl citrate | 3.81 kg (0.30) | 51.2°C (2.2) |
| Dibutyl sebecate | 3.48 kg (0.33) | 62.0°C (3.6) |

*Source*: From Ref. 3.

The water-soluble plasticizers, TEC and PEG 6000, lowered the $T_g$ of the films to a greater degree than the hydrophobic plasticizers, TBC, and dibutyl sebecate, and films containing the hydrophilic plasticizers exhibited stronger adhesion. The researchers attributed these findings to the extent of the polymer–plasticizer interactions and the effectiveness of the plasticizing agent in lowering the internal stresses within the film coating. The addition of plasticizing agents to coating formulations generally decreases the internal stresses within the film by decreasing both the elastic modulus ($E$) and the glass transition temperature ($T_g$) of the film coating (11,47,48).

The influence of plasticizers in the coating on adhesion to hydrophilic and hydrophobic tablet compacts was also investigated (46). Adhesion of the films

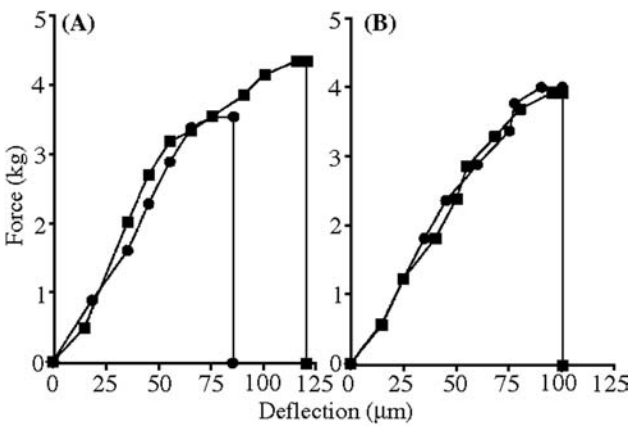


**Figure 5** Force–deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of plasticizer type and tablet hydrophobicity: (**A**) 20% (w/w) polyethylene glycol 6000; (**B**) 20% (w/w) tributyl citrate; (■) 0% hydrogenated castor oil in tablet core; (●) 30% hydrogenated castor oil in tablet core. *Source*: From Ref. 46.

plasticized with PEG 6000 was found to be significantly influenced by the hydrophobicity of the tablet surface, as shown in Figure 5A.

These findings are in agreement with previous research showing that increasing tablet hydrophobicity decreased adhesion of both cellulosic and acrylic polymers (2,23). Interestingly, when TBC was incorporated into the coating formulation, no significant differences in the adhesive properties of the acrylic film were found, as seen in Figure 5B. Furthermore, these findings were correlated with thermomechanical data, where the $T_g$ of the films plasticized with PEG 6000 was dependent on tablet hydrophobicity, while the amount of wax in the tablet core was not found to affect the $T_g$ of the TBC-plasticized polymer.

### Pigments and Fillers

Conflicting reports have been published on the influence of fillers or pigments on polymer adhesion to various substrates. Adhesion of ethylcellulose films cast on aluminum surfaces decreased with the addition of chalk, whereas the incorporation of talc into cellulosic films improved polymer adhesion (49). The addition of titanium dioxide and ferric oxide to methyl methacrylate films sprayed onto polymeric and tin substrates had no effect on adhesion, while mica and talc were found to decrease adhesion (41). Okhamafe and York (4) suggested that the effects of additives in coating formulations were dependent on the balance between their influence on the internal stress of the film coating and the strength of the film–tablet interface.

Several studies have investigated the influence of talc in coating formulations on the adhesion of polymers to tablet compacts. Talc is a hydrophobic substance that is generally added to the coating formulation to reduce the tackiness of the lacquer during the coating process. Talc has been found to decrease the adhesion of polymers to tablet compacts (4). The hydrophobic particles become embedded within the polymeric film and interfere with hydrogen bond formation between the tablet surface and the film coating. In addition, talc causes a stiffening of the film and increases the internal stresses within the polymer, as evidenced by an increase in the $T_g$ of the polymer (50,51).

Pigments commonly used in pharmaceutical systems include aluminum lakes of water-soluble dyes, opacifiers such as titanium dioxide, and various inorganic materials including the iron oxides. Pigments differ significantly in their physical properties, including density, particle shape, particle size, and morphology, and these differences contribute to the complex relationship with aqueous film coatings (52–54). In addition to affecting the mechanical properties of films, the incorporation of pigments into coating formulations has also been found to influence polymer adhesion. Fisher and Rowe (15), for example, found a 45% reduction in the force of adhesion of HPMC films with the addition of 10% titanium dioxide to the coating formulation. Okhamafe and York (50) showed that increased concentrations of titanium dioxide produced an increase in the $T_g$ of HPMC films, which the authors attributed to the restriction in the mobility of the polymer chains by the presence of the additives.

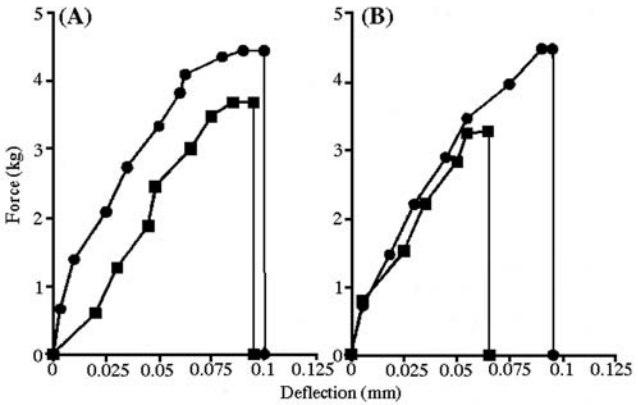


**Figure 6** Force–deflection profiles obtained from butt adhesion experiments of aqueous-based Opadry® and Opadry® II as a function of tablet hydrophobicity: (**A**) 0% hydrogenated castor oil in tablet core; (**B**) 30% hydrogenated castor oil in tablet core; (■) Opadry; (●) Opadry II. *Source*: From Ref. 3.

Felton and McGinity (55) conducted a study that compared the adhesive properties of Opadry® and Opadry® II, two complete HPMC film-coating systems commercially available from Colorcon (West Point, Pennsylvania, PA). The Opadry II product was formulated with maltodextrins to achieve better adhesion, especially to hydrophobic substrates. Indeed, the addition of the maltodextrins to the cellulosic coating system enhanced polymer adhesion to both hydrophilic and hydrophobic tablet compacts, as shown in Figure 6.

### Surfactants

Previous researchers have used the wettability of a tablet by a polymeric solution as a tool to predict the strength of film–tablet adhesion (1,56). A polymer solution that spreads more readily across the tablet surface allows for more interactions with the polymer chains and the formation of a greater number of bonds. Many of the polymeric materials commercially available today, however, are formulated as aqueous-based dispersions. Since it is the polymer, not the solvent, that interacts with and adheres to the tablet surface, wettability by polymeric dispersions may not be a valid indicator of film–tablet adhesion.

Surfactants have been incorporated into polymeric solutions to improve the spreadability of the coating across the tablet (57), emulsify water-insoluble plasticizers in aqueous dispersions (47,58), and modulate drug release (59,60). Felton et al. used surfactants to alter tablet wettability by polymeric dispersions (61). While the contact angle between the polymer dispersion and the tablet surface was dependent on the type and concentration of the surfactants added to the

coating formulation, no correlation between tablet wettability and polymer adhesion was found.

## PROCESSING PARAMETERS AND COATING CONDITIONS

The magnitude of internal stresses that inevitably develop during the coating process is dependent upon the interrelationship between many parameters involving both the polymeric coating material and the core substrate (12). These stresses include stress due to shrinkage of the film upon solvent evaporation, thermal stress due to the difference in the coefficient of thermal expansion of the substrate and polymer, and volumetric stress due to the swelling or contraction of the substrate (8). Processing parameters may influence the development of these stresses. Okutgen et al. (62), for example, determined the dimensional changes in tablet cores as a function of temperature, simulating temperature variations that tablets generally undergo during the coating process. Tablets containing Avicel® (FMC Biopolymer, Philadelphia, Pennsylvania) maize starch, and Starch® 1500 (Colorcon, West Point, Pennsylvania) all contracted when exposed to elevated temperatures and expanded during the cooling phase, while Emcompress® (JRS Pharma, Patterson, New York) tablets exhibited the opposite behavior. These dimensional changes in the tablet core will influence the internal stresses within the films of the final coated products and may ultimately affect polymer adhesion. Selection of tableting excipients and polymeric coating materials with similar coefficients of thermal expansion should minimize internal stresses within the film and could improve polymer adhesion (11).

The process of film formation from polymeric dispersions requires the initial deposition of the atomized polymer droplets onto the substrate surface, followed by evaporation of the water, and subsequent coalescence of the polymer chains. The time necessary to form a completely coalesced film has been shown to be dependent on the temperature used during the coating process, the nature and concentration of the plasticizer incorporated into the coating formulation, and the postcoating storage temperature (63,64). Many commercially available polymeric materials for pharmaceutical film-coating operations require a postcoating thermal treatment or curing step to obtain a fully coalesced film, and this postcoating drying has also been shown to influence adhesion as well as the thermomechanical properties of the film (65). Storage at elevated temperatures was found to increase the force required to separate an acrylic film from the tablet surface, with adhesion equilibrated within four hours of storage at 40°C or 60°C (65). These findings were attributed to an increased number of polymer–substrate interactions resulting from the coalescence of the film. As the solvent evaporates during curing, the polymer droplets coalesce, and the number of potential polymer–substrate binding sites increases, as shown in Figure 7.

In addition to processing temperature and postcoating curing, the spray rate will influence the extent of surface dissolution of the substrate and subsequent interfacial mixing at the film–tablet interface (31). As mentioned previously, surface dissolution and physical mixing at the interface allows for drugs or excipients

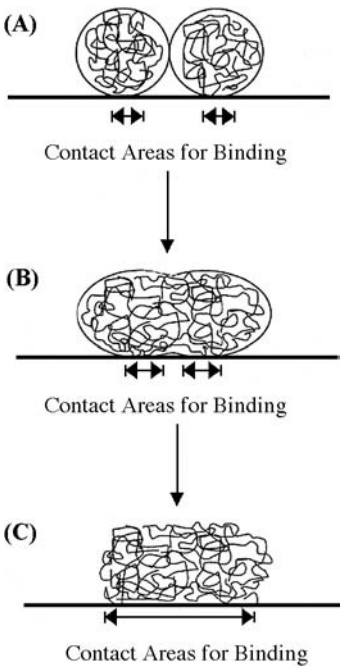


**Figure 7** Schematic of the increase in potential polymer–substrate interactions as film formation proceeds: (**A**) closely packed polymer spheres due to water evaporation; (**B**) initiation of coalescence and polymer chain interdiffusion due to additional water evaporation; (**C**) completed film formation. *Source*: From Ref. 65.

in the tablet to migrate into the film (31), which can influence internal stresses and thus affect polymer adhesion.

## Influence of Aging and Storage Conditions on Polymer Adhesion

Exposure of coated solids to various temperatures or relative humidities can influence the internal stresses within a film coating and thus affect polymer adhesion. Okhamafe and York (4), for example, showed that adhesion of pigmented and nonpigmented cellulosic films decreased during storage at 37°C and 75% relative humidity (RH). In another study, two weeks of storage at high RH (93%) caused a decrease in adhesion of an acrylic polymer to lactose tablets (46). These findings were attributed to increased internal stresses in the polymeric films due to differences in the expansion coefficient of the polymer and tablet, and volumetric stresses due to the swelling of the tablet core. Although previous researchers have demonstrated that water functions to plasticize polymers (66,67), the swelling of the film and the tablet as water diffuses through the coating during storage weakened the film–tablet interfacial bonding and created new stresses within the polymer.

Felton and McGinity (46) also reported decreased film–tablet adhesion after three months of storage at 0% RH. These findings were attributed to increased internal stresses within the coating due to evaporation of residual water in the polymeric film. Three months of storage at 40°C resulted in no significant change in the measured force of adhesion, with only small decreases in the elongation at adhesive failure and adhesive toughness. The authors suggested that, since the tablets were stored at a temperature above the $T_g$ of the film, the polymer chains were more mobile (68) and positioned themselves to minimize internal stresses.

Decreased adhesion between a polymeric film and a capsule shell has been reported to occur during the storage of film-coated hard gelatin capsules at high humidity (36). The film coating and the gelatin swell to varying degrees and affect the internal stresses within the film. In another study involving film-coated soft gelatin capsules (17), storage at high humidity was found to improve adhesion of an acrylic polymer plasticized with TBC to the capsule containing PEG 400 as the fill liquid. The authors theorized that the fill liquid from the capsule may migrate into the film coating, functioning to further plasticize the polymer and lower the internal stresses of the film.

## CONCLUSIONS

Although good adhesion between a polymer and the surface of a solid is desirable for a pharmaceutical product, limited research on polymer adhesion has been conducted on systems of pharmaceutical interest. The two major forces that influence adhesion are the strength of the interfacial bonds and the internal stresses within the film. Factors that influence interfacial bonding or internal stresses will therefore affect polymer adhesion. Rougher, more irregular surfaces provide greater interfacial contact between the film and the tablet surface and generally provide for better adhesion. Excipients used in the substrate can also influence the extent of interfacial bonding between the polymeric film and the solid. Additives in the coating formulation, including the solvent system, plasticizer, and pigments, influence internal stresses and thus alter polymer adhesion. Processing parameters used during coating may also affect adhesion. Although many variables have been found to influence polymer adhesion, and direct comparison of the numerical values from one study to another is not practical, further experimentation involving adhesion of polymeric films to solid substrates will provide the pharmaceutical scientist with a better understanding of the mechanisms involved in polymer adhesion.

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# 7

# Influence of Coloring Agents on the Properties of Polymeric Coating Systems

**Nasser N. Nyamweya**

*Pharma Polymers, Degussa, Piscataway, New Jersey, U.S.A.*

**Stephen W. Hoag**

*School of Pharmacy, University of Maryland, Baltimore, Maryland, U.S.A.*

## INTRODUCTION

Coloring agents are widely used in the pharmaceutical industry and are an important component of many oral solid dosage forms. A coloring agent, or colorant, may be defined as an excipient that imparts color when added to a drug product. Colorants may be incorporated into solid dosage forms by adding them directly to the dosage form (e.g., adding a colorant to a tablet granulation); incorporating the colorant into capsule shells; or adding the colorant to a coating formulation that would be applied onto the surface of a drug product. Coloring agents may be added to pharmaceutical coatings for a number of reasons including the following:

1. To enhance product appearance, esthetic appeal, and product elegance
2. To improve or facilitate product identification for the manufacturer, healthcare professional, and patient
3. To provide protection from light for photosensitive compounds
4. To provide a brand image and help differentiate the drug product from competitive products
5. To help reduce or prevent counterfeiting

Although coloring agents do not provide any direct therapeutic effects, by improving the appearance of the drug product, they can contribute to increasing patient compliance. The use of coloring agents helps to provide drug products

with a distinct appearance, which makes it easier for the pharmacist and patient to distinguish between different drug products, thereby reducing the possibility of dispensing and medication errors. Patients taking several different medications will find them easier to distinguish if they have different colors. A unique appearance also contributes to enhancing the brand image of a drug product, which may provide a significant marketing advantage over competitive products. In combination with other factors that can be used to increase the uniqueness of the drug product, such as shape and markings, the addition of color can help to make it more difficult to counterfeit drug products.

Since certain terms for colorants are sometimes used interchangeably, it is important to first provide definitions for the terms "dyes" and "pigments," as they appear in this chapter. The term "dye" applies to colorants that are soluble in water, while the term "pigment" applies to colorants that are insoluble in water. The same terms can also be applied to colorants added to nonaqueous liquids. The coloring power of a dye results from the dye molecules being dissolved, while that of pigments is due to dispersion of the pigment particles. The most commonly used colorants in film-coating applications are aluminum lakes, iron oxides, and titanium dioxide. Dyes are also used in some cases, although this would usually be in combination with an insoluble colorant.

The visual observation of color requires the following components:

1. A light source (e.g., sunlight)
2. An object (e.g., a red film-coated tablet)
3. An observer

Light is a form of electromagnetic radiation and is characterized by its wavelength. The visible light that is observable by the human eye has wavelengths between about 380 and 780 nm (1). Coloring agents impart color by selectively absorbing and reflecting certain wavelengths of light within this region. For example, in the case of a tablet that appears red under white light, the colorant in the film coating would predominantly absorb the blue and green wavelengths while the red wavelengths would primarily be reflected from the surface of the tablet (Table 1).

The eye, which contains light-sensitive receptors, would detect the reflected red wavelengths and send a signal to the brain, which would interpret the color of the coated tablet to be red. In addition to absorbance and reflection, light may be transmitted through an object, as in the case of a transparent film. Films that do not transmit or transmit very little light are opaque. In translucent films, some light is transmitted while some light is reflected by scattering.

The color of organic dyes results from the select absorption of certain wavelengths of light by chromophores. Chromophores are the part of a molecule responsible for light absorption and hence the color observed. For organic dyes, these moieties include conjugated double bonds common to functional groups such as carbonyl, azo, and ethenyl (3). The absorption of light by chromophores can be enhanced or modified by chemical groups called auxochromes. Examples of auxochromes include amino, alkylamino, methoxy, and hydroxyl groups (3).

**Table 1** Absorbed Colors and Complementary Colors at Different Absorption Wavelengths

| Wavelength (nm) | Color of absorbed light | Complementary color |
|---|---|---|
| 400–420 | Violet | Yellow-green |
| 420–450 | Indigo blue | Yellow |
| 450–490 | Blue | Orange |
| 490–510 | Blue-green | Red |
| 510–530 | Green | Purple |
| 530–545 | Yellow-green | Violet |
| 545–580 | Yellow | Indigo blue |
| 580–630 | Orange | Blue |
| 630–720 | Red | Blue-green |

*Source*: From Ref. 2.

With both inorganic and organic pigments, color arises from absorbed light producing electronic transitions. Electronic transitions in inorganic pigments involve the bonding between transition metal ions and the surrounding geometrical arrangement of molecules or ligands (3). In addition to the chemical composition, the color of pigments may also be influenced by physical properties such as particle size and particle size distribution. Pigment particles can also scatter and reflect light, thereby influencing the opacity of the film coating (3).

## COLORING AGENTS USED IN FILM COATING

### Dyes

The dyes typically used in pharmaceutical applications are synthetic compounds, which are more stable and available in a wider range of colors than natural dyes. A range of colors are available, including blue, green, orange, red, and yellow. In addition to their common names, the dyes used in oral dosage forms may be labeled as FD&C (certified for use in food, drugs, and cosmetics) or D&C (certified for use in drugs and cosmetics), a designation given by the U.S. Food and Drug Administration (FDA). The certification refers to the testing of a colorant by the FDA to ensure that it meets identity and purity specifications. The stability of a dye may be affected by heat, light, pH, oxidizing agents, and reducing agents, although some dyes are more stable than others to the effects of these factors.

### Pigments

#### Aluminum Lakes

Aluminum lakes are produced by precipitating and adsorbing a water-soluble dye onto a water-insoluble substrate, typically aluminum hydroxide (4). The chemical bonding of the dye to the aluminum hydroxide substrate results in improved

stability to light and heat. The exact nature of the adsorption process is not well understood, but it is believed to be a combination of ionic bonding, hydrogen bonding, and van der Waals forces (5). The nomenclature of lakes includes the name of the dye and the substrate (e.g., Sunset Yellow or FD&C yellow no. 6 aluminum lake). Lakes are insoluble in water within a certain pH range. Lakes are available in several colors and shades, depending on the type and amount of dye used. Common lake colors include blue, orange, red, and yellow. Additional colors or shades may be obtained by mixing two or more lakes of different colors. The amount of dye in a lake may range from 3% to 60% (6).

### Iron Oxides

Iron oxides are available in the colors black ($Fe_3O_4$), red ($Fe_2O_3$), and yellow ($Fe_2O_3.H_2O$). They are prepared by the precipitation of iron salts (black and yellow iron oxides), by calcination (red iron oxide), or by blending different iron oxides (brown iron oxide) (7). Iron oxides do occur naturally, but synthetic forms of iron oxides are used predominantly due to their higher quality and the difficulties involved in purifying the natural forms (7,2). Iron oxides have excellent light and heat resistance (8).

### Titanium Dioxide

Titanium dioxide is a white pigment widely used to make films opaque or increase their opacity. Opacity is the degree to which a film containing a pigment can obscure the appearance of a substrate to which the film is applied (2). The opacifying effect of titanium dioxide is due to its high refractive index, which results in the scattering of visible light. The range of light that is scattered can be varied by changing the particle size (9). The optimal particle size for scattering visible light is 200 to 300 nm, when the particle size is about half the wavelength of visible light. Titanium dioxide is manufactured using naturally occurring minerals such as ilmenite ($FeO\text{-}TiO_2$) and rutile, although the latter is less abundant (2). Titanium dioxide has different polymorphic forms of which rutile and anatase are the most commonly used commercial forms. The rutile form has a higher density and refractive index, but the anatase form is softer and less abrasive (10). When titanium dioxide is used in combination with iron oxides or lakes, it tends to produce pastel shades due to its extreme whiteness. Titanium dioxide has excellent heat and light stability.

### Talc

Talc is commonly used as an antiadherent or detackifier in film-coating formulations. Although talc may often not be thought of as a coloring agent because of its antiadherent function in film coating, it does have a white to grayish-white color and is listed as a color additive in the U.S. Code of Federal Regulations (11). Talc is a natural mineral and its composition and physical properties may vary depending on the location where the talc is mined and the method by which it is processed. It is a hydrated magnesium silicate [$(Mg_3SiO_4O_{10}(OH)_2$], which may contain small amounts of aluminum silicate, aluminum and iron oxides, calcium

carbonate, and calcium silicate, depending on the country of origin (12). Lin and Peck characterized several different United States Pharmacopoeia talc grades and found variations in physical properties such as particle size and surface area (13). Talc is a relatively soft mineral and is hydrophobic in nature.

#### Pearlescent Pigments

Pearlescent pigments are pigments that impart a shiny, pearl-like luster when incorporated into film coatings. These pigments are available in a variety of colors including blue, gold, green, red, and silver (14). They are prepared by coating mica (potassium aluminum silicate) platelets with titanium dioxide and/or iron oxide, creating a multilayered structure. Incident light undergoes multiple reflection and refraction when transmitted through a coating containing these pigments, resulting in the pearlescent visual effect.

### Regulation of Coloring Agents

The use of coloring agents in drug products is regulated by local or regional regulatory agencies, and many individual countries have lists of approved colorants. Some colorants, such as iron oxides, are widely accepted globally. Daily intake or usage limits may apply, depending on the specific type of pigment. Since regulations on the use of colorants can vary considerably between different countries, drug product manufacturers need to be cognizant of these regulations when developing formulations for international markets (15). Drug product manufacturers should also work with their color suppliers to determine whether the colorant being used will meet the regulatory requirements in the countries where the drug product will be marketed. For further information on the regulation of coloring agents, the reader is referred to Ref. (6).

## PROPERTIES OF COLORING AGENTS

### Dyes

The solid state properties of a dye (e.g., particle size, surface area, and density) are usually not as important in film-coating applications as they are for pigments because dyes are used in coating formulations after dissolving them in liquid media. Dyes can therefore be distributed in film coatings at the molecular level, while in contrast, pigments exist as much larger undissolved particles. Although smaller size is an advantage in terms of producing a more pronounced and intense coloring effect, the use of dyes in film coating has been limited due to a tendency for the dye molecules to migrate with the evaporating solvent during drying. This migration results in an uneven distribution of color and a mottled film coating. Recently, Signorino and Meggos developed uniform, nonmottled coating formulations using dyes with the addition of immobilizing agents (16,17). The use of dyes is also limited by their lower stability compared to pigments with regard to factors such as pH, light, and heat, which can result in changes in the appearance or color fading of coated products.

## Pigments

Pigments are preferred in most film-coating applications since they are insoluble and do not migrate with the evaporating medium during coating, which results in a more uniform color distribution and batch-to-batch control of the film-coating color. Pigments may be characterized by a number of physical tests, including particle size, surface area, morphology, density, refractive index, and surface charge in aqueous media. Table 2 compares selected physical properties for various pigments.

The particle size of a pigment can affect the distribution of color in the film coating, sedimentation in liquids, and the surface roughness of the film coating. Because pigments are insoluble colorants, the color they produce is dependent on how well they are dispersed. Rowe investigated the effect of particle size of red iron oxide on the appearance of hydroxypropyl methylcellulose films and observed significant changes in color with different pigment particle sizes (20). Wou and Mulley studied the influence of the particle size of several aluminum lakes and reported significant differences in color, depending on the degree of pigment dispersion (21). A reduction in lake particle size was observed to result in an increased color strength, with submicron particles having the greatest effect on color strength. In order to achieve adequate dispersion of pigments in powder form, high-shear mixing equipment is often recommended to ensure that agglomerates are broken down and that a uniform color distribution results. An alternative to using pigments in powder form is to use predispersed pigment concentrates (suspensions) (22,23). These color concentrates may contain more than one pigment or may use pigments in conjunction with dyes.

The density of a pigment particle affects its sedimentation rate, especially in coating solutions or dispersions that have a low viscosity. In colloidal polymer

**Table 2** Selected Physical Properties of Pigments Used in Film-Coating Applications

| Pigment | Particle size (μm) | Surface area ($m^2/g$) | Density ($g/cm^3$) | Morphology |
|---|---|---|---|---|
| Aluminum lakes (dye content) | | | | |
| FD&C Blue no. 2 (36.3%) | 2.24 | 19.45 | 1.94 | Irregular |
| FD&C Red no. 40 (38.0%) | 1.96 | 21.69 | 1.84 | Irregular |
| FD&C Yellow no. 6 (37.4%) | 2.68 | 16.13 | 1.83 | Irregular |
| FD&C Yellow no. 10 (17.8%) | 3.37 | 34.67 | 2.02 | Irregular |
| Iron oxides | | | | |
| Black | 0.5–1 | 3.84 | 4.98 | Cubical |
| Red | 0.32 | 7.56 | 5.41 | Spherical |
| Yellow | 0.5–1 | 13.07 | 4.32 | Acicular |
| Titanium dioxide | 0.2 | 7.60 | 3.78 | Rounded |

*Source*: From Refs. 18 and 19.

dispersions, which typically have low viscosity, commonly used pigments will often tend to settle unless the liquid in which they are dispersed is subjected to flow or mechanical agitation. Approaches to minimizing sedimentation include using pigments with small particle size distributions, ensuring continuous mixing of the coating dispersion, minimizing the length of the tubing used to deliver the coating dispersion to the coating equipment, and using tubing with a smaller internal diameter to help ensure higher liquid flow rates.

Insoluble colorants can acquire a surface charge in aqueous media and develop an electrical double layer around their surface in order for the system to maintain electrical neutrality. In this respect, they have the surface characteristics of a charged colloidal particle. Figure 1 shows the electrical double layer of a negatively charged colloidal particle.

The charged surface attracts ions of an opposite charge (counter-ions), which are strongly bound to the surface of the colloid forming the Stern layer. Beyond the Stern layer, a more diffuse layer of counter-ions is observed due to the repulsive forces from counter-ions in the Stern layer. At the same time, ions with the same charge as the surface of the colloidal particle are seen in the diffuse layer, as the repulsive forces from the surface start to decrease with increasing distance and are increasingly shielded by the presence of counter-ions. At a certain distance from the charged surface, the concentration of both types of ions reaches an equilibrium with the ions in the bulk medium. This distribution of ions and charge in the double layer creates a potential that decreases from the surface of the particle to the bulk medium (Fig. 2).

As the charged particle moves in the medium, it does so with the tightly bound ions of the Stern layer as well as an associated layer of ions. The shear plane is the point beyond which ions in the diffuse layer do not move with

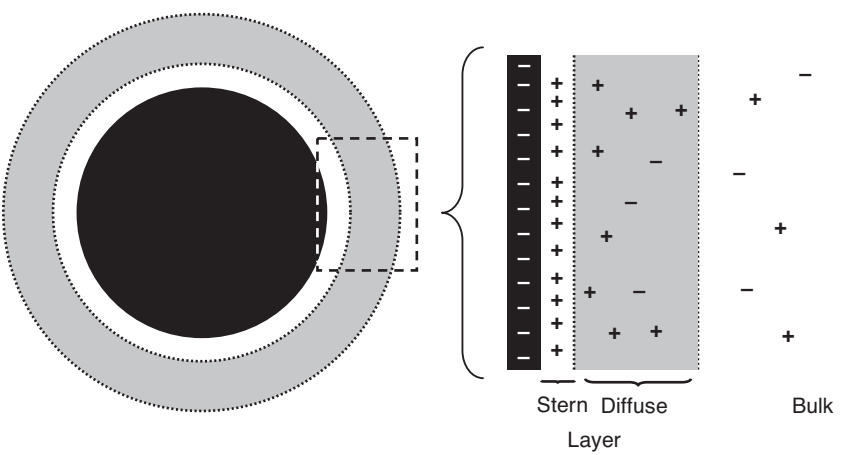


**Figure 1** Electrical double layer of a negatively charged colloidal particle.

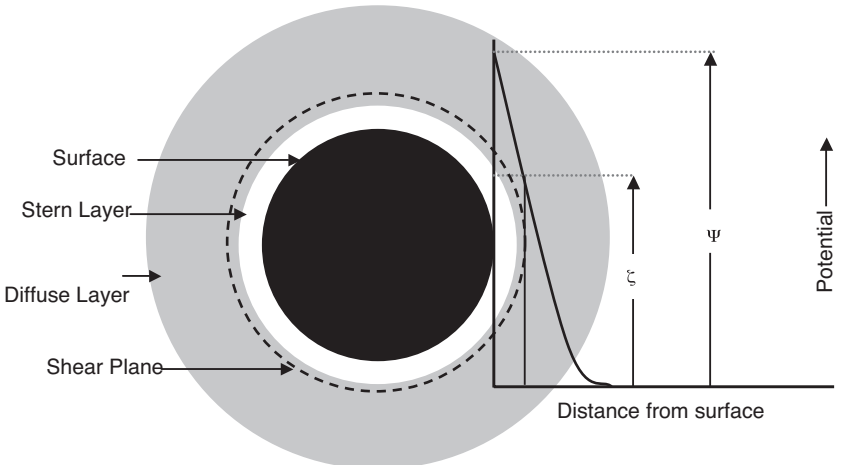


**Figure 2** Change in potential from the surface of a colloidal particle to the bulk medium. *Symbols*: ζ, zeta potential; Ψ, surface potential.

the particle. The potential at the shear plane is the zeta potential, an important determinant of the stability of colloidal particles and how they interact with each other in aqueous media. Factors that decrease the zeta potential, such as ions or electrolytes, will allow colloidal particles to approach each other more closely and increase the likelihood of aggregation or coagulation. The effect of a strong electrolyte on the stability of an aluminum lake is shown in Figure 3,

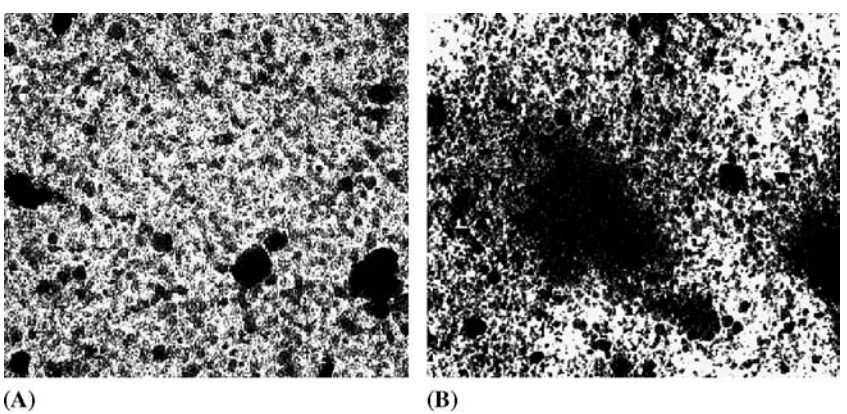


**Figure 3** FD&C blue no. 2 lake photomicrographs after 60 minutes in (**A**) $H_2O$ and (**B**) 1 M KCl.

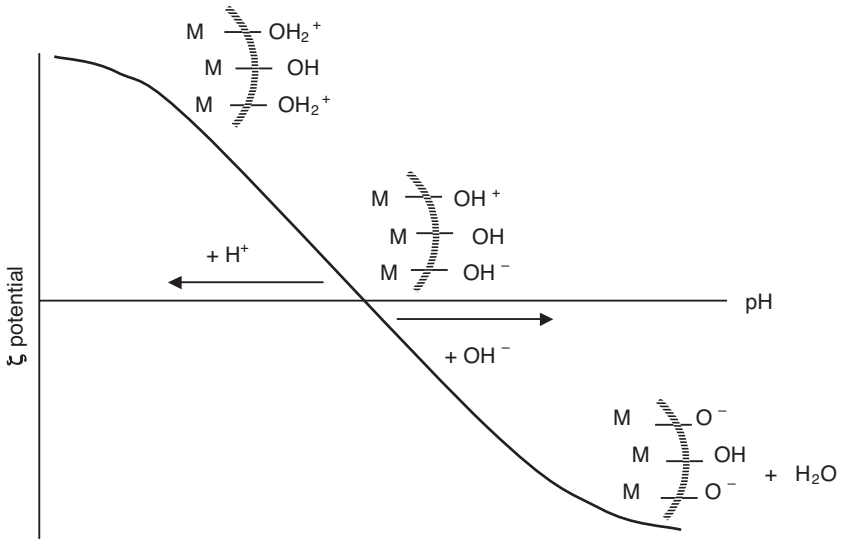


**Figure 4** Influence of pH on the zeta potential of a pigment [metal (M) oxide or hydroxide] in aqueous media.

where the pigment particles are observed to aggregate in a solution of potassium chloride.

For pigments, surface charge may result from and be influenced by the ionization of species on the surface of the pigment and the adsorption of ions from the medium. The surface charge can vary depending on the pH and composition of the system. In the case of metal oxide or hydroxide-based pigments (e.g., iron oxides, titanium dioxide, and aluminum lakes), the surface charge can be influenced by the pH of the medium (Fig. 4).

In fact, the surface charge may be positive or negative depending on the pH of the medium. At a certain intermediate pH value, the pigment particles will have no net charge (referred to as the isoelectric point). At this pH, the particles will be least stable due to the absence of repulsive forces.

In the case of aluminum lakes, pH may also influence the stability of the pigment particles. Although aluminum lakes are generally referred to as water-insoluble colorants, at low or high pH values, dissociation of the lake can occur. Desai et al. characterized the effect of pH on the stability of aluminum lakes in aqueous media (24). The study found that although aluminum lakes were stable in aqueous media at intermediate pH values, at more acidic or basic pH values, the aluminum hydroxide substrate of the lake dissolved, resulting in the release of the adsorbed dye into solution. Similar findings were reported by Nyamweya et al., with the optimal pH stability range being observed to be 4 to 7 (Fig. 5) (18).

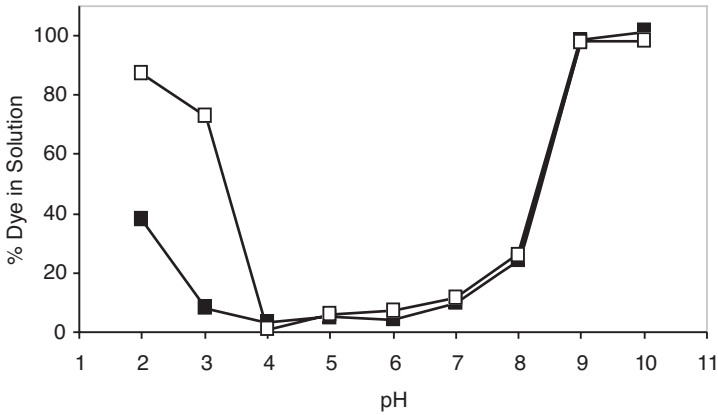


**Figure 5** Effect of pH on the dissolution of an FD&C blue no. 2 aluminum lake after: (■) 1 hour and (□) 24 hours. *Source*: From Ref. 18.

## INFLUENCE OF COLORING AGENTS ON POLYMER COATING DISPERSIONS

### Solution and Colloidal Interactions

The majority of currently used polymer dispersions for film coating are applied in liquid form, in which the film-forming polymer exists in the form of a solution (dissolved polymer molecules) or an aqueous colloidal dispersion. However, there are a number of processes that can be used to apply a coating to a product in a dry state. Examples include compression coating, dry powder coating, and electrostatic coating. It would be expected that in such systems, due to the absence of water or solvents, the potential for interactions between the colorant and the polymer would be much less than for coatings applied in the form of solutions or dispersions.

Film-coating formulations in which the polymer is dissolved may be either aqueous or organic solvent based. In polymer solutions, incorporation of pigments is usually less of an issue with regard to physical stability. Very few studies have characterized the interaction between pharmaceutical polymer solutions and pigments. Gibson et al. studied the interactions between hydroxypropyl methylcellulose and pigments (an aluminum lake, iron oxides, titanium dioxide, and talc) in aqueous solutions of the polymer using immersion calorimetry (25). An exothermic reaction was observed following the immersion of pigments into solutions of the polymer. Sawyer and Reed studied the adsorption behavior of hydroxypropyl methylcellulose onto the surface of oxide particles from aqueous suspensions. The more hydrophilic particles (alumina and silica) with highly hydroxylated surfaces did not adsorb the polymer, while the more hydrophobic talc particles showed a significant adsorption of polymer (26). The authors suggested

that the mechanism for the interaction of the polymer with talc was a hydrophobic interaction where the adsorption of the polymer reduced the free energy of the particle–water interface.

In film-coating formulations in which the polymer is not dissolved, but rather exists in the form of colloidal particles, the physical stability of the dispersion needs to be maintained for a successful film-coating process. Colloidal polymer dispersions were introduced in order to enable the aqueous-based coating of functional polymers (e.g., enteric and sustained-release polymer coatings). The particle size of the colloidal particles is typically in the submicron range. A colloid in this case may be defined as a system comprising a dispersed phase (polymer particles) and a dispersion medium (water). Stable colloidal dispersions can be defined as systems in which the original constituent particles retain discreteness, with no aggregation or agglomeration. The stability of colloidal systems may be affected by a number of factors including the following:

1. The particle size of the colloidal particles
2. The surface charge of the colloidal particles
3. The pH of the dispersion
4. The viscosity of the dispersion
5. The composition of the dispersion (e.g., the presence and concentration of electrolytes, pigments, and water-soluble polymers)

Additionally, the stability of colloidal dispersions may be adversely affected when such systems are subjected to factors such as high shear forces, warm temperatures, and freezing. Instability may be manifested in the form of aggregation or coagulation of the colloidal polymer particles. Colloidal particles have a relatively large surface area and hence a high free energy. Equation 1 shows the relationship between the surface area and the free energy in a latex colloidal system.

$$dG = \gamma dA \tag{1}$$

where $G$ is the free energy, $\gamma$ is the interfacial tension, and $A$ is the surface area. Due to the small particle size and the relatively large surface area of colloidal particles, in the absence of a stabilization mechanism, aggregation would be favored, as it would decrease the surface area and consequently the free energy of the system. Therefore, colloidal systems need to have a stabilization mechanism to prevent aggregation. Colloids can be stabilized by the following processes:

1. *Electrostatic repulsion*: This arises from like particles having a similar surface charge, leading to mutual repulsion.
2. *Steric stabilization*: This arises from adsorbed species (e.g., surfactants), which prevent the particles from aggregating.
3. *Electrosteric stabilization*: This is due to a combination of electrostatic repulsion and steric stabilization.

With colloidal systems, there may be a potential for interaction with colorants, which can lead to coagulation of the dispersion, rendering it unusable for film coating. Aggregated material will not only lead to clogging of the dispersion delivery and spray systems, but it will also hinder the coalescence of colloidal polymer particles and the formation of a uniform film coating.

Depending on the manufacturing process, the polymer, and the composition of the dispersion used for film coating, differential commercial coating products may have different pH values. For example, some film-coating dispersions used in enteric coatings have low pH values, due to the acidic nature of their functional groups. The addition of lakes to acidic dispersions can therefore result in dissociation of aluminum lake pigments. One approach to preventing this type of interaction is to increase the pH of the acidic dispersion to a pH range in which aluminum lakes would not dissociate.

In colloidal systems, the surface charge acquired by the polymer particles plays an important role in the physical stability of the system. Factors that affect the surface charge of the colloidal polymer particles can lead to aggregation or coagulation of the system. The addition of electrolytes or ions to a colloid in sufficient concentrations can affect the surface charge and increase the tendency for coagulation to occur. Nyamweya et al. investigated the effect of adding several dyes to anionic, cationic, and nonionic Eudragit® colloidal polymer dispersions (18). Figure 6 shows the minimum amount of dye required to cause coagulation of the colloidal dispersions (critical coagulation concentration).

The dyes that were studied were all anionic molecules. Differences in the critical coagulation concentrations were observed based on the surface charge of the colloidal dispersion. The authors related these differences to the zeta potential of the polymer dispersions, as shown in Figure 7.

The positively charged Eudragit RS 30 D [poly(ethyl acrylate-co-methyl methacrylate-cotrimethylammonioethyl methacrylate chloride),1:2:0.1] colloidal

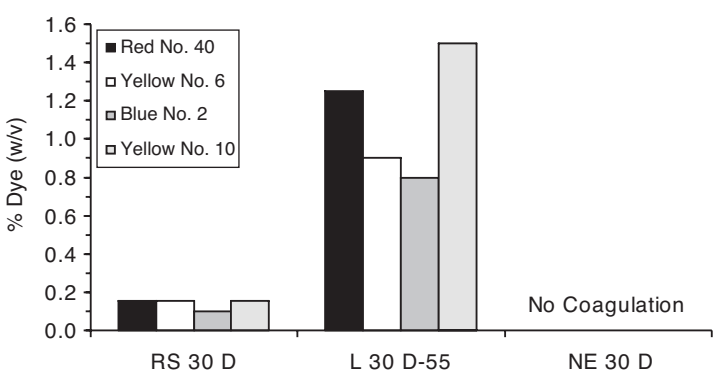


**Figure 6** Dye critical coagulation concentrations for Eudragit® polymer dispersions. *Source*: From Ref. 18.

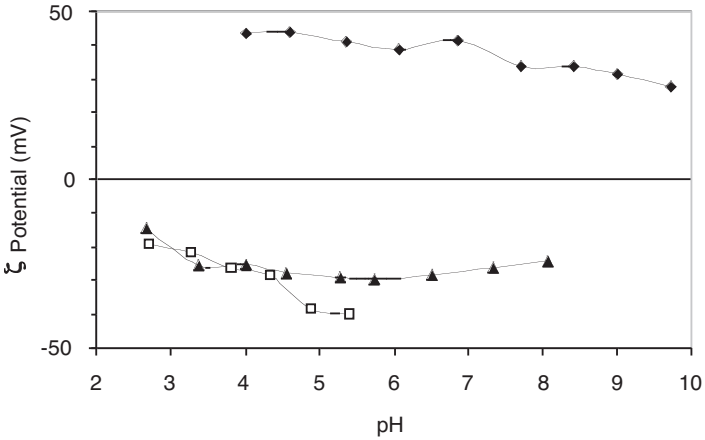


**Figure 7** Zeta potential as a function of pH for Eudragit® L 30 D55 (□), Eudragit RS 30 D (◆), and Eudragit NE 30 D (▲). *Source*: From Ref. 18.

dispersion had the lowest critical dye coagulation concentration. This polymer dispersion is stabilized by electrostatic repulsion arising from cationic quaternary ammonium groups in its structure, which give rise to a positive zeta potential (18). The addition of negatively charged anionic dyes results in neutralization of the stabilizing positive surface charges, leading to coagulation of the polymer dispersion at relatively low dye concentrations. In comparison, higher dye concentrations were required to cause coagulation of the anionic Eudragit L 30 D55 [poly(methacrylic acid-co-ethyl acrylate),1:1] colloidal dispersion, because like the dyes, it is negatively charged. High dye concentrations eventually resulted in coagulation of this polymeric dispersion due to compression of the stabilizing electrical double layer. It was observed that increasing the pH of the polymer dispersion to a pH range of 5.0 to 5.2 enhanced dispersion stability, and stable dispersions with dyes that did not coagulate were prepared. Increasing the pH results in an increased absolute value of the zeta potential (Fig. 7), which makes the polymer more stable in the presence of dyes.

In contrast the nonionic polymer dispersion, Eudragit NE 30 D [poly(ethyl acrylate-co-methyl methacrylate),2:1] was stable, and coagulation in the presence of dyes was not observed. Eudragit NE 30 D is a chemically neutral polymer and has a nonionic emulsifier, nonoxynol 100. The high stability of Eudragit NE 30 D in the presence of dyes was attributed to the steric stabilization of the polymer dispersion.

Interactions between colloidal polymer dispersions with pigments have been reported in the literature. Dangel et al. observed coagulation in methacrylic acid copolymer dispersions following the addition of red iron oxide–based pigment suspensions (27). Similar findings for the same copolymer dispersion were reported by Flößer et al. (28). In both these studies, coagulation was also dependent on the

type of plasticizer used. In the former study, the presence of polyvinylpyrrolidone was a factor in dispersion stability, and the authors reported that the coagulation tendency disappeared when this excipient was not included in the dispersion. In another study, the addition of red iron oxide and iron oxide-pearl luster pigments was also observed to cause coagulation of methacrylic acid copolymer dispersions, which was prevented by the addition of sodium carboxymethylcellulose (29). The authors attributed the enhanced dispersion stability to steric stabilization of the pigments and an increased viscosity from the dissolved sodium carboxymethylcellulose molecules.

Nyamweya et al. studied the interactions between Eudragit RS 30 D, Eudragit L 30 D55, and Eudragit NE 30 D polymeric aqueous dispersions and four aluminum lakes (18). The stability of the polymer–pigment dispersions was studied by microscopy and particle size measurements. The stability of the polymer dispersions in the presence of lakes was found to be dependent on the pH and surface charge of the components. Eudragit RS 30 D dispersions were stable in the presence of all the lakes. The addition of aluminum lakes to Eudragit L 30 D55 resulted in coagulation. The authors attributed the coagulation to the low pH of the dispersion, which resulted in dissociation of the lakes and release of electrolytes, which affected the stabilizing surface charges of the polymer. Increasing the pH of the polymer dispersion to a pH at which the lakes were stable prevented coagulation.

Although the nonionic polymer Eudragit NE 30 D was stable in the presence of FD&C red no. 40 or yellow no. 6 lake, aggregation was observed following the addition of FD&C blue no. 2 or D&C yellow no. 10 lake. The differences in stability between the different lakes were found to be related to their surface charge. Lakes with positively charged surfaces promoted an interaction with the negative surface charges of the polymer. The lakes that did not cause coagulation were found to have a negative surface charge at the pH at which the experiments were performed. It was observed that the unstable dispersions could be stabilized by the addition of surface-active agents to the pigment dispersions prior to adding them to the polymer dispersion.

Ishikawa et al. investigated the colloidal stability of Eudragit L 30 D55, Eudragit RS 30 D, and Eudragit NE 30 D in the presence of yellow iron oxide and titanium dioxide at different pH values (30). Eudragit L 30 D55 was evaluated over a pH range of 2 to 5, while the Eudragit RS 30 D and Eudragit NE 30 D dispersions were evaluated over the pH range of 2 to 11. Stable polymer–pigment dispersions were observed for the Eudragit RS 30 D and Eudragit NE 30 D at all pH values in the presence of either pigment. The Eudragit L 30 D55 dispersion was also stable with either pigment from a pH range of 3 to 5, but coagulated when the pH was lowered to a value of 2. However, aggregation of the polymer dispersion when the pH was adjusted to a value of 2 also occurred in the absence of pigments due to a reduction of the absolute value of the zeta potential (31).

Kucera and Aßmus investigated the effects of aluminum lake pigments on the coagulation of Eudragit EPO [poly(butyl methacrylate-co-(2-dimethylamino-

ethyl) methacrylate-comethylmethacrylate),1:2:1] aqueous dispersions (32). In this study, the authors were able to prevent coagulation of the polymer dispersion in the presence of aluminum lakes by the addition of stabilizing excipients such as povidone or poloxamer.

### Formulation of Pigmented Coating Dispersions

Products used in pharmaceutical film coating are commercially available in the form of powders, granules, solutions, or colloidal dispersions. Some products require the addition of other excipients (e.g., plasticizers and antiadherents) to the polymer, while other products are available as fully formulated or ready-to-use products (with the required excipients already added by the manufacturer). The advantages of fully formulated systems for drug product manufacturers are a reduction in the number of excipients that must be obtained and a reduction in preparation time and processing steps. On the other hand, there is less flexibility to change the composition of the film-coating formulation, which may become necessary in certain cases, such as when there is an excipient compatibility issue with a component in the film coating.

Many colloid-based systems are shear sensitive and the use of low-shear type mixers is often recommended for stirring the dispersions. However, because many pigments and antiadherents are optimally dispersed with high-shear type mixers, a pigment dispersion is typically made separately and then added to the polymer dispersion with low-shear mixing. For some products, it is important to follow the order of addition in which the pigment dispersion is added to the polymer dispersion to reduce the possibility of coagulation. Adding pigments in a diluted state is preferable as opposed to directly adding them to colloidal polymer dispersions, since it provides a more gradual change to the medium in which the colloidal polymer particles are dispersed. To prevent settling of pigment particles, continuous low-shear stirring of the coating dispersion is recommended during the coating process.

## INFLUENCE OF COLORING AGENTS ON POLYMER FILMS AND COATED PRODUCTS

Although the main reasons for adding coloring agents are to modify the visual characteristics of the dosage form or provide protection from light, the addition of colorants may unintentionally influence the mechanical properties, permeability, and drug-release characteristics of a film coating. In some cases, undesirable effects in the appearance of the film coating (e.g., increased surface roughness) may occur with the incorporation of pigments. With the addition of increasing amounts of colorant, pigment particles at some point will start to reduce intermolecular bonding between polymer molecules and affect the properties of the film. The amount of insoluble excipients that can be added to a polymer film without adversely affecting its intended functions or applications (e.g., sustained-release

properties) is sometimes referred to as the pigment binding capacity, although actual quantitative measured values of this term seem to be absent in the pharmaceutical literature. Polymers with a high pigment capacity can be defined as those that can incorporate very high levels of insoluble additives while still retaining their functional characteristics.

A more well-defined concept, in this regard, is the critical pigment volume concentration (CPVC) (33,34). According to this theory, below the CPVC, the polymer is able to completely bind and surround the pigment particles, forming a dense and continuous film (Fig. 8).

The addition of pigments will initially reduce the permeability of the polymeric film below the CPVC due to an increased tortuosity of diffusion pathways, while above the CPVC, there is incomplete binding of the pigment particles by the polymer, resulting in the formation of voids within the film (35,36). In the latter case, there is an increase in film permeability and a reduction in the mechanical strength of the film.

### Appearance

The appearance that a coloring agent and film coating impart to a drug product plays an important role in the development of a visually esthetic product. From a therapeutic standpoint, color may play a role in enhancing patient compliance. Furthermore, color is an important attribute by which different drug products may be distinguished and can hence play an important role in reducing dispensing and patient medication errors. Color may also be reflective of the quality of the product and coating process, since color is a readily observable feature of the drug product. Nonuniform distribution of color in the coating, mottled coloration, and color fading may be indicative or suggestive of issues involving product quality, changes in the stability of the product, and changes or lack of control in the manufacturing and coating process. Several studies have used color to assess the efficiency and uniformity of the coating process (37,38). Since color is a basic feature of product identification, the consistency of drug product color can be an important factor in the quality control of pharmaceutical products (39). Consequently, if any changes are made that influence the color of a commercial drug product (such as changes in coating composition or level), color matching of the old and new formulations is important for maintaining the appearance and identity of the product.

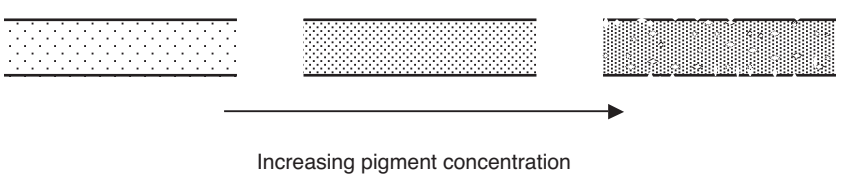


**Figure 8** Effect of increasing pigment volume levels in a polymer film.

Color in film-coated products may be assessed by visual comparison to standards with a defined color or more objectively by the use of color measurement instruments such as spectrophotometers or tristimulus colorimeters. Color can be measured using color scales such as the Commission Internationale l'Eclairage or the International Commission on Illumination (CIE) *X*, *Y*, *Z*, or CIE *L*a*b** scales (40). The *X*, *Y*, *Z* functions are based on the average spectral responses (tristimulus values) to red, green, and blue light of human observers. The tristimulus values are based on the three types of cone-shaped receptors in the human eye that are responsible for color vision. Different colors stimulate the cone receptors to different degrees, giving rise to the range of colors visible to the human eye (41). The *X*, *Y*, *Z* values may be converted into uniform color scales such as the CIE *L*a*b** scale (39). In the CIE *L*a*b** model, color is a function of the values of *L**, *a**, and *b**, which are coordinates in a three-dimensional space (Fig. 9).

*L** indicates lightness (ranging from black to white), *a** indicates redness-greenness, and *b** indicates yellowness-blueness.

In addition to protecting photosensitive products from light, pigments may also serve to mask the appearance of the underlying substrate, which can be important for cores that have an unpleasant appearance. The addition of a film coating to cores to obscure their appearance may be one approach to preparing blinded drug products for clinical trials where the goal is to reduce any bias that may result from observed differences in the drug products being evaluated. Felton and Wiley used overcoating with a hydroxypropyl methylcellulose coating containing iron oxide and titanium dioxide pigments to color blind a sustained-release tablet with

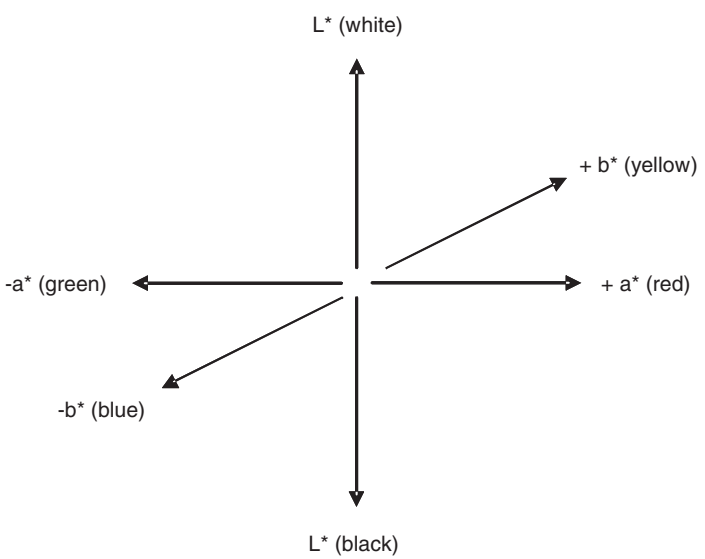


**Figure 9** The coordinates of the CIE *L*a*b** color space.

a pigmented film coating (42). In such instances, the opacity or hiding power of the film coating is an important factor and will depend on the type and amount of colorant in the film as well as the thickness of the coating. Most polymers used in film coatings will usually form relatively transparent or translucent films and as such will not provide much hiding power without the incorporation of pigments.

Rowe investigated the effect of several pigments on the opacity of hydroxypropyl methylcellulose–based films (43). In these studies, opacity measurements of the films were evaluated using a contrast ratio. The contrast ratio (in %) was determined by dividing the light reflectance values from a coated black substrate by the light reflectance values from a coated white substrate. With increasing contrast ratio values, the core substrate would become less visible and increasingly more difficult to see. At equivalent pigment levels, films containing talc had a relatively low contrast ratio (<50%), while titanium dioxide and iron oxides (black, red, and yellow) had high contrast ratios (>90%). The contrast ratio values for aluminum lakes varied from less than 70% to more than 95% and increased in the order yellow < orange < red < blue. Additionally, the contrast ratio values were observed to increase with increasing dye content of the lake. Increasing either the pigment concentration or the film thickness resulted in higher contrast ratio values (44,45).

In addition to color, the appearance of a coated product may also be evaluated in terms of gloss and surface roughness. Gloss results from the specular reflection of incident light from a smooth surface as shown in Figure 10, where the light is reflected in the opposite direction at an equal angle. In contrast, a rough surface reflects incident light diffusely, scattering it in many directions.

Gloss is desirable as it enhances the elegance and esthetic appeal of the drug product. For example, high gloss contributes to the visual appeal and elegance of pigmented hard gelatin capsules. Rowe studied the effect of pigment particle size on the gloss of film-coated tablets and found that gloss decreased with increasing pigment concentration (46). Gibson et al. observed a similar relationship in gloss reduction for titanium dioxide and an aluminum lake, although black iron oxide exhibited a decrease in gloss at low pigment levels followed by an increase in

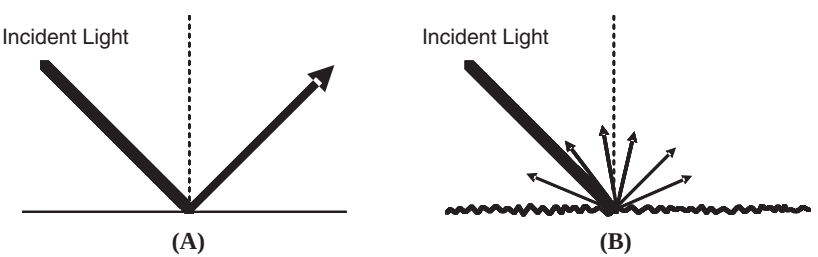


**Figure 10** Specular and diffuse reflection of incident light from (**A**) smooth and (**B**) rough surfaces. Dotted line is normal to the surface.

gloss at higher pigment levels (47). The authors used the gloss measurements to determine CPVCs for the pigments in hydroxypropyl methylcellulose films.

In contrast to gloss, roughness is an undesirable feature in a coating, especially if it is clearly visible to the naked eye. The effect of pigment concentration on surface roughness was investigated by Rowe, who reported that while low pigment concentrations resulted in a minor increase in the surface roughness of film-coated tablets, at higher pigment concentrations (above the CPVCs), the surface roughness increased considerably (48).

## Light Protection

Light can influence the stability of many active pharmaceutical ingredients. For some drug products, light-induced interactions and decomposition may be associated with changes in color. The magnitude of the effects of light on the stability of photolabile compounds can vary considerably, from very small amounts of degradation after several weeks of light exposure for some drugs to extensive decomposition in the order of minutes for extremely photosensitive actives (49).

For active pharmaceutical ingredients that are light sensitive, the incorporation of appropriate pigments into the film coating may be an approach by which drug product stability can be improved. The ability of a pigment to provide light protection depends on the ability of the pigment to reduce the transmittance of light to the substrate or core drug product. Incident light may be reflected, absorbed, or transmitted by a polymeric film coating. Increasing the amount of light that is reflected or scattered will reduce the amount of light that is transmitted to the drug in the core. The amount of light reflected at a polymer–pigment interface can be related to the refractive indices of the components by Equation 2 (assuming normal incident light and no absorption) (50):

$$R = \left[\frac{n_1 - n_2}{n_1 + n_2}\right]^2 \tag{2}$$

where $R$ is the amount of light reflected at the interface, $n_1$ is the refractive index of the pigment, and $n_2$ is the refractive index of the polymer. Increasing the difference between the refractive indices of the pigment and the polymer will increase the amount of light reflected. Rowe and Forse compared the refractive indices of several film-coating polymers and pigments (50). The refractive indices of the film-coating polymers were approximately 1.5, while the refractive indices of pigments ranged from 1.50 to 1.54 for aluminum lakes; 1.54 to 1.59 for talc; 1.94 to 2.51 for yellow oxide; 2.49 to 2.55 for titanium dioxide (anatase form); and 2.94 to 3.22 for red iron oxide. Many pigments are anisotropic and have more than one refractive index depending on their orientation.

A number of authors have investigated the use of pigmented coatings in stabilizing light-sensitive drugs. Nyqvist and Nicklasson compared the effects

of titanium dioxide and yellow iron oxide in hydroxypropyl methylcellulose coatings applied to tablets of a light-sensitive drug substance (51). The pigments reduced the light-induced changes in the color of the active in the core, with a combination of iron oxide and titanium dioxide in the film coating providing the best stability.

Teraoka et al. evaluated the effects of hydroxypropyl methylcellulose–free films containing titanium dioxide or tartrazine (FD&C yellow no. 5) on the stability of the photolabile drug nifedipine (52). In this study, a sample of the drug was dispersed on a glass plate, which was then covered by a polymer-free film using a special holding device and then exposed to light. Light transmission measurements indicated that the different colorants transmitted light over different wavelengths, with tartrazine having lower light transmission in the visible region and titanium dioxide being more effective in the ultraviolet region. Films containing a mixture of equivalent parts of each colorant had lower light transmittance than either of the individual colorants at equivalent concentrations in the polymer film. When placed on the dispersed drug, films with the binary colorant combination provided better protection against photodegradation of the active than films with a single colorant.

Béchard et al. investigated the influence of titanium dioxide concentration and film-coating thickness on the photostability of nifedipine tablets coated with hydroxypropyl methylcellulose (53). The tablets were exposed to fluorescent light for up to three weeks. The authors found that acceptable light protection against drug degradation was obtained for films having contrast ratio values above 98%,

**Table 3** Photostability of Various Molsidomine Tablet Formulations Light After Exposure

| | Drug decomposition (%) | | | |
|---|---|---|---|---|
| Formulation | After 1 hr | After 3 hr | After 6 hr | After 12 hr |
| Uncoated tablets | 7 | 20 | 25 | 33 |
| Coated tablets | | | | |
| *$TiO_2$ level, film thickness* | | | | |
| 4.8% $TiO_2$, 35 μm | 2.5 | 5 | 9.5 | 19.5 |
| 4.8% $TiO_2$, 73 μm | 0 | 0 | 0 | 2 |
| 9.9% $TiO_2$, 33 μm | 0 | 0 | 0 | 3 |
| *$TiO_2$ level, iron oxide level, film thickness* | | | | |
| 4.8% $TiO_2$, 0.9% red iron oxide, 37 μm | 0 | 0 | 0 | 0 |
| 4.8% $TiO_2$, 0.9% yellow iron oxide, 39 μm | 0 | 0 | 0 | 0 |

*Source*: From Ref. 54.

which was only achieved by using thick film coatings with high levels of titanium dioxide.

Aman and Thoma evaluated the effectiveness of different formulation approaches in stabilizing light-sensitive molsidomine tablets, including (*i*) incorporating light-absorbing excipients into the core tablets; (*ii*) incorporating pigments (iron oxides or titanium dioxide) into the core tablets; and (*iii*) coating the tablets with pigmented hydroxypropyl methylcellulose films (54). Light absorbers and pigments both improved the stability of the tablets when incorporated into the cores, with pigments being more effective. However, in both cases, significant drug degradation was still detected upon exposure to light in the time period that was studied. The formulation of a photostable drug product was only achieved by film coating (Table 3) or blister packaging.

The authors' results indicated that coating thickness, pigment concentration, and pigment type could influence the stability of the active. A combination of iron oxides and titanium dioxide in the film coating provided the most stable tablets.

## Mechanical Properties

Film coatings that are applied to solid dosage forms should have sufficient mechanical properties to withstand further processing and handling after the film-coating process, packaging, and transportation of the drug product until it reaches the patient. Brittle film coatings may lead to the formation of cracks, which could compromise the release characteristics of the drug product. The adsorption of polymer molecules on the surface of pigment particles can result in a restriction of polymer mobility (55), which can increase the elastic modulus of the polymer and make the coating more brittle. The addition of pigments to polymer films has been shown to be a factor in increasing coating defects (56). These effects may be due to insoluble particles acting as stress concentrators, thereby promoting the initiation of cracks in the film and/or the presence of interactions between the additive and the polymer (19). Poorly dispersed pigments may also play a role by acting as a focus for localized stress in polymer film coatings (57). Possible formulation approaches for reducing pigment-related coating defects include reducing pigment levels, increasing the amount of plasticizer, and using a more flexible or tougher polymer.

High internal stresses in polymer films may lead to a defect known as edge splitting, where the film breaks and peels back from the edges of a coated tablet. Rowe observed an increase in edge splitting in tablets coated with hydroxypropyl methylcellulose films with the addition of lakes and iron oxides (56). In contrast, talc was observed to lower the incidence of edge splitting. Furthermore, the inclusion of talc or magnesium carbonate in hydroxypropyl methylcellulose films containing a yellow lake pigment was found to lower the incidence of edge splitting (58). In contrast to the other pigments studied, the talc and magnesium carbonate particles were both platelet shaped, suggesting that particle morphology plays an important role in reducing the incidence of edge splitting in film coatings.

The mechanical properties of polymer films are usually characterized by tensile testing, in which a polymer film is subjected to a tensile force until it breaks, with the recorded data used to generate a stress–strain curve. The mechanical behavior may be reported in terms of strength at break (the value of stress at which the film breaks), elongation at break (the value of strain at which the film breaks), elastic modulus (the ratio of stress to strain in the initial linear region of the stress–strain curve), and toughness (the energy required to break the polymer film).

Several studies have reported that the addition of pigments can lead to significant changes in the mechanical properties of polymeric films. Porter found that the diametral crushing strength of tablets coated with a hydroxypropyl methylcellulose film decreased when pigments (titanium dioxide and an aluminum lake) were incorporated into the coating (59). In the same study, tensile tests on free films showed a reduction in strength with the addition of the pigments. Okhamafe and York evaluated the effects of different types of titanium dioxide and talc on the mechanical properties of unplasticized and plasticized hydroxypropyl methylcellulose films (60). In general, the addition of the pigments resulted in a reduction in tensile strength and elongation while the elastic modulus increased. In a related study, some of the differences in the mechanical behavior of the pigmented polymer films were attributed to differences in pigment particle size, surface area, and morphology (61).

Aulton and Abdul-Razzak studied the effects of three aluminum lakes and titanium dioxide on the mechanical properties of hydroxypropyl methylcellulose films (62). The inclusion of the pigments generally resulted in more brittle polymer films. Aluminum lakes with different colors but equivalent particle size showed very similar effects on the mechanical properties of the polymer films. However, some differences in film toughness were observed when lakes of the same color but different particle size were compared: the finer particle size grades yielded slightly tougher polymer films. Gibson et al. evaluated the effects of aluminum lakes, iron oxides, and talc on the mechanical properties of hydroxypropyl methylcellulose films (19,63). Increases in the modulus values were observed in most cases with the addition of pigments to unplasticized polymer films, while the effects of pigments on the modulus of plasticized films were noticeably less. In general, the pigments lowered the tensile strength, elongation at break, and toughness of the polymer films, although to different degrees depending on the pigment. The differences in the effects of the different pigments were in part related to the shape of the pigment particles. Comparing the data to data from studies that examined the effects of pigments on the incidence of edge splitting, the authors reported that all pigments increased the incidence of edge splitting with the exception of talc, which reduced the occurrence of this defect. Stress-relaxation experiments indicated that talc enhanced the ability of the polymer films to relax in response to applied stress, a finding that the authors attributed to the lamellar shape and orientation of the talc particles, which facilitate stress relief by slippage of adjacent particles within the polymer film.

The majority of studies that have investigated the effects of pigments on the mechanical properties of polymers have focused on hydroxypropyl methylcellulose. Reports on the effects of pigments on the mechanical properties of other polymers are very limited. Hsu et al. investigated the effect of titanium dioxide on the mechanical properties of polyvinyl alcohol films and observed a reduction in the tensile strength, elongation at break, and film toughness with increasing pigment levels (64). Nyamweya investigated the influence of aluminum lakes on the mechanical properties of sustained-release (Eudragit RS PO) and enteric (Eudragit L 100-55) polymethacrylate polymer films (65). The addition of aluminum lakes increased the rigidity of the polymeric films as evidenced by increases in the elastic modulus. The elongation at break of the polymer films decreased with the addition of aluminum lakes, indicating a reduction in film flexibility. Both of these findings were in accordance with previous studies that investigated the effects of insoluble additives on hydroxypropyl methylcellulose–based films. However, it was observed that the tensile strength of the films was relatively unchanged (Eudragit L 100-55 films) or even increased (Eudragit RS PO films) with the incorporation of lakes. The effects of an aluminum lake on the mechanical properties of the plasticized Eudragit RS PO films are illustrated in the stress–strain curves generated from tensile testing in Figure 11.

The majority of studies that have evaluated the effects of pigments on the mechanical properties of film-coating polymers have been conducted using free films. Okhamafe and York investigated the effects of pigments on the mechanical properties of hydroxypropyl methylcellulose film coatings applied to aspirin tablets using an indentation apparatus (66). The hardness and modulus of the films increased with the addition of talc while incorporation of titanium dioxide did not increase either the hardness or modulus. Nyamweya studied the effect of

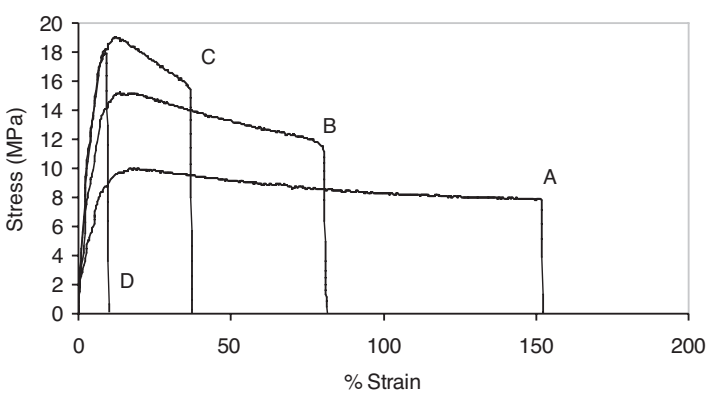


**Figure 11** Effects of FD&C yellow no. 6 aluminum lake on the stress–strain profile of plasticized Eudragit® RS PO films: (**A**) 0% (w/w) lake; (**B**) 10% (w/w); (**C**) 20% (w/w); and (**D**) 40% (w/w) lake.

incorporation of aluminum lakes into Eudragit L 30 D55 and Eudragit RS/RL 30 D film coatings on tablet-crushing strength and found that tablets coated with pigmented coatings had slightly higher crushing strength values compared to tablets coated with unpigmented films (65).

## Thermal Properties

A few studies have investigated the effect of pigments on the glass transition temperature of film-coating polymers. The glass transition temperature, a fundamental property of an amorphous polymer, is the temperature at which a polymer undergoes a change from a hard, brittle glassy state to a soft, flexible rubbery state. It is well known that excipients that lower the glass transition temperature, such as plasticizers, make polymers less brittle and more flexible. It is therefore of interest to determine what effect pigments, which have been shown to have significant effects on the mechanical properties of polymers, would have on the glass transition temperatures of these polymers.

Okhamafe and York evaluated the effect of talc and titanium dioxide on the glass transition temperature of hydroxypropyl methylcellulose films (67). Increases in the glass transition temperature of plasticized and unplasticized pigmented films of up to 15°C to 16°C were observed. Talc had a greater effect on the glass transition temperature of the polymer films than titanium dioxide. The differences between the different pigments in their effects on the glass transition temperatures of the films were attributed to differences in their shape, surface area, and interaction with the polymer. Other authors have noted an increase in the glass transition temperature of hydroxypropyl methylcellulose films with the addition of titanium dioxide (25).

Nyamweya studied the effects of four aluminum lakes on the glass transition temperature of plasticized Eudragit RS PO and Eudragit L 100-55 films (Fig. 12) (65).

Although the lakes had very little effect on the glass transition temperature of Eudragit RS PO, significant increases in the glass transition temperature of Eudragit L 100-55 films were observed, suggesting a greater degree of interaction between the pigments and the latter polymer. In the case of Eudragit RS PO, changes in the mechanical properties of the films (Fig. 11) could therefore not be attributed to a change in the glass transition temperature of the polymer. For Eudragit L 100-55 films, the increases in the glass transition temperature could in part account for the changes in mechanical properties of the polymer films; however, for most of the lakes, the $T_g$ of the polymer did not increase beyond a level of 10% (w/w) lake while the mechanical properties continued to show a concentration dependency at higher pigment levels.

## Permeability

For many solid dosage forms, especially drug products that are sensitive to moisture, it is desirable to have a film coating with low water vapor permeability.

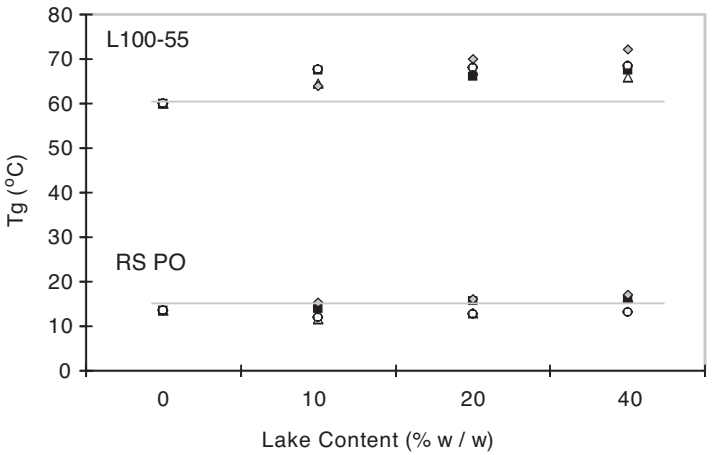


**Figure 12** Effect of aluminum lakes on the glass transition temperature of plasticized Eudragit® L 100-55 and Eudragit RS PO films. *Symbols*: □, blue no. 2 lake; ◇, red no. 40 lake; ○, yellow no. 6 lake; △, yellow no. 10 lake.

Polymeric film coating can be an effective method to reduce the transmission of water vapor. The effectiveness of a film coating in this regard will depend on the type of polymer, added excipients, and the thickness of the film coating. An effective moisture-protective coating may also reduce the need for specialized protective product packaging. Besides the reduction of water vapor uptake from the environment, film permeability can also be important in controlling the release of the active. For example, low permeability to salivary fluids is important in coated taste-masking applications while low permeability for an enteric coating to gastric fluids would be important in protecting an acid-sensitive drug from degradation in the stomach.

A number of studies have investigated the effects of pigments on the water vapor permeability of polymer films. Porter studied the effect of titanium dioxide and an aluminum lake on the moisture permeability of hydroxypropyl methylcellulose films (57). The addition of pigments reduced the permeability of the polymer films. The findings were attributed to the pigment particles acting as a barrier to moisture and increasing the diffusion path length for permeating water molecules. Initially, a decrease in film permeability was observed, followed by an increase in permeability at higher pigment levels. However, pigmented films were still less permeable to moisture than unpigmented films at all pigment concentrations studied, suggesting that the pigment levels were below the CPVCs. Okhamafe and York studied the influence of different grades of talc and titanium dioxide on the moisture permeability of hydroxypropyl methylcellulose–based films (33,36). In general, the film permeability coefficients were observed to first decrease and then increase with increasing pigment levels. Hsu et al. investigated the effect of titanium dioxide on the water vapor permeability of polyvinyl

alcohol films and reported slight increases in permeability at low pigment levels followed by a sharp increase in permeability at high pigment levels (64).

List and Kassis investigated the effects of talc and titanium dioxide on the water vapor permeability of Eudragit L 30 D55 films. They found that the incorporation of talc reduced the water vapor permeability of plasticized Eudragit L 30 D55 films while the addition of titanium dioxide resulted in an increase in film permeability to water vapor (68). The increased permeability of the polymer films with titanium dioxide was attributed to the hydrophilic nature of this pigment. Porter and Ridgway investigated the effect of red iron oxide on the permeability of two enteric polymers, cellulose acetate phthalate, and polyvinyl acetate phthalate (35). The addition of iron oxide had little effect on the permeability of polyvinyl acetate phthalate–free films, while the permeability of the cellulose acetate phthalate films initially decreased and then increased with increasing pigment concentrations. Similar effects were observed when enteric-coated tablets were tested for permeability to simulated gastric fluid using an acid-uptake test.

## Drug Release

In functional film coatings, which are designed to control the release rate of the drug, the addition of colorants to the film coating has been reported to have various effects on the drug-release profile. Ghebre-Sellassie et al. investigated the effect of kaolin on the dissolution of pellets coated with Eudragit NE 30 D and found that increasing levels of kaolin resulted in increasing drug-release rates (69). Chang and Hsiao reported increased dissolution rates with the addition of talc to Eudragit RS 30 D–coated pellets (70).

Maul and Schmidt investigated the effect of the addition of pigments on the release profiles of Eudragit L 30 D55 enteric-coated pellets (29). Platelet-shaped pigments (talc, mica, iron oxide–coated mica, and titanium dioxide–coated mica) were found to reduce the drug-release rate of the coated pellets, while spherical (titanium dioxide) or needle-shaped pigments (red iron oxide) had little effect on or led to an increase in drug release in acidic media. Slower drug-release rates were observed for films containing platelet-shaped pigments with either hydrophilic or hydrophobic surfaces, suggesting that particle shape has a greater effect on drug release than surface chemistry. Furthermore, it was observed that platelet-shaped pigments with a larger particle size had a greater effect on reducing drug-release rates than those with a smaller particle size. The alignment of platelet-shaped particles, which tend to lie flat and parallel to the surface of the film, may serve as a barrier to the movement of water (29,71). Similar findings were reported in a later study that investigated the effects of the same pigments on drug-release profiles of pellets coated with Aquacoat® ECD or Eudragit RS 30 D sustained-release polymers (72).

Nyamweya evaluated the effects of FD&C yellow no. 6 and D&C yellow no. 10 aluminum lakes on the dissolution profiles of enteric (Eudragit L 30 D55) and sustained-release (Eudragit RS/RL 30 D) polymer film-coated tablets (65). The

effects of the aluminum lakes on the dissolution profiles of Eudragit L 30 D55–coated tablets are shown in Figure 13.

The Eudragit L 30 D55 dispersion was partially neutralized prior to the addition of the lakes to prevent coagulation. In the acid stage of the dissolution test, leaching of the lake dyes from the film coating was observed after the tablets were placed in the dissolution medium, due to dissociation of the lake substrate at the low pH of the medium. However, the enteric properties of the coating were not adversely affected, and similar dissolution profiles were observed between the pigmented and unpigmented coated tablets. When the aluminum lakes were incorporated into Eudragit RS/RL 30 D films, a slower initial hydration of film coating was observed compared to unpigmented film-coated tablets. However, subsequent dissolution rates were relatively similar (Fig. 14).

The low pH of the dissolution medium did not lead to faster drug-release rates, as may have been expected to occur as a result of lake dissociation at low pH values.

A recent study has shown the importance of the source of talc on drug release from controlled-release coated products. Annamalai et al. studied the effects of talc of various grades from several manufacturers on the dissolution profiles of methacrylate–based enteric and sustained-release coated tablets (73). The study found that the source and grade of talc could have a significant effect on drug release from tablets coated with either polymer. Since talc is a naturally occurring mineral, the effects of changing to a new talc source (e.g., due to a change in supply from a mine being depleted) need to be considered, since this could in certain cases result in changes in the dissolution profile of a drug product.

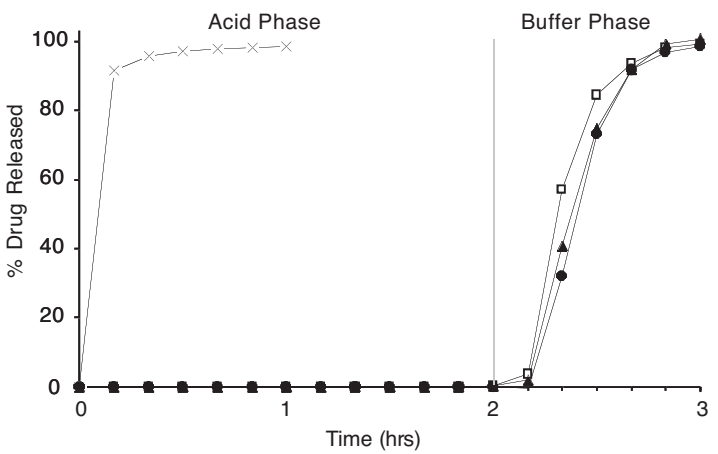


**Figure 13** Dissolution profiles of tablets coated with Eudragit® L 30 D55 (dissolution media: 0.1 N HCl for two hours, followed by pH 6.8). *Symbols*: □, 0% lake; ●, 30% yellow no. 6 lake; ▲, 30% yellow no. 10 lake.

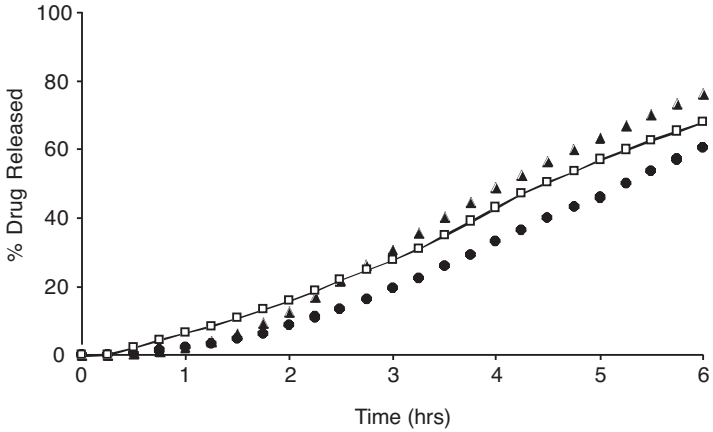


**Figure 14** Dissolution profiles of tablets coated with Eudragit® RS 30 D (dissolution medium, 0.1 N HCl). *Symbols*: □, 0% lake; ●, 30% yellow no. 6 lake; ▲, 30% yellow no. 10 lake.

## SUMMARY

Coloring agents are important components of coated pharmaceutical drug products and can be used in enhancing product elegance, product identification, product differentiation, and the stability of light-sensitive compounds. Coloring agents also play an important role in reducing medication errors and may contribute to the development of drug products with unique visual features, making them more difficult to counterfeit. There are a number of coloring agents available, and, from a regulatory standpoint, the intended regions and countries where drug products containing the colorant will be marketed should be considered. Pigments may influence the properties of polymer dispersions and films in a number of ways, which may have a significant effect on the performance of the drug product. An understanding of the physical and chemical properties of colorants as well as how they interact with the polymers used in coating applications will enable the formulation of coated products with colorants.

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# 8

# Process and Formulation Factors Affecting Drug Release from Pellets Coated with Ethylcellulose Pseudolatex Aquacoat®

**Juergen Siepmann and Florence Siepmann**

*College of Pharmacy, University of Lille, Lille, France*

**Ornlaksana Paeratakul**

*Department of Pharmaceutical Technology, Srinakharinwirot University, Bangkok, Thailand*

**Roland Bodmeier**

*College of Pharmacy, Freie Universität Berlin, Berlin, Germany*

## INTRODUCTION

Ethylcellulose is one of the most widely used water-insoluble polymers for the coating of solid dosage forms (1). Although coating with organic polymer solutions is still widespread, aqueous ethylcellulose dispersions have been developed to overcome problems associated with organic solvents (environmental concerns, high cost, residual solvents, toxicity, and explosion hazards) (2,3).

Two aqueous ethylcellulose pseudolatexes are commercially available: Aquacoat® manufactured by FMC Biopolymer (Philadelphia, PA, U.S.A.) and Surelease® by Colorcon (West Point, PA, U.S.A.). Aquacoat (30% solids content) is prepared by a direct emulsification–solvent evaporation method (4). The pseudolatex is stabilized with sodium lauryl sulfate (SLS) and cetyl alcohol and requires the addition of plasticizers prior to use. Surelease (25% solids content) is prepared by a phase inversion–in situ emulsification technique (5). It contains

ammonium oleate as a stabilizer and dibutyl sebacate (DBS) as a plasticizer. Upon drying and film formation, ammonia evaporates, leaving oleic acid as a plasticizer within the film. Detailed information about the composition and properties of Aquacoat and Surelease are presented in other chapters in this book. In addition to the colloidal ethylcellulose dispersions, a micronized ethylcellulose powder with an average particle size of a few micrometers is available in Japan from Shin-Etsu (Tokyo, Japan) (6,7). The polymeric powder is dispersed in water with the addition of relatively large amounts of plasticizer prior to use.

This chapter summarizes research with Aquacoat and discusses some important formulation and process variables published in related references.

## ADDITIVES IN THE AQUEOUS POLYMER DISPERSIONS

Additives in aqueous colloidal polymer dispersions can be classified into those added during or shortly after the preparation of the polymer dispersion and those added just prior to use. The first group includes surfactants necessary to physically stabilize the dispersion during preparation and storage, preservatives for microbiological stability, and antifoaming agents. Plasticizers, antitack agents, or additives modifying the permeability of the ethylcellulose film [e.g., hydrophilic polymers such as hydroxypropyl methylcellulose, (HPMC)] are added shortly before the application of the polymer dispersion.

These additives will not only fulfill their task (such as in the case of surfactants of physically stabilizing the dispersion), but will also be present in the final film coating. They can therefore affect various film properties, such as mechanical stability and, in particular, the permeability and hence drug release from coated dosage forms. The effects of various additives on these properties are discussed below.

### Surfactants

Surfactants play an important role in the preparation, formulation, and application of colloidal polymer dispersions. The surfactants are used to lower the interfacial tension between the organic polymer solution and the aqueous phase during pseudolatex formation and to prevent agglomeration and coalescence of the dispersed polymer particles during storage. However, the surfactants will also be present in the coating during and after drying, and therefore, they can affect the film formation process and thus can potentially modify the film structure and release properties.

Cellulose acetate membranes prepared from aqueous dispersions containing SLS as a stabilizer underwent phase separation (8–10). Above a certain concentration, SLS altered the structure as well as the mechanical and permeation properties of cellulose acetate films due to the redistribution of the surfactant into small islets during the film formation process. In Aquacoat, SLS (4% w/w of total solids), an anionic surfactant, is used in combination with cetyl alcohol (9% w/w of total

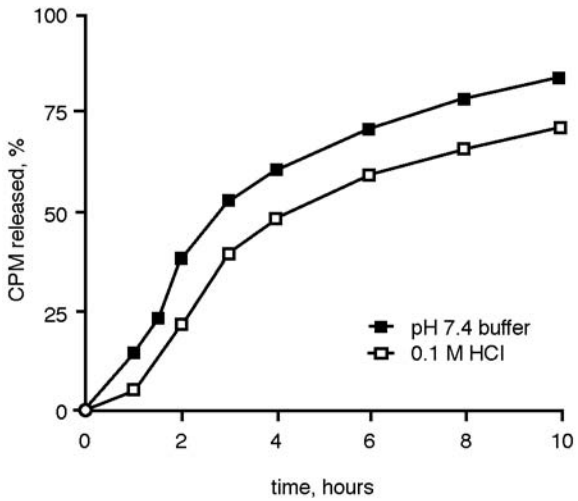


**Figure 1** Chlorpheniramine maleate release from cured Aquacoat®-coated beads in pH 7.4 phosphate buffer and 0.1 M HCl. *Source*: From Ref. 14.

solids) to stabilize the ethylcellulose dispersion. Ethylcellulose is a nonionic polymer; the drug release is expected to be pH independent for drugs with pH-independent solubility. However, several studies with Aquacoat-coated beads showed a faster drug release in simulated intestinal fluid when compared to in simulated gastric juice. Goodhart et al. attributed the faster drug release to the ionization of SLS (3,11), whereas Lippold et al. suggested that the presence of carboxyl groups on the polymer chain was responsible for the pH-dependent effects (12,13).

In order to clarify the effect of surfactant and cosurfactant levels, drug-loaded beads were coated with ethylcellulose pseudolatexes containing varying concentrations of the surfactant (SLS) and cosurfactant (cetyl alcohol). Chlorpheniramine maleate (CPM) was used as the model drug because of its pH-independent solubility at physiological pH levels (14).

The CPM release from cured Aquacoat-coated beads is shown in Figure 1.

The drug was released faster in pH 7.4 buffer. Similar results were also observed with beads coated with self-prepared ethylcellulose pseudolatexes having a composition identical to that of Aquacoat. To clarify the contributions of SLS and ethylcellulose to the pH-dependent drug release, ethylcellulose pseudolatexes with varying surfactant concentrations were prepared. The effect of SLS concentration in the coating on the drug release is shown in Figure 2.

The difference between the drug releases in the two media increased with increasing concentration of SLS. On visually comparing the release profiles in the two media at higher SLS concentrations, it appeared that the release profiles in 0.1 M HCl were similar to the release profiles in pH 7.4 buffer after a lag time. The faster initial drug release in pH 7.4 buffer may be an indication of better wetting of

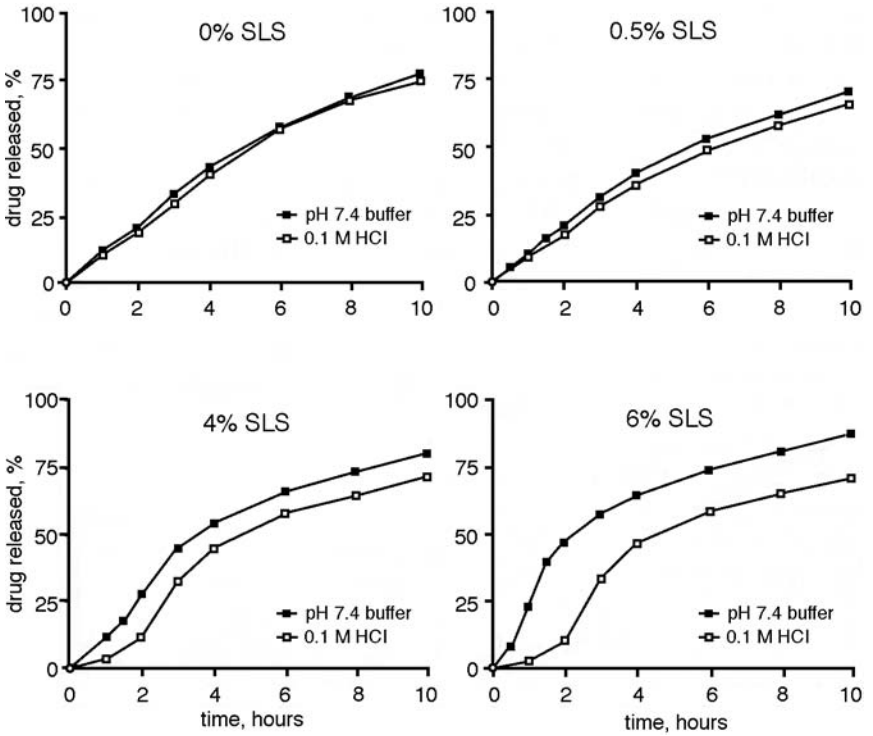


**Figure 2** Effect of SLS concentration (% w/w of coating) on the chlorpheniramine maleate release in pH 7.4 phosphate buffer and 0.1 M HCl from cured beads. *Abbreviation*: SLS, sodium lauryl sulfate. *Source*: From Ref. 14.

the beads with this medium when compared to 0.1 M HCl. SLS, an anionic surfactant with a $pK_a$ of 1.9, is surface-active particularly in the ionized state. It is approximately 10% ionized in 0.1 M HCl as against complete ionization in pH 7.4 buffer. The wetting hypothesis was confirmed by measuring the contact angles between pseudolatex-cast ethylcellulose films and the two dissolution media. As shown in Table 1, the contact angle was the same on surfactant-free ethylcellulose films.

The contact angle decreased with increasing concentrations of SLS in the film and was significantly lower on films wetted with pH 7.4 buffer than on the films wetted with 0.1 M HCl. A lower contact angle indicated better wetting and therefore explained the initial faster drug release in pH 7.4 buffer. No dissolution media effects were seen with drug-release profiles from beads coated with SLS-free ethylcellulose pseudolatexes.

In addition to SLS, cetyl alcohol, a cosurfactant present in Aquacoat, also had a pronounced effect on the drug release. Cetyl alcohol, a long-chain fatty alcohol, is present in Aquacoat at a concentration of 9% w/w of total solids to stabilize the pseudolatex. Its effect on the drug release was investigated by dis-

**Table 1** Contact Angles Between Ethylcellulose Pseudolatex–Cast Films and 0.1 M HCl or pH 7.4 Phosphate Buffer

| Film | 0.1 M HCl | 0.1 M pH 7.4 buffer |
|---|---|---|
| Aquacoat® | 67.9 ± 3.9 | 40.8 ± 3.8 |
| Sodium lauryl sulfate (%) | | |
| 0 | 63.6 ± 2.1 | 63.1 ± 1.9 |
| 2 | 62.3 ± 0.6 | 38.6 ± 3.0 |
| 4 | 50.4 ± 3.1 | 31.0 ± 1.8 |
| 6 | 47.9 ± 1.5 | 24.1 ± 0.8 |
| Cetyl alcohol (%) | | |
| 0 | 17.5 ± 1.3 | 10.4 ± 1.4 |
| 9 | 50.4 ± 3.1 | 31.0 ± 1.8 |

solving different amounts into the organic polymer–plasticizer solution prior to emulsification of the organic phase into the aqueous phase during pseudolatex formation. The drug release decreased with increasing concentration of the co-surfactant (Fig. 3).

The presence of cetyl alcohol rendered the film coat more hydrophobic, as indicated by an increased contact angle (Table 1). The pH sensitivity of the films decreased with increasing amount of cetyl alcohol.

These results clearly demonstrated that the pH-dependent drug release from Aquacoat-coated beads was caused by the presence of the anionic surfactant, SLS, and not the polymer. The surfactant system present in aqueous colloidal polymer dispersions should be taken into consideration when developing a latex- or pseudolatex-coated dosage form because of its potential impact on the film formation and drug-release properties. In addition, charged surfactants such as SLS could form insoluble complexes with cationic drugs present in the core (15,16). Cationic drugs (e.g., CPM, propranolol HCl, diltiazem HCl, and quinidine sulfate) interacted with the anionic surfactant, SLS, and formed a water-insoluble ion–pair complex. This interaction could affect the release of cationic drugs from dosage forms coated with Aquacoat.

## Water-Soluble Additives

Water-soluble additives have been incorporated into ethylcellulose coatings to modify the drug release. Typical water-soluble additives include (*i*) low-molecular-weight materials including various sugars (e.g., sucrose, lactose, sorbitol), salts (e.g., sodium chloride, calcium phosphate), and surfactants such as SLS, and (*ii*) hydrophilic polymers including polyethylene glycol, polyvinylpyrrolidone and, in particular, cellulose ethers such as HPMC (8,11,17–22). During dissolution studies, these additives leach from the coating membrane or hydrate in the coating in the case of high-molecular-weight polymers, resulting in a more permeable

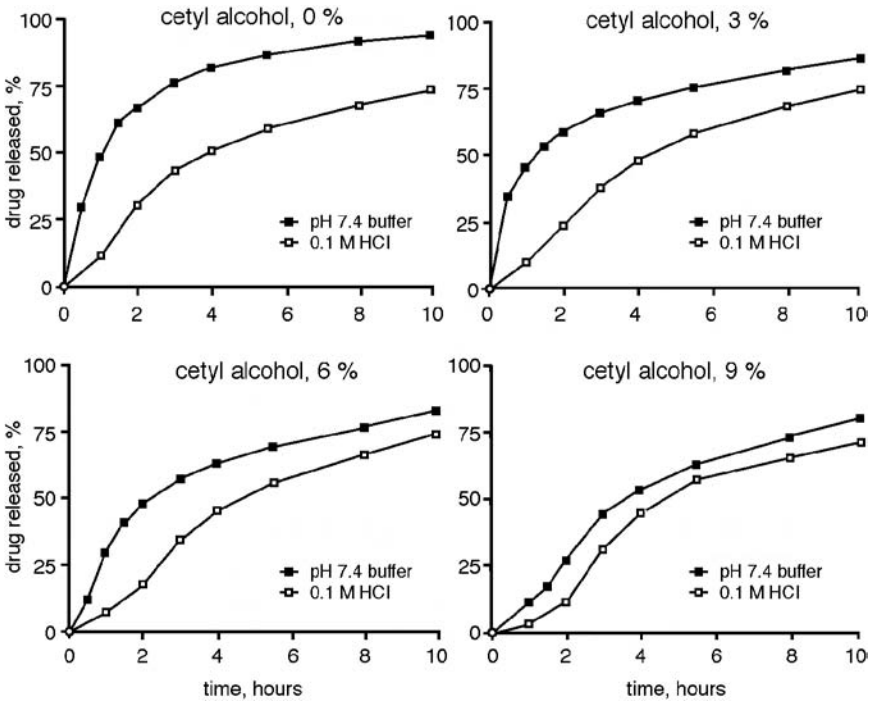


**Figure 3** Effect of cetyl alcohol concentration (% w/w of coating) on the chlorpheniramine maleate release in pH 7.4 phosphate buffer and 0.1 M HCl from cured beads. *Source*: From Ref. 14.

membrane and generally in a faster drug release. However, a decrease in drug release with increasing HPMC concentration was observed with acetaminophen as a model drug; this was attributed to the lower solubility of the drug in the HPMC-containing Aquacoat film (23). Appel and Zentner (24) used urea as a pore-forming agent with Aquacoat to form microporous films in order to increase the release of drugs from coated osmotic tablets. The drug release could also be increased by incorporating drug powder in the coating formulation (21). Theophylline was incorporated into the coating and resulted in faster drug release due to an increase in film porosity after dissolving from the coating.

The water-soluble high-molecular-weight polymers are usually not considered as true pore-forming agents because they do not completely leach out from the coating to leave a well-defined pore structure. A critical HPMC concentration was identified below which very little polymer leaches from the coating and no pores are formed. Above 24% HPMC, the polymer leaches from the ethylcellulose films, resulting in pore formation and an increase in drug release (25). Using an interesting experimental set-up developed by the same research group (a pres-

surized cell device in which the permeability was measured in dependence on an applied tensile stress), the permeability properties of ethylcellulose/HPMC were shown to increase with increasing HPMC content (26).

While coating with the HPMC-containing ethylcellulose dispersion (Aquacoat), we observed the appearance of a sediment in the colloidal dispersion upon standing, indicating destabilization of the colloidal ethylcellulose particles by HPMC (27,28). With organic solvent–based coatings, HPMC and the water-insoluble polymer ethylcellulose are codissolved in an organic solvent/solvent mixture and therefore applied as a mixed polymer solution. Combining HPMC with the colloidal ethylcellulose dispersion prior to the coating process results in HPMC being in solution and the water-insoluble polymer in colloidal dispersion. It is a well-known fact in colloidal science that water-soluble polymers can cause flocculation of dispersed polymer particles (29–31). The addition of HPMC to the ethylcellulose pseudolatex results in the flocculation of the colloidal polymer particles above a critical HPMC concentration. Flocculation is indicated by the appearance of a sediment upon standing. Photomicrographs of the dispersions showed no aggregates with HPMC-free polymer dispersions, whereas flocculation became visible at concentrations in excess of 3% HPMC E5, with the number of aggregates clearly increasing with increasing concentrations of HPMC.

The critical HPMC concentration necessary to cause flocculation moved to lower concentrations with increasing molecular weight of the water-soluble polymer. The higher molecular-weight grades were more efficient flocculants. In addition to the type and concentration of HPMC, the solids content also affected the flocculation of the colloidal dispersion. The HPMC concentration necessary to cause flocculation decreased with increasing solids content of the polymer dispersion.

The observed flocculation phenomena could interfere with the film formation of the colloidal polymer dispersion upon removal of water and thus could affect the drug release from the polymer-coated dosage forms. The HPMC concentrations commonly used in the coating of solid dosage forms (3–10% w/w), based on the water-insoluble polymer, often fell into the flocculated region. This may have important implications for the film formation and coating with aqueous colloidal dispersions. A steep increase in drug release was observed at HPMC concentrations above the critical flocculation concentration (32).

Recently, the addition of small amounts of another hydrophilic polymer [poly(vinyl alcohol)–poly(ethylene glycol) (PVA–PEG) graft copolymer, marketed under the trade name Kollicoat IR by BASF (Ludwigshafen, Germany)] has been proposed for Aquacoat-based film coatings (33,34). In contrast to HPMC, this additive does not cause flocculation of the coating dispersion. Figure 4 shows how the resulting drug-release rate from coated beads can effectively be adjusted by varying the PVA–PEG–graft copolymer content.

The significant increase in film coating permeability can primarily be attributed to the following two phenomena:

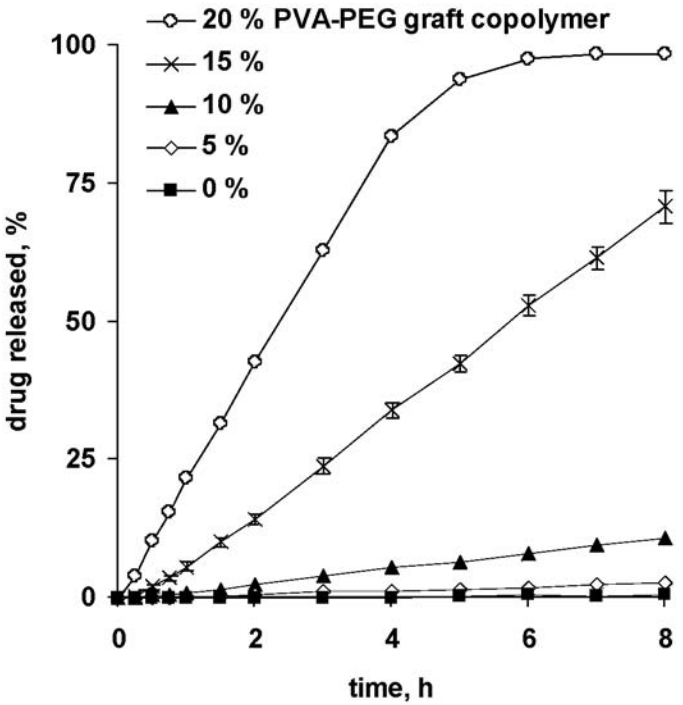


**Figure 4** Effect of the addition of varying amounts of PVA–PEG graft copolymer to Aquacoat® on drug release from theophylline beads in phosphate buffer pH 7.4. *Abbreviation*: PVA–PEG, poly(vinyl alcohol)–poly(ethylene glycol). *Source*: From Ref. 33.

1. The presence of the hydrophilic copolymer within the macromolecular network leads to a marked increase in water-uptake rate and extent (Fig. 5A, symbols indicate experimental results). Interestingly, water penetration into free, thin films identical in composition to the film coatings is predominantly diffusion controlled, with constant diffusivities, irrespective of the additive content in the investigated range (Fig. 5A, curves indicate fittings of a mathematical theory based on Fick's law). Thus, apparent water diffusion coefficients can be determined, and the effects of the film composition on the hydration behavior quantitatively predicted.
2. PVA–PEG–graft copolymer (at least partially) leaches out of the films upon exposure to aqueous release media, resulting in increased rates and extent of dry mass loss of the polymeric systems (Fig. 5B).

Both phenomena, leading to increased water content and decreased dry film masses (and hence less dense polymeric structures), result in increased drug permeability and release rates.

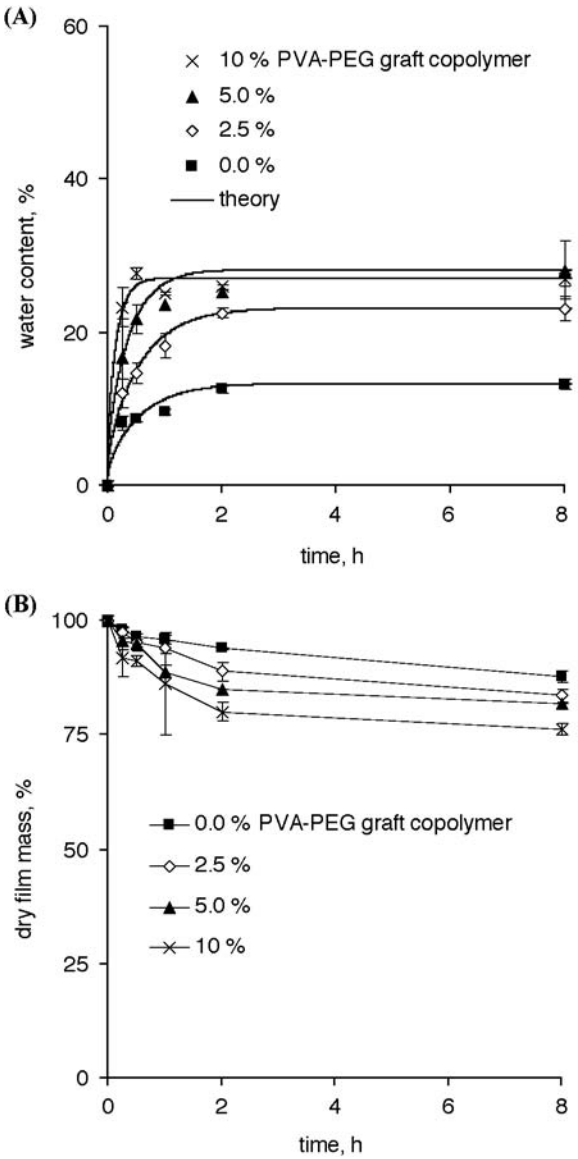


**Figure 5** Effect of the addition of varying amounts of PVA–PEG–graft copolymer to Aquacoat® on the (**A**) water-uptake behavior of free, thin films upon exposure to 0.1 M HCl (symbols represent experiments, curves represent mathematical modeling based on Fick's law); (**B**) dry mass loss of free, thin films upon exposure to phosphate buffer pH 7.4. *Abbreviation*: PVA–PEG, poly(vinyl alcohol)–poly(ethylene glycol). *Source*: From Ref. 33.

Interestingly, drug transport through the polymeric networks is also primarily diffusion controlled, with constant diffusivities, irrespective of the PVA–PEG–graft copolymer content. Figure 6A shows as an example the release of theophylline from free, thin films in phosphate buffer pH 7.4 (symbols indicate experiments; curves indicate mathematical modeling).

As variations in the film thickness alter the length of the diffusion pathway, the results have been normalized to this parameter. Based on these calculations, the apparent diffusion coefficient of theophylline in these polymeric systems (being a measure of drug mobility) could be determined (Fig. 6B). The diffusivity significantly increased with increasing additive PVA–PEG–graft copolymer content, irrespective of the type of release medium. This knowledge and appropriate solutions of Fick's law can help to quantitatively predict the effects of the film coating composition on the resulting drug-release kinetics from coated dosage forms. However, it must be pointed out that the drug-release mechanisms of coated systems are generally more complex than of free, thin films. Additional phenomena such as convective water influx at early time points and the creation of significant hydrostatic pressure within bead cores (potentially resulting in the formation of water-filled cracks in the film coatings) can also be of major importance. This is discussed in more detail in the section titled Drug-Release Mechanisms.

A further example of a water-soluble, macromolecular additive that does not cause flocculation of the coating dispersion is propylene glycol alginate (34). As it contains free carboxylic groups, the resulting film coating properties (including water uptake and dry mass loss behavior as well as drug permeability) are pH dependent and, thus, triggered by the environment within the gastrointestinal tract. At nonacidic pH, the carboxylic groups are ionized, leading to a more pronounced hydration and leaching of propylene glycol alginate out of the film coatings. For certain drugs, e.g., weak bases with pH-dependent solubility, this type of coating can be advantageous: At low pH (in the stomach), the elevated drug solubility is combined with a relatively low film permeability, whereas at higher pH (in the intestine), the decrease in drug solubility might be compensated by a simultaneous increase in film coating permeability. Combinations of Aquacoat and the enteric polymer Eudragit® L can also be used for this purpose (35).

## Water-Insoluble Additives

Insoluble ingredients may be included in the coating formulations for a variety of reasons. One application is to use materials such as magnesium stearate or talc as antitack or separating agents that help reduce agglomeration or sticking of coated particles during the coating process (11). Talc and kaolin are the most commonly used ingredients in aqueous film coating. In general, the separating agent should be inert with respect to the drug and the release characteristics of the film. Surface and morphological properties including the hydrophilicity of insoluble filler particles have been shown to be important factors that may contribute to the properties of the final film (36). The amount of insoluble filler incorporated in the

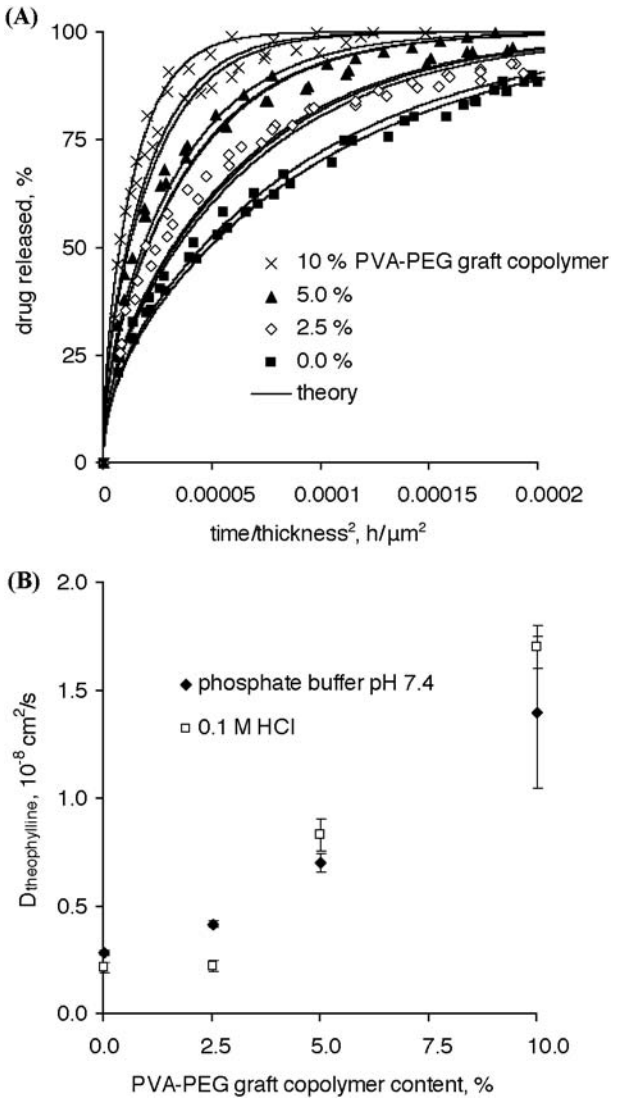


**Figure 6** Effect of the addition of varying amounts of PVA–PEG–graft copolymer to Aquacoat® on the (**A**) release of theophylline from free, thin films in phosphate buffer pH 7.4 (symbols represent experiments; curves represent mathematical modeling based on Fick's law) (the time is normalized to the film thickness to account for slight variations in this parameter); (**B**) apparent diffusion coefficient of theophylline in the polymeric systems upon exposure to phosphate buffer pH 7.4 or 0.1 M HCl. *Abbreviation*: PVA–PEG, poly(vinyl alcohol)–poly(ethylene glycol). *Source*: From Ref. 33.

aqueous dispersion must be optimized without exceeding the maximum carrying capacity of the polymer or critical pigment volume concentration. The pigment concentration has a strong influence on the final film properties such as mechanical strength and permeability (37–39). Care must be taken when incorporating coloring agents into an aqueous dispersion of high pH value, such as Surelease, because the basicity of the dispersion can destroy dye–substrate complexes. Colorants such as aluminum lakes should be replaced with inorganic pigments such as titanium dioxide (40).

## Plasticizers

Plasticizers are usually high-boiling organic solvents used to impart flexibility to otherwise hard or brittle polymeric materials. Plasticizers generally cause a reduction in the cohesive intermolecular forces along the polymer chains, resulting in various changes in the polymer properties, such as a reduction in tensile strength, increases in elongation and flexibility, and reduction in the glass transition or softening temperature of the polymer.

With aqueous colloidal polymer dispersions, the addition of plasticizers is required for systems having a minimum film formation temperature (MFT) above the coating temperature (41). During plasticization, the plasticizer diffuses into and softens the polymeric particles, thus promoting particle deformation and coalescence into a homogeneous film. The effectiveness of a plasticizer for a particular polymer or polymer dispersion depends on the plasticizer–polymer compatibility and the permanence of the plasticizer in the film during coating, storage, and contact with artificial or biological fluids.

With aqueous polymer dispersions, water-soluble plasticizers dissolve, whereas water-insoluble plasticizers have to be emulsified in the aqueous phase of the dispersion. During plasticization, the plasticizer diffuses into the colloidal polymer particles, with the rate and extent of diffusion being dependent on its water solubility and affinity for the polymer phase. With insoluble plasticizers, the plasticized polymer dispersion can be visualized as a three-phase system composed of the water phase, polymer particles, and emulsified droplets. During plasticization, the plasticizer diffuses from the emulsion droplets through the water phase and is then absorbed by the polymer (42).

Factors influencing the rate and extent of the plasticizer uptake by the colloidal particles, such as type and concentration of the plasticizer and type and solids content of the polymer dispersion, were investigated with Aquacoat (43,44). The plasticizers were classified into water-soluble [triethyl citrate (TEC) and triacetin (TA)] and water-insoluble plasticizers [acetyltriethyl citrate (ATEC), acetyltributyl citrate (ATBC), dibutyl phthalate (DBP), DBS, diethyl phthalate (DEP), and tributyl citrate (TBC)].

A separation scheme that allowed the quantification of the plasticizer in the aqueous and polymer phases was developed to determine the distribution of the plasticizer in the colloidal polymer dispersion. The plasticizer present in the

different phases could be separated by centrifugation and/or ultracentrifugation because of differences in the densities of the plasticizers, water, and the polymer particles. The amount of plasticizer in each phase was determined by the high-performance liquid chromatography method (45).

The extent of the partitioning of both water-soluble and water-insoluble plasticizers in Aquacoat after a plasticization time of 24 hours is shown in Table 2.

The water-soluble plasticizers, TEC and TA, were dissolved in both the aqueous and the polymer phase. The higher amount of TA in the aqueous phase, when compared to TEC, could be explained by its higher solubility in the supernatant. With water-insoluble plasticizers, between 85% and 90% of the incorporated plasticizer partitioned into the colloidal polymer particles or polymer phase after 24 hours. The remaining plasticizer existed in the aqueous phase predominantly in the emulsified (between 7% and 14% of the total amount of plasticizer incorporated) and not in the dissolved form. This clearly showed that water-insoluble plasticizers were not completely taken up by the colloidal polymer particles within a 24-hour period, a result previously reported with DBS (13). This may have important implications for coating with polymer dispersions compared to organic polymer solutions, in which the plasticizer is completely dissolved. During coating, in addition to the plasticized polymer particles, the emulsified plasticizer droplets are sprayed onto the solid dosage forms. This could result in

**Table 2** Extent of Plasticizer Diffusion in Aquacoat® (Solids Content, 15% w/w; Level of Plasticizer, 20% w/w of Polymer)

| | Plasticizer concentration (%) | | | |
|---|---|---|---|---|
| | Aqueous phase | | | |
| Plasticizer | Dissolved | Emulsified | Polymer phase | Recovery (%) |
| *Water-soluble* | | | | |
| TEC | 49.87 ± 0.02 | | 50.10 ± 0.18 | 99.97 ± 0.16 |
| TA | 63.96 ± 1.12 | | 35.41 ± 1.67 | 99.36 ± 0.55 |
| *Water-insoluble* | | | | |
| ATEC | 7.63 ± 0.27 | 7.25 ± 0.37 | 84.72 ± 1.33 | 99.60 ± 0.69 |
| ATBC | 0.44 ± 0.01 | 12.19 ± 0.58 | 86.37 ± 1.98 | 98.99 ± 1.39 |
| DBS | 10.77 ± 0.03 | 1.51 ± 0.01 | 87.43 ± 0.25 | 99.73 ± 0.25 |
| DEP | 2.46 ± 0.15 | 10.59 ± 1.23 | 87.41 ± 1.02 | 100.46 ± 0.37 |
| DBP | 0.37 ± 0.01 | 13.74 ± 1.46 | 85.92 ± 0.88 | 100.03 ± 0.89 |
| TBC | 0.81 ± 0.01 | 9.88 ± 0.69 | 89.22 ± 0.75 | 99.91 ± 0.06 |

*Abbreviations*: TEC, triethyl citrate; ATEC, acetyltriethyl citrate; ATBC, acetyltributyl citrate; DBS, dibutyl sebacate; DEP, diethyl phthalate; DBP, dibutyl phthalate; TBC, tributyl citrate; TA, triacetin.

an uneven plasticizer distribution within the film, potentially causing changes in the mechanical and especially release properties upon aging. A thermal treatment following the coating (curing step) (11–12,14), which is nowadays widely used to promote further coalescence of the colloidal polymer particles and to overcome stability problems, may also result in a more homogeneous distribution of the plasticizer.

The TEC uptake into the polymer phase increased with increasing polymer content in the polymer dispersion, whereas the fraction dissolved in the aqueous phase decreased. Similar trends were also seen with the water-insoluble plasticizer DBS, with the amounts of plasticizer dissolved or emulsified into the aqueous phase decreasing with increasing pseudolatex solids content. Although most polymer dispersions available for the coating of solid dosage forms are obtained with a solids content of 30%, the coating is generally performed after diluting the dispersions to a solids content between 10% and 15%. In order to have most of the plasticizer present in the polymer particles, it is therefore recommended to add the plasticizer to the concentrated dispersions followed by dilution to the desired solids content just prior to coating, rather than first diluting the dispersion followed by addition of the plasticizer.

The rate at which the plasticizer diffuses into the colloidal particles determines the amount of plasticizer taken up by the polymer as a function of plasticization time. The diffusion or uptake rate thus affects the film formation process. Plasticizers differ greatly in the rate of the diffusion process (42). With water-soluble plasticizers such as TEC and TA, the distribution behavior of the plasticizers was virtually not affected by the mixing time or the degree of agitation.

Iyer et al. (46) determined the uptake of the water-insoluble plasticizer DBS into Aquacoat by using an alkaline partition column to separate the unbound plasticizer, and gas chromatography for the plasticizer assay. The uptake of DBS was found to be complete within 30 minutes, irrespective of the amount used, and the uptake rate was faster with increasing solids content of pseudolatex or when smaller quantities of plasticizer were incorporated. However, a previous study reported the presence of visible DBS droplets in Aquacoat after one week of mixing, indicating incomplete plasticization even after such a long plasticization time (13).

When emulsified in the aqueous colloidal dispersion, a water-insoluble plasticizer exists mainly in either the polymer or the emulsified phase, whereas a minor portion is present as dissolved plasticizer. The rate at which the plasticizer is taken up by the polymer particles corresponds well to the rate at which it is lost from the emulsified phase. Therefore, the rate of uptake can be expressed by the rate at which the emulsified plasticizer disappears from the aqueous phase (into the polymer phase). The effect of the plasticizer (ATBC) concentration (% w/w of polymer) on the rate of ATBC uptake by Aquacoat is shown in Figure 7.

The rate of plasticizer uptake is expressed as the amount of emulsified plasticizer remaining in the aqueous phase as a function of plasticization time. The pseudolatex, having a solids content of 15% w/w, was diluted from the original dispersion (30% w/w) with an equal volume of water. The ATBC uptake

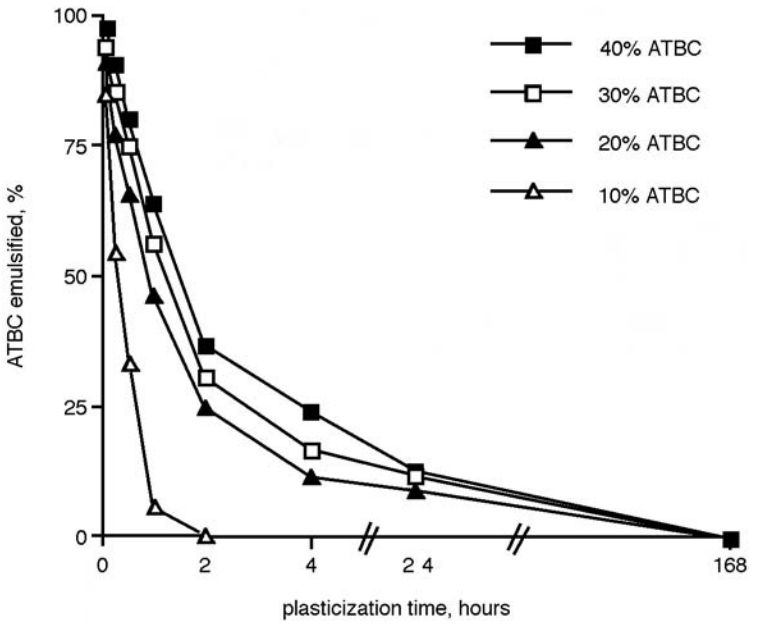


**Figure 7** Effect of ATBC concentration added (% w/w of polymer) on the rate of plasticizer uptake into Aquacoat®, expressed as the amount of emulsified plasticizer (% w/w of total ATBC added) remaining in the aqueous phase as a function of plasticization time (solids content, 15% w/w). *Abbreviation*: ATBC, acetyltributyl citrate. *Source*: From Ref. 47.

was fastest when 10% w/w ATBC was used; it decreased with increasing ATBC concentration. After 24 hours of plasticization, emulsified ATBC droplets were detectable at ATBC concentrations in excess of 10% w/w. The presence of the excess emulsified portion indicated an incomplete plasticizer uptake and therefore possible saturation of the polymer at the plasticizer concentrations used. However, when the dispersions were aged for a longer period, the emulsified plasticizer droplets gradually disappeared and could no longer be detected after one week of mixing.

Based on the experimentally determined uptake kinetics of water-insoluble plasticizers in Aquacoat, an appropriate mathematical theory could be developed taking into account all relevant mass transport phenomena (48). Figure 8A shows schematically the processes taken into account: (*i*) dissolution of the plasticizer droplets in the aqueous phase, and (*ii*) diffusion of the plasticizer within the polymer particles.

Initially, after adding the plasticizer to the aqueous dispersion, dissolution governs the overall transport kinetics (dissolution rate < diffusion rate). But increasing amounts of plasticizer located within the polymer particles lead to

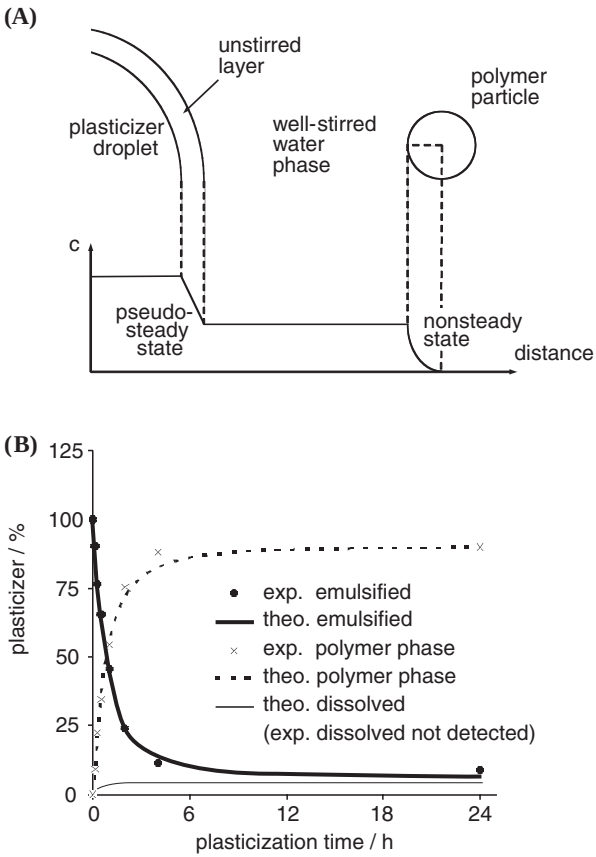


**Figure 8** Mathematical modeling of the uptake of a water-insoluble plasticizer into aqueous ethylcellulose dispersion: (**A**) schematic presentation of the processes taken into account; (**B**) experimentally measured (symbols) and theoretically calculated amounts (curves) of acetyltributyl citrate dissolved versus emulsified in the aqueous phase and taken up into the polymer particles (solids content of the polymer dispersion = 15% w/w, plasticizer concentration = 20% w/w based on polymer). *Source*: From Ref. 48.

decreasing concentration gradients and subsequently declining diffusion rates. A change of the governing mechanism is observed. During the final portion, diffusion controls the uptake kinetics (dissolution rate > diffusion rate). Dissolution and diffusion are taken into account simultaneously in the theory, which was used to determine the exact composition of the three-phase system at any time point (Fig. 8B) as well as the diffusion coefficients and dissolution rate constants of various types of water-insoluble plasticizers in Aquacoat. Knowing these parameters, the minimum stirring time necessary for sufficient plasticizer uptake (to avoid inhomogeneous coatings) can be calculated.

Not only will plasticizers affect the film formation from colloidal polymer dispersions or the mechanical properties of the resulting films, but their choice will also affect the drug release from the coated dosage form (2,3,11,46,49,50). Increasing the concentration of DBS or TEC decreased the drug release from Aquacoat-coated dosage forms (11), probably because of better fusion of the colloidal polymer particles.

The effect of the type of plasticizer on the theophylline release from beads coated with Aquacoat is shown in Figure 9.

The release from beads containing TA as a plasticizer was very rapid, indicating poor film formation even after curing at 60°C for one hour. TEC resulted in intermediate release properties, indicating good film formation, with the release being faster when compared to the water-insoluble plasticizers because of its higher water solubility. TEC has been reported to be a very effective plasticizer for Aquacoat (51). As expected, the drug release was slower with the water-insoluble plasticizers.

The appropriate choice of the type of plasticizer is particularly important when macromolecular release modifiers are added to Aquacoat (52). The affinity of the plasticizer to ethylcellulose can be different from its affinity to the release modifier, resulting in potential redistributions within the polymeric networks and subsequent changes in the release profiles during storage. Importantly, appropriate preparation (in particular curing) conditions can effectively avoid these phenomena.

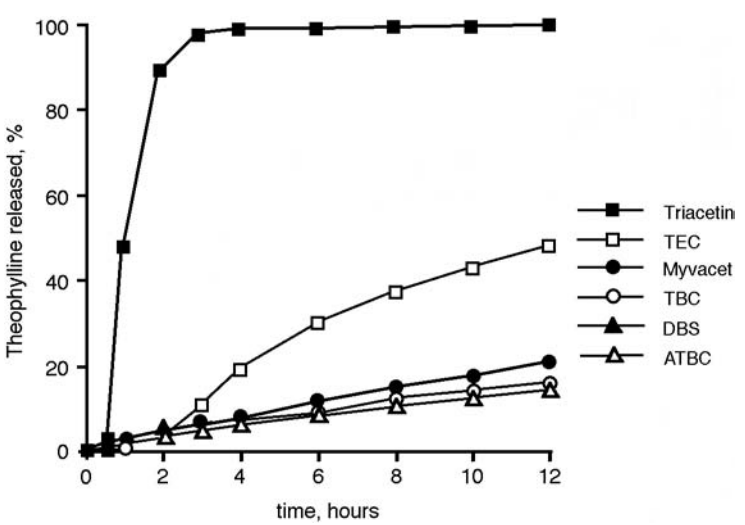


**Figure 9** Effect of types of plasticizer on the theophylline release from beads coated with Aquacoat® in 0.1 M HCl. *Abbreviations*: TEC, triethyl citrate; TBC, tributyl citrate; DBS, dibutyl sebacate; ATBC, acetyltributyl citrate. *Source*: From Ref. 14.

## PROCESS VARIABLES

The coating process and equipment also have a significant impact on the release behavior of controlled-release products as described in various chapters of this book. Process variables such as spray rate, droplet size, bed temperature, spray mode, and so forth can strongly influence the drug release (3–5,53,54).

The coating temperature should be sufficiently high to achieve efficient water removal and subsequent particle coalescence. In general, it should be 10°C to 20°C higher than the MFT of the polymer dispersion (55,56). The drug release with Surelease-coated theophylline pellets decreased on increasing the product temperature from 32°C to 48°C because of a more complete film formation (57). However, an excessively high inlet temperature can potentially cause difficulties in processing such as electrostatic interactions and agglomeration of the beads because of excessive drying or softening and sticking of the coating (5). It could also cause premature coalescence, resulting in a more porous and inhomogeneous film structure.

A process variable of particular importance is the curing of the coated dosage forms, which determines the degree of film formation.

### Curing of Aquacoat®-Coated Solid Dosage Forms

The coalescence of the colloidal polymer particles into a homogenous film is often incomplete after coating with aqueous polymer dispersions. As a consequence, changes in the drug release from the coated dosage form caused by further coalescence during storage have been observed as a function of storage temperature and time (4,7,13,14,58–60).

A curing step or thermal treatment (storage of the coated dosage forms at elevated temperatures for short periods) is often recommended to accelerate the coalescence of the polymer particles prior to long-term storage. Changes in drug release during storage can be circumvented. During the curing step, the coated dosage forms are subjected to a heat treatment above the glass transition temperature of the polymer. This is achieved either by storing the coated dosage forms in an oven or through further fluidization in the heated fluidized bed coater for a short time immediately after the completion of the coating process. The storage temperature should be about 10°C above the MFT (12). Higher curing temperatures could cause excessive tackiness and agglomeration of the solid dosage forms. An HPMC overcoat has been used to overcome tackiness and allow the curing step to be performed in the fluidized bed after coating (61).

CPM-containing beads were coated at 40°C with self-prepared ethylcellulose pseudolatexes identical in composition to Aquacoat (14). In that study, the coated beads were subsequently cured (in an oven) at 40°C, 50°C, and 60°C for periods of 1 to 24 hours. The drug release in pH 7.4 buffer was strongly affected by the curing conditions (Figure 10).

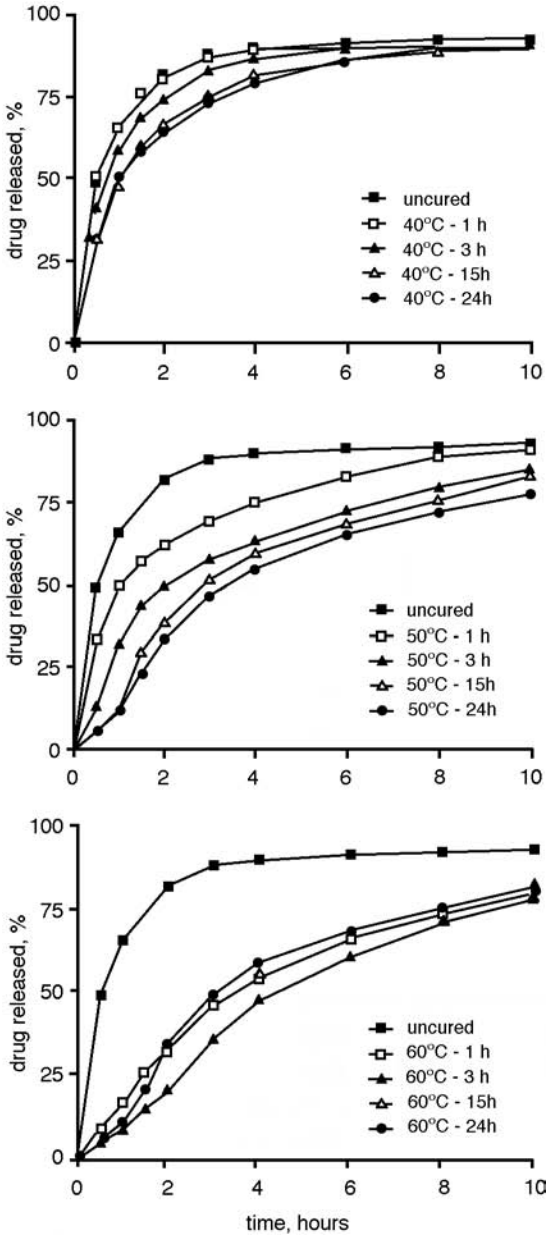


**Figure 10** Effect of curing conditions (curing temperature–curing time) on the chlorpheniramine maleate release in pH 7.4 phosphate buffer. *Source*: From Ref. 14.

Although the bed temperature was above the MFT of the pseudolatex, evaporation of water during the coating process could have resulted in a cooling effect and might have kept the temperature on the bead surface below the MFT (39). While curing at 40°C for 24 hours was insufficient, curing at either 50°C or 60°C resulted in a significant reduction in drug release. The limiting drug-release pattern was approached after curing the beads for one hour at 60°C. This value was also found by other authors (62). At a curing temperature of 50°C, longer curing times were required to approach the limiting drug-release pattern.

As an alternative to oven curing, Aquacoat-coated beads have been cured directly in the fluidized bed after the coated beads have been applied with a thin layer of HPMC (61). The hydrophilic overcoat prevented the sticking and agglomeration of the beads without altering the release profiles of the original coated pellets. The same technique has been used in the coating of pellets with other latex and pseudolatex coating systems (3,63).

The effect of thermal treatment was apparent with CPM-loaded beads coated with Aquacoat plasticized with varying plasticizer concentrations. Figure 11 shows

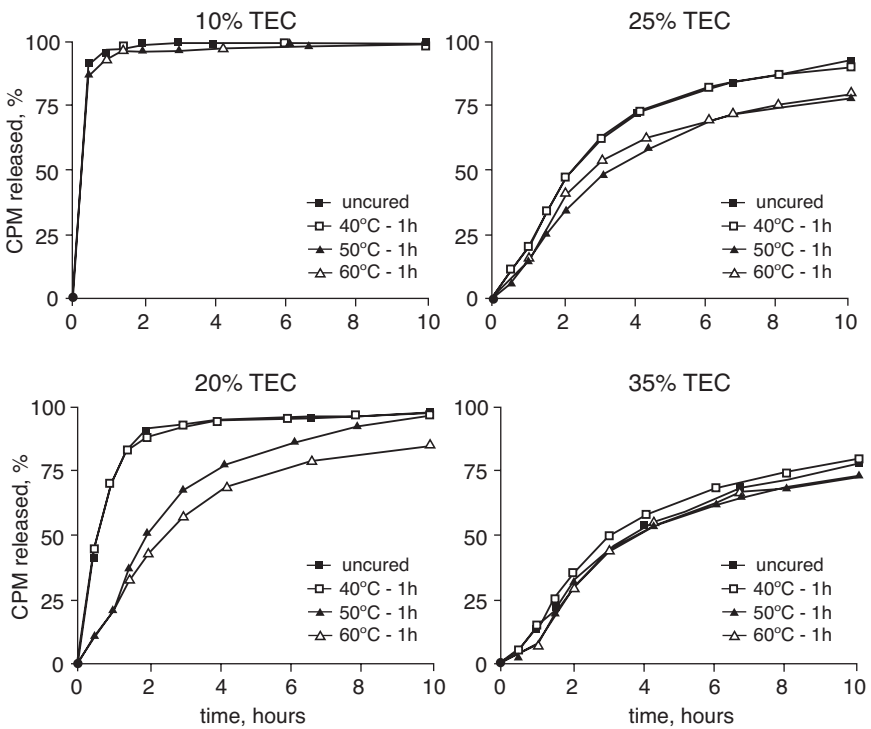


**Figure 11** Effect of TEC concentration and curing conditions (curing temperature–curing time) on the chlorpheniramine maleate release in pH 7.4 phosphate buffer. *Abbreviation*: TEC, triethyl citrate. *Source*: From Ref. 64.

the effect of the plasticizer (TEC) concentration and the curing temperature on CPM release in pH 7.4 buffer.

The drug release was very rapid when low concentrations (10% w/w of polymer) of TEC were used. This concentration range was insufficient for film formation, and curing could not further retard the drug release. With an intermediate concentration of TEC (20% w/w of polymer), curing temperatures of 50°C and 60°C resulted in a significant reduction in the drug release. The drug release approached the limiting pattern as the plasticizer concentration was increased to 25–35% w/w, and similar release profiles were obtained, irrespective of the curing temperatures. A curing step may therefore not be necessary at higher plasticizer concentrations.

Depending on the physicochemical properties of the drug and polymeric coatings, curing can influence the performance of the pseudolatex-coated dosage forms in different ways. While curing of the Aquacoat-coated CPM beads produced a retarding effect on drug release, curing of ibuprofen beads coated with a comparable coating system resulted in more complex drug-release patterns (64).

Figure 12 shows the effect of curing time on ibuprofen release from beads cured at 50°C.

The release was initially rapid, with the beads cured for 15 minutes, and then decreased with increasing curing time up to a curing period of four hours. The ibuprofen release was characterized by a rapid burst followed by a linear portion, indicating a region of constant drug release. At curing times in excess of four hours, the drug release increased. The initial decrease in drug release (up to a curing period of four hours) was due to the further coalescence of the polymer particles in the ethylcellulose film. The increase in drug release (curing periods in excess of four hours) could be explained by the migration of ibuprofen from the bead interior to the bead surface through the ethylcellulose coating during the curing step. After the application of the Aquacoat layer onto the drug beads, the surface of uncured beads was uniform and smooth. However, after the coated beads were subject to a curing step, large drug crystals could be observed throughout the coated surface by scanning electron microscopy. The formation of drug crystals indicated an outward migration of the drug during thermal treatment, which resulted in subsequent drug recrystallization on the film surface. During the thermal treatment of ibuprofen pellets, particle coalescence and migration of ibuprofen to the bead surface occurred simultaneously. When compared to CPM, ibuprofen has a much lower melting point (CPM: 130–135°C; ibuprofen: 75–77°C). The drug–polymer affinity coupled with the drug's low melting point could thus serve as an explanation for the phenomenon of drug migration, a process that was accelerated at elevated temperatures. The diffusion of guaifenesin, another low-melting drug, through Aquacoat coatings during storage of coated beads has also been observed (13). In order to retard or avoid the drug migration during the curing step, the drug beads can be seal-coated with a polymer having a low affinity for the drug, thus avoiding direct contact of the drug and ethylcellulose.

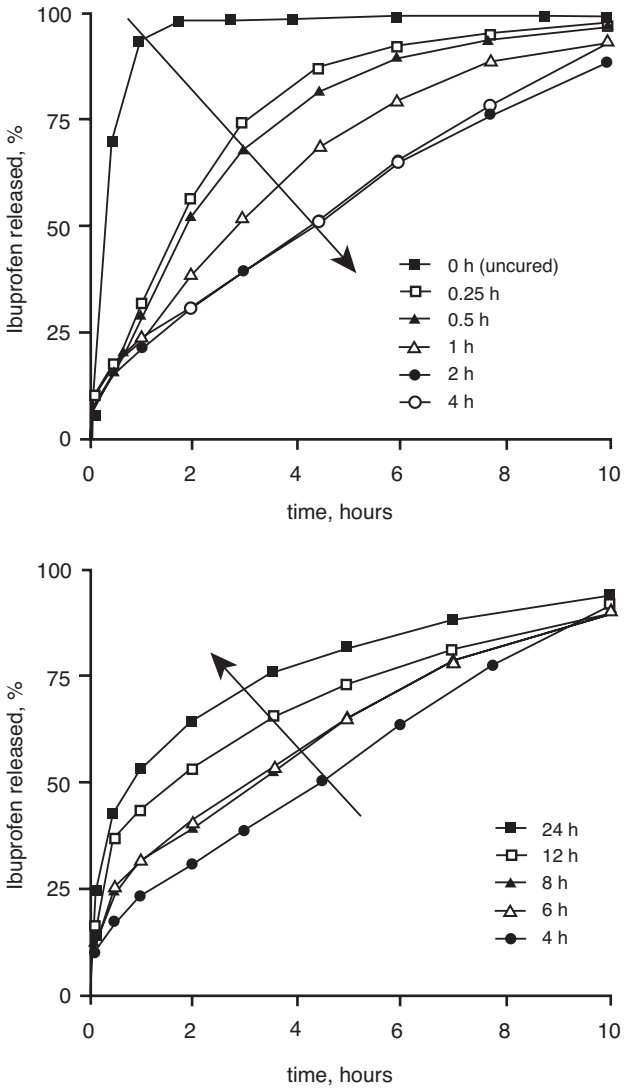


**Figure 12** Effect of curing time on ibuprofen release in pH 7.4 phosphate buffer from uncured and cured Aquacoat®-coated beads (curing temperature 50°C). *Source*: From Ref. 62.

Process variables involved in the coating of solid dosage forms and post-coating thermal treatment can significantly affect the drug release from the pseudolatex beads. Curing of the coated dosage forms not only can positively affect the coalescence of the polymeric particles, resulting in homogeneous films, but can also enhance the interaction of the drug core with the polymer coating. Both

a retardation and an increase in drug release were observed, with the extent being dependent on the drug type and curing conditions. The physicochemical properties of the drug and of the polymeric coatings including their interaction were important factors determining the drug release and the long-term stability of the coated dosage forms.

## MECHANICAL PROPERTIES OF ETHYLCELLULOSE FILMS

Polymer coatings are often characterized with respect to permeability and morphological and mechanical properties. The mechanical properties of dry polymer films are mainly affected by the thermomechanical properties of the polymer, such as glass transition or softening temperature, and by film additives such as plasticizers and fillers. They are rarely measured to predict the performance of the final coated dosage form under applied stress (e.g., compression, shipment) or in an aqueous environment, but primarily to study the effect of certain process or formulation factors on properties such as tensile strength, elongation, and various moduli. However, an important question to be answered relates to the performance of the coated dosage forms in dissolution or biological fluids. With oral drug delivery systems, the drug-release process is initiated by diffusion of aqueous fluids across the polymeric coating. The polymer films are hydrated and can contain significant amounts of water. In addition to film hydration, plasticizers or other film additives might leach into the aqueous environment. What are the mechanical properties of these hydrated films and how could they potentially affect the performance of the drug delivery system? The coated dosage form might be exposed to significant mechanical stress factors caused internally by the buildup of hydrostatic pressure due to water-soluble core ingredients or externally through peristaltic movements in the gastrointestinal tract. A rupturing of the film coat can result in a loss in protective or sustained release properties.

The mechanical properties (e.g., puncture strength and percent elongation at break) of polymeric films in the dry and the wet state can be evaluated and compared using a puncture test (63). They are strongly affected by the type of polymer dispersion. The ethylcellulose pseudolatexes Aquacoat and Surelease resulted in very brittle films in the dry state and weak and soft films in the wet state, with low values for puncture strength and elongation (<5%) in both cases (Table 3).

The brittle nature of the ethylcellulose films can possibly be explained by interchain hydrogen bonding and the bulkiness of the glucose subunits. Surelease, which is an ethylcellulose dispersion already plasticized with DBS, had slightly better mechanical properties in the wet state than Aquacoat films. Both ethylcellulose pseudolatexes are stabilized with anionic surfactants. However, in the case of Surelease, ammonium oleate converts to oleic acid, which then acts as a plasticizer during drying. With Aquacoat films, the presence of SLS might have been responsible for the lower wet strength as well as the higher water uptake when compared to Surelease films.

**Table 3** Mechanical Properties of Dry and Wet Films Prepared from Ethylcellulose Dispersions

| Polymer dispersion (film thickness, μm) | Puncture strength (MPa) | | Elongation (%) | |
|---|---|---|---|---|
| | Dry | Wet | Dry | Wet |
| Aquacoat®[a] (309) | 0.34 (0.11) | 0.10 (0.02) | 0.94 (0.18) | 0.13 (0.02) |
| Surelease® (394) | 0.23 (0.04) | 0.74 (0.10) | 0.62 (0.12) | 4.89 (0.9) |

[a]Plasticized with triethyl citrate (20% w/w).

As curing is often recommended after coating with colloidal polymer dispersions in order to enhance and complete the coalescence of the colloidal polymer particles in a homogenous film, it was thought that curing might improve the mechanical properties of the Aquacoat films. However, as shown in Table 4, the drying temperature and time had only minimal effects on the mechanical properties of films plasticized at two TEC concentrations.

Although the puncture strength increased with both dry and wet films after curing, the elongation was still less than 1%. The water-soluble plasticizer TEC almost completely leached from the films during exposure to aqueous media. In

**Table 4** Effect of Drying Conditions on the Mechanical Properties of Dry and Wet Aquacoat® Triethyl Citrate Films

| Triethyl citrate, % w/w (film thickness, μm) | Puncture strength (MPa) | Elongation (%) | Actual TEC content (%) |
|---|---|---|---|
| *Dry films* | | | |
| Drying temperature and time 40°C–48 hr | | | |
| 20 (385) | 0.21 (0.01) | 0.25 (0.03) | 19.89 (0.86) |
| 30 (356) | 0.23 (0.02) | 0.97 (0.26) | 27.86 (0.23) |
| Drying temperature and time 40°C–24 hr + 60°C–24 hr | | | |
| 20 (385) | 0.35 (0.02) | 0.56 (0.08) | 16.78 (0.28) |
| 30 (361) | 0.34 (0.05) | 1.00 (0.16) | 25.77 (0.46) |
| *Wet films* | | | |
| Drying temperature and time 40°C–48 hr | | | |
| 20 | 0.07 (0.00) | 0.08 (0.01) | 2.61 (0.70) |
| 30 | 0.08 (0.01) | 0.02 (0.00) | 0.84 (0.09) |
| Drying temperature and time 40°C–24 hr + 60°C–24 hr | | | |
| 20 | 0.13 (0.01) | 0.13 (0.02) | 3.98 (0.14) |
| 30 | 0.17 (0.00) | 0.14 (0.00) | 2.81 (0.51) |

dry films, the actual TEC content decreased with increased drying time and temperature, indicating evaporation and/or possible degradation of the plasticizer. In contrast, the mechanical properties of films prepared with another ethylcellulose dispersion, Surelease, were dependent on the coalescence temperature and type of plasticizer (64). No change in mechanical properties was observed at temperatures in excess of 60°C.

Ethylcellulose films when cast from organic solutions were stronger (higher puncture strength) in both the dry and the wet state than Aquacoat films (Table 5).

However, the elongation values were still low. Interestingly, TEC leached almost completely from the pseudolatex-cast film, whereas more than 75% of the original plasticizer was still present in films cast from organic solutions. This can be attributed to the different film coating structures, as detailed in the section titled Drug-Release Mechanisms. The pseudolatex-cast films took up almost 43% of water compared to only 12% by the solvent-cast films.

The permanence of the plasticizer in the film during coating, storage, and contact with artificial or biological fluids is important to assure the stability of the dosage form and consistent drug release. Bodmeier and Paeratakul (65) studied the leaching of water-soluble plasticizers (e.g., TEC) from polymeric films prepared by casting and drying of plasticized Aquacoat dispersion. The leaching was quite rapid from Aquacoat films and increased with increasing level of plasticizer. Although the selection of a leachable plasticizer had no negative effect on the film formation from aqueous polymer dispersions, it could have a significant impact on the permeability and mechanical properties of polymeric coatings during dissolution studies or in a biological environment.

Various pharmaceutically acceptable plasticizers have been used with ethylcellulose dispersions. Plasticizers are added to induce and enhance the coalescence of the colloidal polymer particles into a homogeneous film by reducing the glass transition and MFT and to improve the mechanical properties of the dried films.

**Table 5** Mechanical Properties of Solvent- and Pseudolatex-Cast Ethylcellulose–Triethyl Citrate Films

| Polymeric film (film thickness, μm) | Puncture strength (Mpa) | Elongation (%) | Triethyl citrate content in films (% w/w) | Water content (g, water/ g, polymer) |
|---|---|---|---|---|
| Dry films | | | | |
| Ethylcellulose[a] (313) | 3.04 (0.00) | 2.08 (0.00) | 20.02 (0.75) | – |
| Aquacoat® (385) | 0.35 (0.02) | 0.56 (0.08) | 16.78 (0.28) | – |
| Wet films | | | | |
| Ethylcellulose[a] | 0.56 (0.10) | 0.45 (0.15) | 16.29 (0.81) | 0.116 (0.017) |
| Aquacoat | 0.13 (0.01) | 0.13 (0.02) | 3.98 (0.14) | 0.426 (0.005) |

[a]Solvent cast.

**Table 6** Mechanical Properties of Dry and Wet Aquacoat® Films Plasticized with Different Plasticizers (30% w/w)

| Plasticizer (film thickness, μm) | Puncture strength (MPa) | | Elongation (%) | |
|---|---|---|---|---|
| | Dry | Wet | Dry | Wet |
| *Water-soluble* | | | | |
| TEC (309) | 0.34 (0.11) | 0.10 (0.02) | 1.34 (0.18) | 0.13 (0.02) |
| Triacetin (302) | 0.12 (0.04) | 0.03 (0.01) | 0.10 (0.05) | 0.03 (0.01) |
| *Water-insoluble* | | | | |
| ATBC (314) | 0.16 (0.05) | 0.19 (0.02) | 0.18 (0.09) | 1.69 (0.21) |
| ATEC (323) | 0.18 (0.05) | 0.06 (0.00) | 0.38 (0.15) | 0.31 (0.05) |
| DBP (327) | 0.60 (0.02) | 0.22 (0.02) | 1.21 (0.07) | 2.28 (0.09) |
| DBS (324) | 0.19 (0.04) | 0.09 (0.01) | 0.25 (0.09) | 0.30 (0.06) |
| DEP (324) | 0.18 (0.02) | 0.11 (0.02) | 0.21 (0.12) | 0.28 (0.12) |
| TBC (319) | 0.50 (0.06) | 0.16 (0.01) | 2.25 (0.45) | 1.79 (0.66) |

*Abbreviations*: ATBC, acetyltributyl citrate; ATEC, acetyltriethyl citrate; DBP, dibutyl phthalate; DBS, dibutyl sebacate; DEP, diethyl phthalate; TBC, tributyl citrate.

The effect of the water-soluble plasticizers TEC and TA and of the water-insoluble plasticizers TBC, ATBC, ATEC, DBS, DBP, and DEP on the mechanical properties of dry and wet Aquacoat films are shown in Table 6.

The mechanical properties of Aquacoat films were similar for all plasticizers. Dry films were very brittle and wet films soft and weak, as indicated by a low puncture strength and elongation. The elongation was less than 2% in most cases.

In summary, ethylcellulose films are weak in both the dry and the wet state, with low puncture strength and elongation values. In contrast, acrylic-based polymeric films are stronger and more flexible (63).

## DRUG-RELEASE MECHANISMS

Drug release from polymer-coated dosage forms is often controlled by diffusion through the intact polymeric film, through water-filled channels, or both. As the mobility of most drugs is much higher in aqueous fluids than in (dense) macromolecular networks, diffusion through water-filled pores is generally more important if both types of diffusion pathways are available. In addition to diffusional mass transport, convection may play an important role, for instance, in the case of highly osmotically active inner bead cores. The water influx at early time points can, for example, hinder drug diffusion in the opposite direction. Furthermore, limited drug solubility, drug partitioning between aqueous and polymeric phases, drug–polymer interactions, and (partial) plasticizer leaching into the surrounding bulk fluid, as well as bead swelling and rupture of the film coatings can be involved in the overall control of drug release. Thus, not only the permeability of

ethylcellulose coatings, but also their mechanical stability (in particular in the wet state) is of utmost importance for the underlying drug-release mechanisms (66). As illustrated in Figure 13, the water influx into polymer-coated, drug-layered sugar cores can generate significant hydrostatic pressure inside the systems acting against the film coatings.

In the case of poor mechanical film stability, cracks are created after a certain lag time (as soon as a critical threshold pressure is attained) and drug release occurs primarily via diffusion (and/or convection) through water-filled channels (67). In the case of mechanically stable film coatings, drug release is generally controlled by diffusion through the intact polymeric networks.

The mechanical stability of ethylcellulose film coatings can significantly be altered by adding varying amounts of a more flexible polymer, e.g., Eudragit L (66). Figure 14A shows how the underlying drug-release mechanism from Aquacoat: Eudragit L–coated verapamil HCl-layered sugar cores can be shifted from diffusion through water-filled channels to diffusion through the intact polymeric coatings.

The onset of crack formation can be experimentally monitored using different techniques, e.g., scanning electron microscopy. (However, the risk of artifact creation during sample preparation should not be underestimated.) Also, the changes in the pellets' diameter during drug release can serve as an indicator of crack formation. As long as the film coating remains intact and water continues to diffuse into the beads, their diameter increases. As soon as crack formation occurs, the increase in bead diameter levels off and the generated hydrostatic pressure within the pellets can eventually squeeze out liquids, resulting in pellet shrinking (this phenomenon is more likely in the case of high hydrostatic pressures built up in the bead core). Figure 14B shows as an example the experimentally measured

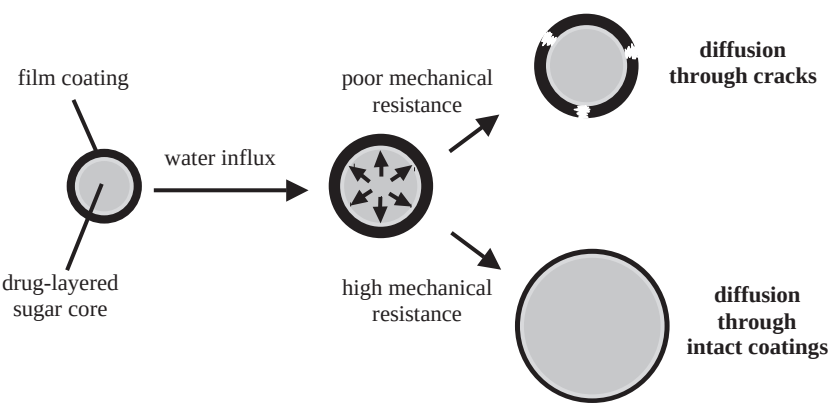


**Figure 13** Schematic presentation of the underlying drug-release mechanisms from polymer-coated, drug-layered sugar cores, depending on the mechanical stability of the film coatings. *Source*: From Ref. 66.

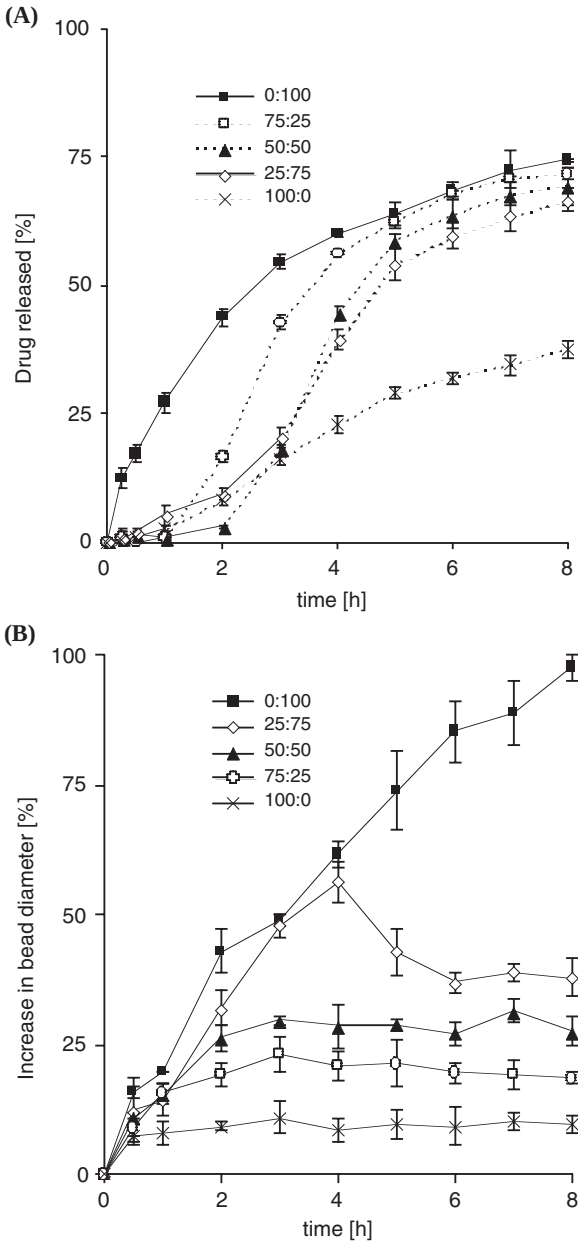


**Figure 14** Behavior of Aquacoat® Eudragit® L–coated (blend ratio indicated in the figures) verapamil HCl-layered sugar cores in 0.1 M HCl: (**A**) drug release; dotted curves indicate diffusion through water-filled cracks, solid curves through the intact film coatings; (**B**) change in pellet diameter. *Source*: From Ref. 66.

changes in pellet diameters of Aquacoat:Eudragit L–coated verapamil HCl-layered sugar cores upon exposure to 0.1 M HCl. The composition of the coatings was varied, resulting in different mechanical stabilities (ethylcellulose-rich films being brittle) and, thus, altered onsets of crack formation (indicated by the leveling off/decreasing bead diameter–time curves). The observed swelling kinetics agree well with the drug-release profiles from these systems (Fig. 14A).

Furthermore, it has been shown that the type of coating technique (using aqueous polymer dispersions vs. organic polymer solutions) significantly affects the inner film coating structure and, hence, the mechanical stability of the macromolecular networks (68). In organic solutions, the mobility of the polymer chains is high, leading to elevated degrees of polymer chain interdiffusion and thus intensive polymer chain entanglement in the resulting film coatings. Consequently, the polymeric barriers are stable. As ethylcellulose is poorly permeable for most drugs, this generally results in low release rates. In contrast, the mobility of the macromolecules within colloidal polymer particles is highly restricted and polymer chain interdiffusion is limited during film formation. Hence, the degree of polymer chain entanglement within the resulting films is lower than in systems prepared from organic solutions. Consequently, the coatings are mechanically weaker and cracks can more easily be formed, causing faster drug release (68,69).

The type of plasticizer can also affect the mechanical properties of ethylcellulose film coatings. It has recently been shown with Aquacoat-coated, propranolol HCl-layered sugar cores that different drug-release patterns can be achieved depending on the type of plasticizer used (water-insoluble DBS versus water-soluble TEC) (50). In contrast to DBS, TEC rapidly leaches out of the coatings, resulting in decreasing mechanical resistances of the films and thus facilitating crack formation. In addition, the hydrophilicity of the plasticizer significantly affects the water-uptake behavior of the film coatings and changes the coatings' toughness and drug permeability upon exposure to the release media. Thus, the type of plasticizer can significantly affect the underlying drug-release mechanisms in Aquacoat-coated dosage forms.

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# 9

# Chemistry and Application Properties of Polymethacrylate Systems

**Brigitte Skalsky and Hans-Ulrich Petereit**

*Research and Development Application Technology, Degussa Pharma Polymers, Röhm GmbH, Darmstadt, Germany*

## INTRODUCTION

### History of Poly(meth)acrylate Applications

More than 70 years ago, poly(methyl methacrylate) (PMMA) was invented as a crystal-clear, unbreakable organic glass of outstanding quality. With the trademark Plexiglas®, it achieved worldwide recognition as a unique synthetic material and a symbol of technical progress. The excellent biocompatibility of PMMA was detected early and it was used for artificial limbs and implants. PMMA is also well tolerated by the skin and the mucosa, so that dental prostheses and contact lenses made of PMMA are used even today. Many medical tools that come into direct contact with blood are made from PMMA or similar copolymers. Macroporous oxirane acrylic beads, commercialized under the trade name Eupergit®, gained significant importance in chemical and medical applications. Enzymes covalently immobilized on Eupergit serve as highly stable, recyclable catalysts in industrial biotransformation (1). Since the polymer does not activate the coagulation of blood, it is also used as an adsorbent for blood purification in extracorporeal therapy (2). Specialty stationary phases for chromatographic separation of biomolecules were developed from Eupergit (3).

### Definitions of Latexes and Their Physicochemical Specifications

Historically, functional pharmaceutical coatings were applied from polymer solutions in organic solvents. The preferred options of aqueous manufacturing

processes are based on enhancing polymer preparations, such as polymer dispersions or latexes, pseudolatexes, or colloidal solutions. The dispersing medium is water, and they are able to form a functional film under the conditions of application, in the presence of functional excipients, i.e., plasticizers.

The term *latex* is often used for aqueous polymer dispersions. It originally described rubber latex, which is called *natural latex*, in contrast to *synthetic latexes*, which are preferably prepared by emulsion polymerization. The term *pseudolatex* is used for dispersions that are prepared by emulsification of organic polymer solutions in water followed by the elimination of the organic solvents (4).

A polymer dispersion or latex is characterized by a particle size between 10 and 1000 nm. The upper limit is imposed by thermal convection and Brownian particle movement. Both together compensate the sedimentation velocity of the particles. The lower limit is defined by the light-scattering effect of the dispersed solids, resulting in a milky appearance. Latexes are characterized by low viscosity even when they have a high solids content. In the technical field of polymer applications, the terms *dispersions* and *latexes* are used synonymously. Systems of smaller particle sizes are called *microemulsions* or *colloidal solutions*. They are nearly transparent and exhibit the Tyndall effect in a light beam.

The term *minimum film-forming temperature* (MFT) is the temperature in degrees Celsius above which a continuous film is formed from dispersions under distinct drying conditions (5,6). Film formation is correlated to the glass transition temperature ($T_g$) of the polymer itself, which is defined as that temperature at which the viscosity of a melted thermoplastic polymer increases considerably while the temperature is continuously decreasing. In molecular terms, this is the temperature at which the flexibility of polymer chains and thus their material properties change. One widely used method for the determination of $T_g$ is the differential scanning calorimetric method described by Turi (7).

## Systematics of Nomenclature and Commercialized Products

The trade name Eudragit® is a composite of the Greek *εὐ*, meaning "good" or "functional" and the German *dragieren*, meaning "(sugar) coating"; thus the meaning of the trademark is "excellent functional coating." The product line includes pharmaceutical copolymers from esters of acrylic or methacrylic acid whose properties are determined by functional groups. The individual grades differ in their proportion of neutral, alkaline, or acid groups and thus in terms of their physicochemical properties. Amongst soluble polymers, a distinction is made between cationic Eudragit E types, soluble in acidic fluids, and anionic Eudragit L, S, and FS types, which dissolve in neutral or alkaline fluids, respectively. Insoluble Eudragit RL/RS types carry hydrophilic quaternary ammonium groups as hydrochlorides, providing different permeability, whereas the insoluble Eudragit NE/NM types include no functional groups. These insoluble polymers absorb water from physiological fluids and swell in a pH-independent way to create diffusional barriers for time-controlled drug release.

While the letters in the trade names include chemical information and functionality, the numbers that follow indicate the polymer concentration (%-w/w) in liquid products or solids. Granules produced by bulk polymerization or extrusion may be milled or micronized to powders and are designated by the letters PO. The different physical forms are based on identical polymers and enable harmonized analytical and regulatory procedures, no matter which physical form was applied.

## CHEMISTRY, PRODUCTION, AND QUALITY

### Chemical Structure

The (meth) acrylic chemistry provides unique polymer properties due to the number of different esters, which can be included in the covalently linked C–C backbone by copolymerization. Thus, physicochemical properties are advantageously influenced to meet physiological needs. Chemical structure, names, and functions are summarized in Tables 1 and 2 .

#### Soluble Polymers

By introducing cationic or anionic functional groups as free acids or esters into the polymer side chain, pH-dependent solubility is achieved, which enables pH-controlled solubility of the polymer coatings and thus defined drug release. In response to the physiological pH profiles of humans, these polymers enable gastrointestinal targeting to either the stomach, small intestine, or colon.

**Acid-soluble polymers:** The cationic monomer dimethylaminoethyl methacrylate (DMAEMA), copolymerized with methyl and butyl methacrylate, ensures acid solubility beneath pH 5 by salt formation with anions present in the gastric fluid (Fig. 1). These salts remain soluble over the entire physiological pH range and are neither precipitated by pH nor enzymes of gastric and intestinal fluids. Thus, the polymer is preferably used for taste or odor masking and moisture protection. The polymer Eudragit E 100 is manufactured by bulk polymerization and extrusion. It was commercialized as granules for solvent coating processes. Recently a micronized modification, Eudragit E PO, with a particle size of approximately 10 μm, was developed, enabling aqueous coating processes from a colloidal solution (8). Thin coatings of 50 to 100 μm provide efficient moisture protection due to low water vapor permeability and also efficient taste-masking properties (Fig. 2).

**Alkali-soluble polymers:** The monomer methacrylic acid (MAA) determines the solubility properties of anionic poly(meth)acrylates, enabling pH-dependent targeting along the gastrointestinal tract. Primarily, the quantities of methacrylic acid in the polymerization process determine the pH of polymer dissolution. However, the ester comonomers significantly contribute to the dissolution and thermal properties as well.

**Table 1** Chemical Structure and Characteristics of Soluble Methacrylate Copolymers

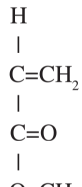
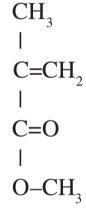
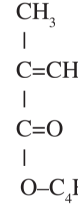
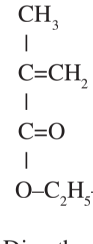
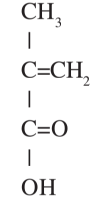
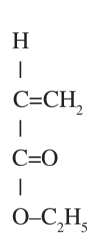
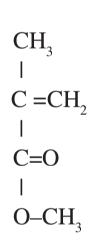
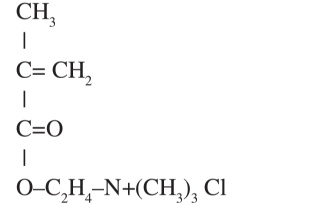
| Monomers | Methylacrylate (MA) | Methylmethacrylate (MMA) | Butylmethacrylate (BMA) | Dimethyaminoethyl methacrylate (DMAEMA) | Methacrylic acid (MAA) |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| Scientific name (IUPAC) | | Structure | Solubility | Eudragit® types | Commercial forms |
| Poly(butyl methyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate) 1:2:1, 150,000 | | MMA-BMA-DMAEMA = 25:25:50 | Below pH 5.0 | E 100 | Granules |
| | | | | E PO | Powder |
| | | | | E 12.5 | Organic solution |
| Poly(methacrylic acid-co-ethyl acrylate) 1:1, 250,000 | | EA-MAA = 50:50 | Above pH 5.5 | L 30 D-55 | Aqueous dispersion |
| | | | | L 100-55 | Powder |
| Poly(methacrylic acid-co-methyl methacrylate) 1:1, 135,000 | | MMA-MAA = 50:50 | Above pH 6.0 | L 100 | Powder |
| | | | | L 12.5 | Organic solution |
| Poly(methacrylic acid-co-methyl methacrylate) 1:2, 135,000 | | MMA-MAA = 70:30 | Above pH 7.0 | S 100 | Powder |
| | | | | S 12.5 | Organic solution |
| Poly(methylacrylate-co-methyl methacrylate-co-methacrylic acid) | | MMA-MA-MAA = 25:65:10 | Above pH 7.0 | FS 30 D | Aqueous dispersion |

**Table 2** Chemical Structure and Characteristics of Insoluble Methacrylate Copolymers

| |  |  |  |
|---|---|---|---|
| Monomers | Ethyl acrylate (EA) | Methyl methacrylate (MMA) | Trimethylammonioethyl methacrylate clorid (TMAEMA) |

| Scientific name | Structure | Permeability | Eudragit® types | Commercial forms |
|---|---|---|---|---|
| Poly(ethyl acrylate-co-methyl methacrylate) 2:1, 800,000 | MMA-EA = 30:70 | Medium | NE 30 D | Aqueous dispersion |
| | | | NE 40 D | Aqueous dispersion |
| Poly(ethyl acrylate-co-methyl methacrylate) 2:1, 600,000 | MMA-EA = 30:70 | Medium | NM 30 D | Aqueous dispersion |
| Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2, 150.000 | MMA-EA-TMAEMA = 60:30:10 | High | RL 100 | Granules |
| | | | RL PO | Powder |
| | | | RL 30 D | Aqueous dispersion |
| | | | RL 12.5 | Organic solution |
| Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1, 150.000 | MMA-EA-TMAEMA = 65:30:5 | Low | RS 100 | Granules |
| | | | RS PO | Powder |
| | | | RS 30 D | Aqueous dispersion |
| | | | RS 12.5 | Organic solution |

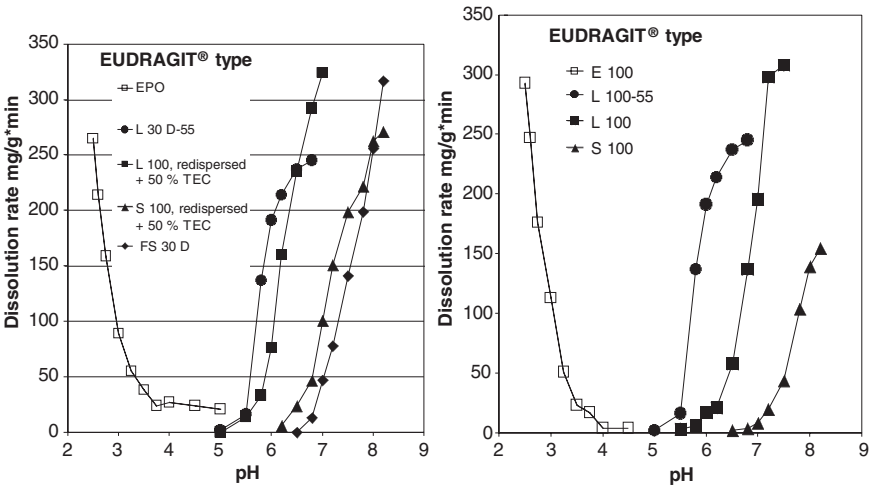



**Figure 1** pH-controlled solubility of methacrylate films from aqueous (*left*) and solvent processing (*right*).

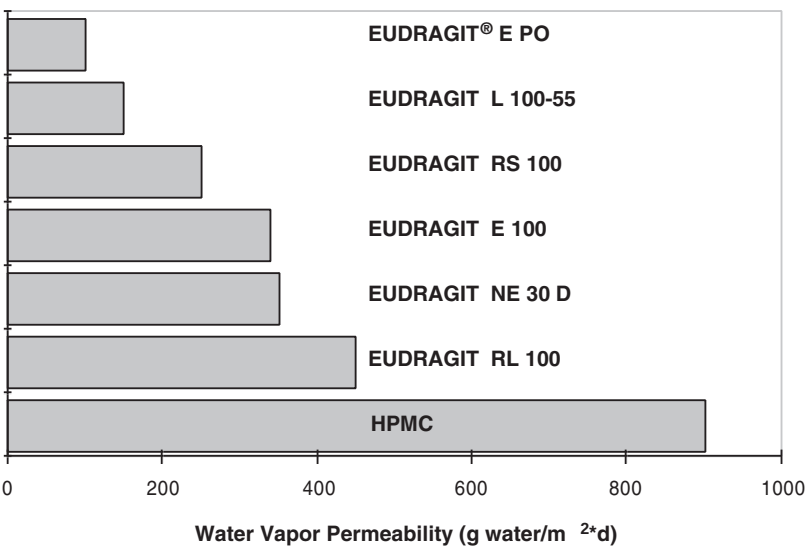



**Figure 2** Water vapor permeability of pharmaceutical coating materials, measured according to DIN 53122 with isolated films of 25 μm thickness. *Abbreviation*: HPMC, hydroxypropyl methylcellulose.

Eudragit L 100 and Eudragit S 100 copolymers, containing 50% (w/w) and 30% (w/w) methacrylic acid, were historically developed for solvent-based coating processes providing drug release above pH 6 and pH 7, respectively. Aqueous Eudragit L/S coatings shift the drug release toward lower dissolution pH values compared to corresponding solvent coatings. Changing the ester monomer from methyl methacrylate (MMA) to ethyl acrylate (EA) reduced the $T_g$ and MFT significantly (Table 3). The polymer was commercialized as a latex dispersion, Eudragit L 30 D-55, and as a powder, Eudragit L 100-55. Due to the influence of the neutral ester monomer, the pH of dissolution was reduced to 5.5, providing reliable enteric protection and a faster drug release in the upper intestine (Fig. 1). Polymer chain flexibility could be increased even further by introducing methyl acrylate as an ester monomer. The aqueous dispersion of a copolymer composed of MAA:MA:MMA = 10:65:25 is commercialized as Eudragit FS 30 D. With the methyl acrylate polymer, the presence of only 10% methacrylic acid provides even faster dissolution above pH 7 than Eudragit S containing 30% methacrylic acid. Both polymers allow colon targeting of drugs. Thermal properties such as $T_g$ and MFT are significantly reduced compared to with Eudragit S 100 (Table 3), and elongation at break is increased up to 300% (12).

### Insoluble Copolymers

Polymerizing neutral esters of acrylic acid or methacrylic acid, including derivatives with quaternary ammonium salts, creates water-insoluble polymers. They absorb water and swell in physiological media. Coatings or matrix structures form

**Table 3** Physicochemical Properties of Pharmaceutical Methacrylate Copolymers

| Type | Mw [g/mole] | Tg,m [°C] | MFT [°C] | Thermal stability of functional group [°C][a] | Elongation at break $\varepsilon_R$ [%] |
|---|---|---|---|---|---|
| Eudragit® E | 47,000 | 48 | NA | 220 | 70[b] |
| Eudragit L 100-55 | 278,000 | 110 | 25 | 157 | 14[c] |
| Eudragit L | 123,000 | >150 | >100 | 190 | NA |
| Eudragit S | 123,000 | 160 | >100 | 186 | NA |
| Eudragit FS | 283,000 | 48 | 14 | 207 | 300 |
| Eudragit NE | 918,000 | −8 | 5 | NA | 600 |
| Eudragit NM | 600,000 | −8 | 5 | NA | 600 |
| Eudragit RL | 31,000 | 50 | 40 | 140 | 300[d] |
| Eudragit RS | 30,000 | 55 | 45 | 140 | 250[d] |

[a]TGA, 1% decomposition within 5 min.
[b]10% (w/w) sodium lauryl sulfate, 15% (w/w) stearic acid.
[c]10% (w/w) TEC.
[d]20% (w/w) TEC.
*Abbreviations*: Mw, molecular weight; MF, minimum film-forming temperature; TGA, thermogravimetric analysis; TEC, triethyl citrate.
*Source*: From Refs. 9–11, 60.

reproducible diffusion barriers. Their biological function may be influenced by specific ions or osmotic pressure, but solubility remains pH independent in biological systems. Thus, these polymers gained significant importance in the formulation of time-controlled release oral single and multiunit dosage forms.

### Neutral Polymers

Latexes are formed by emulsion polymerization of MMA and EA. The polymer is commercialized as Eudragit NE 30 D/NE 40 D and Eudragit NM 30 D. The latter provides a broader application range due to the use of polyethylene glycol-600 stearyl ether NF as an emulsifier. Drug release is controlled by coating thickness. IN addition to the coating of small particles, such as crystals, granules, and pellets, the polymer gained significant importance in the formulation of controlled-release tablets. Particularly, Eudragit NM 30 D can be used in wet granulation processes as a binder for controlled release (CR) matrix tablets. The unique flexibility of the polymer enables the compression of coated particles into rapidly disintegrating controlled-release tablets without a significant influence on the drug-release profile by compression (Table 3).

**Ionic polymers:** In order to expand the variability in the release kinetics from controlled-release single and multiunit dosage forms, hydrophilic polymers containing trimethylammonio ethyl methacrylate chloride (TMAEMACl) as hydrophilic moieties have been developed. Eudragit RL, carrying 10% (w/w) TMAEMACl, provides relatively high permeability, while Eudragit RS includes 5% (w/w) only. The polymers are synthesized by bulk polymerization and can be mixed in any ratio for optimized drug-release profiles. Figure 3 shows how the ratio of RS and RL polymers influence the diffusion rate of two model drugs.

The polymers swell in water depending on their content of hydrophilic quaternary ammonium groups. Since quaternary ammonium groups dissociate completely in physiological media of pH 1 to 8, the permeability of coatings was found to be pH independent. Their particular value in controlled-release dosage forms is based on their miscibility in any ratio (13). Thus, release kinetics can be adjusted to accommodate pharmacokinetic needs and the solubility of the active compound.

## Manufacture

### Bulk Polymerization and Extrusion

Bulk polymerization is a technically well-developed process that is used for the production of the hydrophilic poly(meth)acrylic esters Eudragit RL 100 and Eudragit RS 100, as well as Eudragit E 100. By this process, a mixture of liquid monomers is polymerized under controlled temperature conditions. Polymerization is an exothermic process. Cooling is often necessary in the initial phase to control polymerization kinetics and thus polymer structure. Initiators, preferably peroxides, start the polymerization process by forming radicals and are included as end groups in the polymer chains. Chain transfer agents, which moderate the

molecular weight, react with polymer radicals and are also found as terminal groups in the polymer chains. To obtain free-flowing granules, bulk polymers are extruded. During the extrusion process, volatile components of the polymer raw material such as residual monomers, solvents, and polymerization modifiers can be evaporated by vacuum. However, the limited thermal stability of functional groups in methacrylate copolymers has to be considered (14).

### Emulsion Polymerization

The anionic methacrylic acid copolymers Eudragit L 100-55, Eudragit L 100, Eudragit S 100, and Eudragit FS 30 D and the copolymers of neutral (meth)acrylic esters Eudragit NE 30 D and Eudragit NM 30 D are produced by radical emulsion polymerization (15,16). The mechanism of emulsion polymerization for water-insoluble or poorly soluble (meth)acrylic monomers is illustrated in Figure 4.

The monomers are dispersed in water by stirring and emulsifier addition, which stabilizes the monomer droplets. Polymerization is started by adding a hydrophilic initiator into the water phase containing monomer molecules dissolved or solubilized in micelles if the emulsifier concentration is above the critical micelle concentration (CMC). During the initial phase, particle formation is completed rapidly. The polymer chain growth reaction is maintained by monomer diffusion from the surface of the monomer droplets via the water phase to the

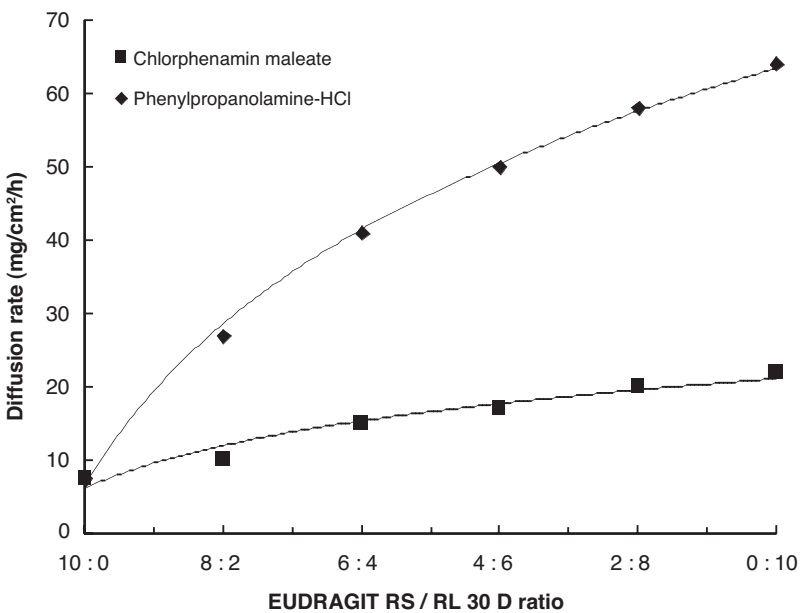



**Figure 3** Diffusion rate of drugs through isolated films prepared from mixtures of Eudragit® RL 30 D and Eudragit RS 30 D tested in diffusion cells. *Source*: From Ref. 13.

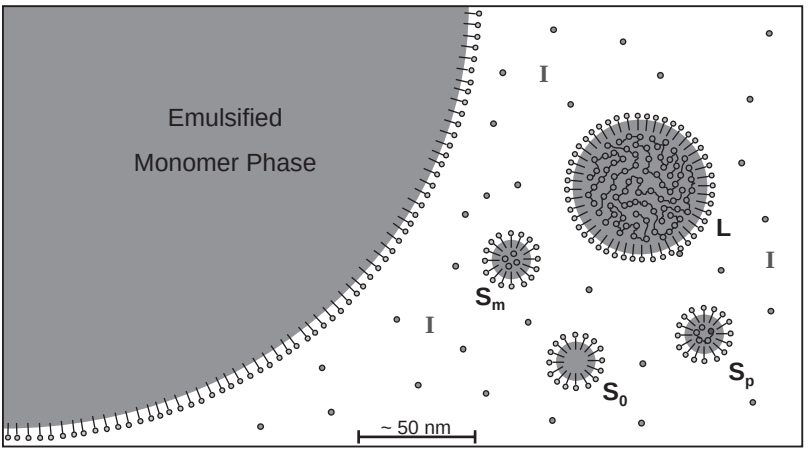



**Figure 4** Mechanism of particle formation by emulsion polymerization. (o) monomer molecule in the water phase, (-o) water soluble emulsifier molecule, (I) initiator molecule, (So) empty micelles of emulsifier and monomer molecules, (Sm) micelles of emulsifier and monomer molecules, (Sp) micelles oligomer radicals, (L) dispersed, final, end polymerized latex particles.

latex particles. In the latex, the molecular weight of the polymer can be controlled by the concentration and the decomposition rate of the initiator and chain transfer agent. Modern test methods of molecular weight distributions are based on gel permeation chromatography using polyester gels (9,10). The data are summarized in Table 3.

Typical initiators are peroxides, which start polymer chain growth by radical reactions with monomers. Finally, they are chemically bound and built into the polymers as terminal alcoholic or ester groups. The amount of residual monomers can be reduced by optimizing the polymerization conditions at the end of the process, and they can also be eliminated by evaporation.

### Further Processing

**Drying:** Aqueous latex dispersions of methacrylic acid copolymers can be processed to free-flowing powders by spray- or freeze-drying. The resulting products consist of loose agglomerates of uncoalesced latex particles if the temperature during the drying process is held below the MFT. Such solid materials can be redispersed in water, forming a stable latex dispersion that is nearly identical to the original latex in its relevant technical characteristics such as particle size, film formation, and coating functionality (17). The methacrylic acid copolymers Eudragit L 100, Eudragit L 100-55, and Eudragit S 100 are produced in this manner, providing longer storage stability and enabling compression.

Another process that can be used even with softer polymer latexes is freeze-drying. The process avoids coalescence of soft dispersions such as Eudragit

NE 30 D and Eudragit FS 30 D. The dried agglomerates show poor flow properties due to their irregular shape and stickiness caused by low glass transition temperatures. Hence, these products are preferably used in thermal processes such as melt extrusion (18,19) or injection moulding.

**Milling:** Polymers from bulk polymerization are available in the form of cylindrical granules, because the final process step is extrusion. Hence the materials need to be milled, in order to enable dispersing in water or direct compression to matrix tablets. As the glass transition temperatures of these polymers are low, the milling process needs to be controlled exactly, particularly in terms of temperature. Pin mills or jet mills are used due to efficient cooling of the high air flow. They create suitable narrow particle size distributions with maxima between 10 and 100 μm. Finally, sieving is performed in conventional equipment.

**Direct dispersion of ionic insoluble polymers:** A production process was developed to directly disperse extruded granules and milled powders of Eudragit RL 100 and Eudragit RS 100 to latexes. The statistical distribution of the polar groups enables direct emulsification in water without surfactants at elevated temperatures above the polymer $T_g$ (Table 3). At the dispersing temperature of 80ºC, the flexibility of the polymer chains is increased, and, supported by the ionic effects of the quaternary groups, a self-dispersing process starts forming latexes with mean particle sizes of approximately 100 nm. Although particle size distributions of thermally dispersed cationic polymers are broader than those from emulsion polymerization, reliable film formation is ensured by the addition of hydrophilic plasticizers in coating suspensions. For industrial production, the dispersion process is supported and accelerated by a disperser. Thus, the polymers are available as 30% aqueous dispersions (Eudragit RL/RS 30 D) for solvent-free granulation and coating processes (13).

## Pharmaceutical Quality

### Polymer Characterization and Quality Control

Pharmaceutical quality is based on the high purity of raw materials, specific manufacturing equipment, and controlled polymerization processes, as described above. The procedures exceed the directions of ISO9001 and ISO14001. Quality control involves identity, functional, and purity testing.

The proof of identity involves infrared–spectroscopic methods. As functional groups determine the polymeric properties in dosage forms, their assay, preferably determined by titration, serves as proof of identity and functionality. Further meaningful tests include particle size, loss on drying, viscosity, refraction index, and relative density. Purity testing includes traditional pharmaceutical tests such as sulfated ash/residue on ignition and heavy metals. Polymer-specific tests determine residual monomer content. These important procedures, which are described specifically in every pharmacopoeia, verify functionality in dosage forms, as well as the low toxicity of the polymeric excipients.

**Table 4** Registration and Toxicological Information on Pharmaceutical Methacrylate Copolymers

| Type | Year of introduction | Pharmacopoeia monographs and DMFs | Daily dose considerations |
|---|---|---|---|
| Eudragit® E | 1959 | Basic Butylated Methacrylate Copolymer—Ph. Eur.<br>Aminoalkyl Methacrylate Copolymer E—JPE<br>DMF 1242 (USA)<br>PR-MF 6918 (Canada) | 20 mg/kg |
| Eudragit L | 1954 | Methacrylic Acid Copolymer, Type A—NF<br>Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)—Ph. Eur.<br>Methacrylic Acid Copolymer L—JPE<br>Polimetacrilatos Tipo A—Ph. Mex.<br>DMF 1242 (USA)<br>PR-MF 6918 (Canada) | 1–2 mg/kg |
| Eudragit S | 1954 | Methacrylic Acid Copolymer, Type B—NF<br>Methacrylic Acid–Methyl Methacrylate Copolymer (1:2)—Ph. Eur.<br>Methacrylic Acid Copolymer S—JPE<br>Polimetacrilatos Tipo B—Ph. Mex.<br>DMF 1242 (USA)<br>PR-MF 6918 (Canada) | 1–2 mg/kg |
| Eudragit L 100- 55 | 1972 | Methacrylic Acid Copolymer, Type C—NF<br>Methacrylic Acid–Ethyl Acrylate Copolymer (1:1)—Ph. Eur.<br>Dried Methacrylic Acid Copolymer LD—JPE | 8 mg/kg |

| | | | |
|---|---|---|---|
| | | Polimetacrilatos Tipo C—Ph. Mex.<br>DMF 2584 (USA)<br>PR-MF 8216 (Canada) | |
| Eudragit FS | 1999 | DMF 13941 (USA) | 15 mg/kg |
| Eudragit NE/NM | 1972/2006 | Polyacrylate Dispersion 30%—Ph. Eur.<br>Poly(ethylacrylat-methylmethacrylat)-Dispersion 30%—Ph. Eur.<br>Ethyl Acrylate Methyl Methacrylate Copolymer Dispersion—JPE<br>DMF 2822 (USA)<br>PR-MF 6918 (Canada) | 20 mg/kg |
| Eudragit RL | 1968 | Ammonio Methacrylate Copolymer, Type A—NF<br>Ammonio Methacrylate Copolymer (Type A)—Ph. Eur.<br>Aminoalkyl Methacrylate Copolymer RS—JPE<br>DMF 1242 (USA)<br>PR-MF 6918 (Canada) | 10 mg/kg |
| Eudragit RS | 1968 | Ammonio Methacrylate Copolymer, Type B—NF<br>Ammonio Methacrylate Copolymer (Type B)—Ph. Eur.<br>Aminoalkyl Methacrylate Copolymer RS—JPE<br>DMF 1242 (USA)<br>PR-MF 6918 (Canada) | 10 mg/kg |

*Abbreviation*: DMF, drug master file.

Residual monomer content in commercial Eudragit products for pharmaceutical purposes can be determined by liquid chromatography. The total content of residual monomers is below 0.3% in commercial products and even lower in sprayed films due to the evaporation of the volatile substances during the coating process.

Particular physical and microbiological aspects have to be considered in the context of aqueous polymer dispersions. Physical stability, indicated by the particle size of the dispersed phase, can be achieved over a period of more than 18 months under ambient conditions. Latexes are sensitive to freezing, thermal stress, the addition of electrolytes, and pH changes that affect the physical stabilization of latex particles by ionic charges or react by salt formation or ion exchange with the particles or their stabilizing components.

Neutral poly(meth)acrylate latexes are sensitive to microbial contamination of the dispersing medium, water. Active chlorine can be added (5–10 ppm) in the form of sodium hypochlorite solution for disinfection. The weakly cationic, hydrophilic dispersions are preserved with 0.25% sorbic acid. Additionally, 0.1% hydrogen peroxide may be added, if required. Microbial growth in anionic polymethacrylic acid copolymer latexes is avoided in acidic environments below pH 3, as a result of the free carboxylic groups in the polymer chain (20). Thus Eudragit L 30 D-55 and Eudragit FS 30 D are self-preserved by the pH of the dispersion, provided the pH remains in the range of 2 to 3.

### Toxicology and Registration

The Eudragit polymers were first introduced to the pharmaceutical industry more than 50 years ago (Table 4).

Owing to the carbon backbone, degradation of the polymer chains in the human body, e.g., by hydrolysis, can be excluded and has never been observed. The polymeric structure is not affected by gastric acids or by digestive enzymes such as pepsin, trypsin, chymotrypsin, amylase, and lipase. Absorption, distribution, metabolism, and excretion (ADME) studies with radiolabeled polymers confirm that the polymers are not absorbed in the intestine but are rapidly excreted in the feces and remain chemically unchanged.

Studies in different animals including nonrodents confirm very low to negligible acute oral and dermal toxicity (>2000 mg/kg). Polymer-specific no-effect levels were investigated in chronic application studies for up to 52 weeks in dogs and pigs. Considering safety factors, dosage considerations were established, which ensure application of the polymers in conventional oral pharmaceutical dosage forms (Table 4). The polymers do not elicit teratogenic effects. In vitro data (Ames test, Mouse Lymphoma Assay, UDS) do not suggest any mutagenic potential.

## PROPERTIES, HANDLING AND FUNCTIONS

### Film-Forming Mechanisms

Aqueous latex dispersions exhibit a special film-forming mechanism. With drying progress the dispersed latex particles move closer to each other until they

form a dense sphere package. During further evaporation, the remaining water is squeezed out and the latex particles flow together and form a homogeneous film by coalescence. One driving force of the film-forming process is the generation of surface tension energy (2). However, the capillary forces developing in the channels between the latex particles in the dense sphere package obviously play a more important role. It can be calculated using the Laplace equation for the capillary pressure, $P = 2\ \gamma/r$, where $\gamma$ is the interfacial tension between water and air and $r$ is the radius of the latex particles (22) or the curvature of the aqueous meniscus (23). Both parameters—surface tension and particle radius—were assumed by Bindschaedler et al. (24) to be valid also in film-coating processes. Hence they need to be considered during the development phase of dispersions. Precondition for complete coalescence is a sufficient softness of the latex given by the polymer itself or adjusted by plasticizer addition.

The final film structure, which is in equilibrium with the coated core and the surrounding atmosphere, can be reached within a few minutes or, in some cases, may require several hours or even days, depending on the polymer and the processing parameters. Changes in the permeability and the dissolution rate profile may occur during this period. Thus, final testing should be performed when equilibrium has been reached. Film formation can be followed by scanning electron microscopy (SEM). Incomplete film formation may show individual latex particles in a densely packed arrangement, as seen in Figure 5. Under optimal film-forming conditions, films formed from latex dispersions are free of pores. When film-forming conditions are critical and high amounts of hydrophilic additives are present in the film, the permeability can be increased.

## Compatibility and Formulations

Common additives used in poly(meth)acrylate formulations and their impact on film properties and processing are described below. Examples of formulations containing various additives are shown in Table 5.

### Plasticizers

The addition of a plasticizer lowers the MFT to a certain extent, depending on the quantity added and the plasticizer's suitability for the specific polymer.

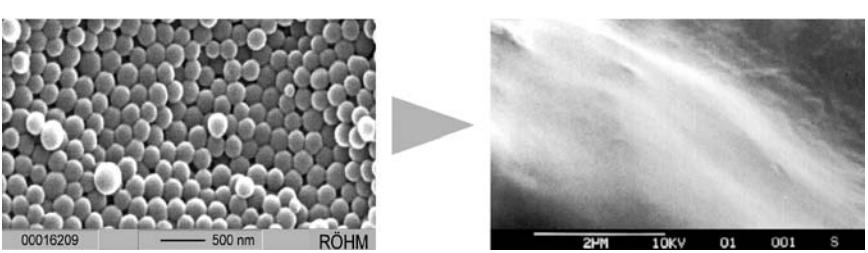



**Figure 5** Dense layer of latex particles during the film-forming process (*left*) and homogeneous film structure after coalescence (*right*).

Flexible polymers such as Eudragit E and Eudragit NE 30 D/NM 30 D usually do not require the addition of plasticizers due to their low $T_g$s; however, in special cases, plasticizers can be added, but sticking tendencies may arise. More brittle polymers such as Eudragit L/S types, Eudragit RL/RS, and Eudragit FS 30 D require plasticizers, usually in the range of 5% to 30%, calculated on dry polymer mass. Higher quantities can be added to achieve specific physical properties that are not required in standard film coatings. For redispersion of Eudragit L 100 and Eudragit S 100, the addition of 50% to 70% triethyl citrate is required to ensure a good redispersion process and a maximum MFT of 10ºC. Not every plasticizer is effective for every polymer (Fig. 6). Unsuitable plasticizers or insufficient amounts of plasticizer may lead to a loss in functionality due to crack formation caused by mechanical stress during the coating process or expansion effects of cores after coating. Insufficient MFT reduction is observed when combining Eudragit RL/RS 30 D with polyethylene glycols (PEGs), Eudragit FS 30 D with PEGs or polysorbate 80, and Eudragit L 30 D-55 with butyl citrates or other lipophilic esters. Besides triethyl citrate, the standard plasticizer in poly(meth)acrylate formulations, the following have successfully been employed: PEGs (preferably PEG 6000), acetyl triethyl citrate, to some extent butyl citrates, polysorbates (preferably polysorbate 80), dibutyl sebacate as a lipophilic plasticizer (preemulsification in water for aqueous formulations with 1% w/w polysorbate 80 and post-stirring over one hour recommended), and triacetin (disadvantage: hydrolysis during storage). As a general rule, it can be stated that at equivalent concentrations, the use of hydrophilic plasticizers leads to coatings with higher permeability and faster dissolution, whereas lipophilic ones reduce permeability and dissolution rate.

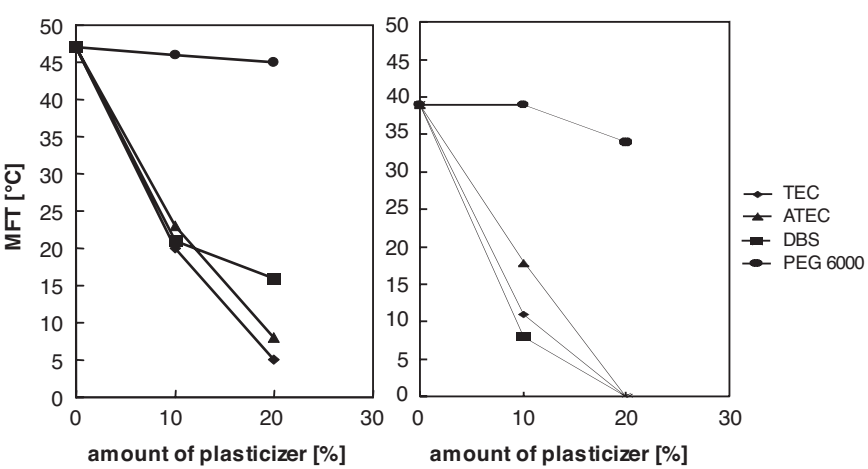



**Figure 6** Plasticization effects of various plasticizers as MFT reduction on Eudragit® RS (*left*) and Eudragit RL (*right*). *Abbreviation*: MFT, minimum film-forming temperature.

Plasticizers some water solubility such as triacetin or triethyl citrate can be added directly to the latexes; freely water soluble or even hygroscopic substances such as PEG and sorbitan esters should first be added as 20% to 35% aqueous solutions for improved physical stability. Water-insoluble plasticizers are usually emulsified in water using some latex-compatible emulsifier, i.e., 1% w/w polysobate 80 and mixed with the latex until equilibrium distribution is reached. Lipophilic plasticizers require longer stirring times, of several hours, when combined with aqueous polymer dispersions, in order to ensure proper distribution and equilibrium formation between the phases.

### Glidants or Antitacking Agents

To avoid sticking or agglomeration of the products during coating, drying, and storage, glidants are added to the spray suspensions. These materials are suspended separately and then added to the polymer mixtures. These materials can also be added in powder form by sprinkling. For coated particles, the addition of 0.5% to 2% talc, fumed silica, e.g., Aerosil® 200, or precipitated silica, e.g., Sipernat® PQ, can resolve tacking problems during storage. The powders can be added to the fluidizing particles after the coating process, or by spray application of an aqueous suspension. Alternatively, thin aqueous coatings based on glycerol monostearate (mono- and diglycerides NF) or hydroxypropyl methylcellulose (HPMC) will produce similar effects. The most commonly used glidants for poly(meth)acrylate formulations are described below.

Talc is often used in combination with pigments. Since it is a product derived from mineral sources, there is the risk of microbial contamination. Hence, it can contain free ions that may react with other components in the coating formulation and thus cause instabilities. Typical quantities are 25% to 100% based on dry polymer mass. With equal amounts of talc and polymer, opaque coatings are obtained. With more than 200% talc based on polymer weight, the permeability of the films increases and dissolution of enteric coatings in intestinal fluid will be delayed. Because larger particles may reduce permeability and the dissolution rate, the desired particle size and distribution should be specified (25,26).

Glycerol monostearate (mono- and diglycerides NF) is an excellent alternative to talc or magnesium stearate as a glidant in all aqueous formulations (27). Due to its high efficacy, typically 5% to 20% based on polymer mass is sufficient to achieve comparable effects. Glycerol monostearate is water insoluble. Fine-particle dispersions are prepared by emulsification in hot water (70–80ºC) in the presence of polysorbate 80. The main advantages compared to talc are the low risk of microbiological contamination, improved compatibility, and lower effective concentrations, which reduce total coating amounts and hence save production costs.

Precipitated silica (silicon dioxide NF) can be used in quantities up to 40% based on polymer mass. It has a matting effect and increases the permeability of film coatings. It is typically used for extended-release particle coatings and is not recommended for enteric coatings.

Magnesium stearate is somewhat more effective than talc and often provides good sealing of the film coatings and low permeability. However, it can only be used in organic polymer solutions or in aqueous formulations based on Eudragit NE/NM or Eudragit E, since coagulation or thickening may occur with other aqueous poly(meth)acrylate dispersions. Because of the reaction between magnesium ions and the carboxylic groups of the polymers, magnesium stearate is incompatible with anionic polymethacrylate latexes.

### Pigments and Dyes

The pigment-binding capacity of poly(meth)acrylates is excellent. Up to two to three parts by weight of solid additives, and in specific instances even up to 10 parts, can be incorporated into one part of dry polymer without affecting the film's properties. The pigment quantity necessary to cover an underlying surface of unpleasant or irregular color is about 2 to 3 mg/cm$^2$. This can be incorporated into a film of 10 to 15 μm thickness, which is about 1 to 1.5 mg dry polymer/cm$^2$. Titanium dioxide is a commonly used white pigment that has extremely high coverage power. It is combined with color pigments to obtain the desired shades. Its hard, abrasive properties are disadvantageous as it can lead to black spots on the coatings caused by grinded metal from the pan wall. For colored film coatings, the color pigments can be added to the functional coating, which may require higher polymer application, or alternatively be applied as a colored top coat. When white tablets are to be coated, smaller quantities of pigments are sufficient. Both aluminium lakes and iron oxide pigments are suitable. Colored lakes of poorer quality often contain significant amounts of water-soluble dyes, which may cause coagulation of the polymer, as these dyes often are strong electrolytes. Water-soluble dyes often lead to inhomogeneous, marbled colors, which rub off during handling. Dyes show lower stability against chemical influences and light than lakes and thus tend to fade at a faster rate.

### Emulsifiers and Stabilizers

Stabilization is recommended for latex dispersions that contain pigments or electrolytes that may change the zeta-potential and hence cause coagulation. This occurs immediately after mixing or when the mixture is sheared. Emulsifiers and stabilizers such as polysorbates, low viscous carboxymethylcellulose sodium (CMC-Na), polyvinylpyrrolidone, or sodium dodecyl sulfate are often added to pigment suspensions. Depending on the quantity and quality of destabilizing excipients in the formulation, 2.5% to 10% (calculated on dry polymer mass) stabilizers are required. Freshly dispersed pigments are most aggressive when primary particles are ruptured and new surfaces are produced by intensive milling processes. Such pigment dispersions should be mixed with some of the same emulsifier used in the latex and stored overnight for aging. Stabilizing agents used in formulations of anionic latexes are preferably nonionic emulsifiers such as sorbitan esters, which are also used in emulsion polymerization processes. They also act as plasticizers and are normally incorporated in the pigment suspension

to improve their compatibility. The best stabilizing principle for anionic dispersions is partial neutralization using alkaline substances, preferably 1N NaOH for Eudragit L 30 D-55. Since the stability of anionic methacrylate latexes and their compatibility with additives are to some extent higher at pH 5 than at pH 2 to 3, which is the specified pH of commercial latex Eudragit L 30 D-55, the pH may be raised to about 5.0 to 5.4. When different anionic poly(meth)acrylates are to be mixed, pH modification should be done before mixing the polymer dispersions and by using the same agent.

### Flavors and Sweeteners

The addition of flavors to film coatings is mostly limited due to their complex chemistry and limited stability. Sweet-tasting film coatings can be prepared by the addition of saccharin sodium, usually in amounts of 2% to 10%, based on dry polymer mass, depending on the desired sweet taste intensity.

## Polymer Combinations and Functionality Modifications

### Poly(meth)acrylate Mixtures

Lehmann and Dreher (28) provided a detailed summary of possible poly(meth)-acrylate combinations. In the following paragraphs, the most common combinations are described. Beyond these, other combinations are possible as well. In general, however, when combining aqueous latexes, the ionic character of the polymers and the pH values of the dispersions have to be considered in terms of possible instabilities.

**Combinations of anionic (meth)acrylate polymers:** Mixing organic solutions of different anionic poly(meth)acrylates allows adjusting the dissolution pH of the film coating for the purpose of gastrointestinal targeting (Fig. 1). The combination of Eudragit L and Eudragit S is of particular importance. When mixing aqueous redispersed latexes thereof, the situation is different. The resulting film coatings contain domains of both polymers that dissolve at their specific pH. Between the lower and the higher solution pH, one polymer can act as pore former by dissolving and releasing the drug slowly. Beyond the higher pH, both polymers dissolve, resulting in enhanced drug release.

**Combinations of anionic and neutral (meth)acrylate polymers:** If highly flexible enteric coatings are required, especially for the preparation of multiparticulate tablets, higher plasticization of the brittle Eudragit L 30 D-55 becomes necessary. Since it is not useful to increase the plasticizer level beyond 20%, the combination with Eudragit NE 30 D as the highest flexible poly(meth)acrylate is the solution of choice (28). With up to 50% of the neutral polymer in the film, the coating maintains its enteric behavior and shows significant increase in film flexibility. At higher amounts, the properties of this polymer become dominant and dissolution of the coating will be delayed.

**Table 5** Example Formulations

| | | Enteric coating | | | Extended release | | |
|---|---|---|---|---|---|---|---|
| | Taste-masking and moisture protection (Eudragit® E PO) (g) | Small intestine release (Eudragit L 30 D-55) (g) | Colonic delivery (Eudragit FS 30 D) (g) | Flexible coating (Eudragit L 30 D-55/ NE 30 D) (g) | Low permeability (Eudragit NE 30 D) (g) | Low permeability (Eudragit RS 30 D) (g) | Medium permeability (Eudragit RL/RS 30 D) (g) |
| Polymer dispersion | 100.5 | 730.0 | 603.0 | L 30D-55 248.5<br>NE 30 D 248.5 | 416.5 | 392.0 | RS 470.50<br>RL 52.5 |
| DPS | 100.5 | 219.0 | 181.0 | L 30 D-55: 74.5<br>NE 30 D: 74.5 | 125.0 | 117.6 | RS 141.2<br>RL 15.8 |
| *pH adjustment* | | | | | | | |
| 1 N NaOH | | | | 0.03 | | | |
| Citric acid | | | | 1.0 | | | |
| *Plasticizer* | | | | | | | |
| SLS | 10.0 | | | | | | |
| TEC | | 22.0 | 9.0 | 15.0 | | 23.5 | 31.5 |
| *Antitack agent* | | | | | | | |
| GMS | | 6.5 | 7.0 | 4.5 | | | 8.0 |
| Polysorbate 80 | | 2.5 | 3.0 | 0.4 | | | 3.5 |
| Talc | | | | | 125.0 | 59.0 | |
| Mg-stearate | 35.0 | | | | | | |
| *Solubilizer* | | | | | | | |
| Stearic acid | 15.0 | | | | | | |
| Water | 840.0 | 239.0 | 378.0 | 482.0 | 458.5 | 525.5 | 434.0 |
| *Total* | 1000.0 | 1000.0 | 1000.0 | 1000.0 | 1000.0 | 1000.0 | 1000.0 |
| *Polymer content* | 10.0% | 21.9% | 18.1% | L 7.5%<br>NE 7.5% | 12.5% | 11.8% | RS 14.1%<br>RL 1.6% |
| *Solid content* | 16% | 25% | 20% | 17% | 25% | 20% | 20% |

*Abbreviations*: DPS, dry polymer substance; SLS, sodium lauryl sulfate; TEC, triethyl citrate; GMS, glyceryl monostearate.
*Source*: From Ref. 60.

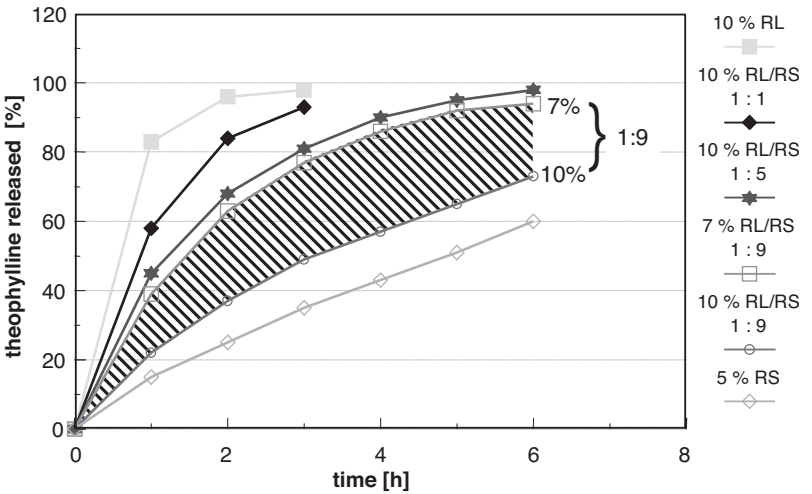



**Figure 7** Drug-release variations by permeability adjustment in combining Eudragit® RL/RS 30 D in various ratios and applying different coating amounts.

Mixtures of anionic and neutral poly(meth)acrylates can also be useful when preparing controlled-release formulations of weakly basic actives showing high solubility in acidic media and reduced solubility at higher pH values. In the stomach, the polymer combination ensures low permeability for a highly soluble active, whereas in neutral to weakly alkaline intestinal fluid, the entero-soluble component dissolves and compensates for the reduced solubility of the drug, resulting in constant release rates over the entire pH range. With minor amounts of entero-soluble polymer in the mixed film, only the permeability increases when the pH enters the range above the dissolution pH of this component, but the film remains stable. These effects can be used in many variations for controlled-release preparations, especially for the coating of small particles when disintegration effects play a minor role and the release is mainly diffusion controlled by the permeability of the encapsulating membrane (29).

When preparing such mixtures, it has to be considered that the polymer dispersions have different pH values (Eudragit L 30 D-55: pH 2–3/Eudragit NE 30 D: pH 7–8). In order to avoid coagulation, it is necessary to adjust the pH of both dispersions to the same level before mixing. If there is no specific requirement, the pH is adjusted to 5. For this purpose, 1N NaOH is added to Eudragit L 30 D-55. The pH of Eudragit NE 30 D can be reduced by the addition of 20% (w/w) citric acid solution or 1N HCl. To ensure a stable pH, the dispersions should be post-stirred for 20 minutes with pH control. Afterwards, while stirring gently, the neutralized Eudragit NE 30 D is slowly poured into the Eudragit L 30 D-55. Dilution of the dispersions before mixing can also enhance stability. The remaining preparation is done as usual for aqueous spray suspension preparation. When the

content of Eudragit NE 30 D exceeds 50%, the MFT of the combination becomes less than 25ºC, which enables coating without plasticizer addition.

**Combinations of insoluble ionic poly(meth)acrylates:** Eudragit RL and Eudragit RS can be mixed with each other in any ratio either in the organic or in the aqueous form to adjust the intermediate permeability and to obtain a specific release pattern (30). The quality and quantity of excipients to be used in formulating films are the same for both. Since the Eudragit RL features are dominant in these combinations, the quantity of Eudragit RS in the combination usually is much higher for extended-release effects. Typical ratios are RS:RL = 95:5 or 90:10 or 80:20. An example using coated theophylline granules as a model is shown in Figure 7. By varying polymer ratio and coating quantity, two effective controls are provided that allow maximum flexibility for tailor-made formulation design.

### Permeability Enhancement

To increase the permeability of film layers or to modify the tortuosity of matrix structures made of poly(meth)acrylates, several water-soluble or water-swellable substances can be added, such as sucrose, lactose or other saccharides, starch, micronized cellulose, soluble cellulose ethers, poly(vinylpyrrolidone), poly(vinyl alcohol), or PEGs and PEG derivatives. However, water-soluble cellulose ethers have limited compatibility. They stimulate slow agglomeration and coagulation within several hours or days. Alternatively, fumed or precipitated silica as a water-insoluble but hydrophilic agent can be added to coating formulations in order to increase film permeability.

### Poly(meth)acrylates in Combination with Other Polymers

Hydrocolloids such as HPMC, CMC-Na, or hydroxypropyl cellulose (HPC) can be used in mixtures with methacrylate polymers. Typical are mixtures of HPMC or HPC as pore formers in Eudragit NE 30 D or Eudragit RL/RS 30 D formulations, or CMC-Na in aqueous anionic poly(meth)acrylate dispersions as a stabilizer against coagulation. The physical stability of such formulations has to be investigated individually. Phase separation may be an issue during storage. For protective coatings, rapidly disintegrating combinations of Eudragit RL 30 D with CMC-Na are used (31). To increase flexibility and to optimize film formation of cellulose-based coatings, the soft Eudragit NE 30 D can be added (32).

## Spray Suspension Preparation

While processing latexes, high-shear forces must be prevented. In general, solid excipients should be suspended and homogenized separately from the polymer solution/dispersion before being combined. Useful are rotor/stator systems, e.g., Ultra Turrax®, Silverson®, or toothed colloid mills. Simple propeller stirrers cannot deagglomerate solid particles, which can lead to uneven or rough coating surfaces, or marbled coloration in the case of coarse pigments. Preparation steps are the same for solvent- and aqueous-based spray suspensions: The diluent is placed

into a container and all the other excipients except the polymer(s) are added while homogenizing with a high-speed mixer. The latex dispersion is weighed into another vessel and then diluents, and if required a stabilizer, are added. Finally, the excipient suspension is poured into the latex dispersion while stirring gently. To avoid sedimentation, suspensions should continuously be stirred during the coating process with conventional propeller stirrers.

Commonly, aqueous-based formulations should contain 20% to 25% solids, whereas Eudragit E PO colloidal solutions are adjusted to 15% to 20% solids. Higher solid contents require extremely well-controlled coating processes in order to guarantee good film formation.

To some extent, aqueous dispersions are sensitive to microbial contamination and hence should be used within 24 hours after preparation. However, longer storage times may be evaluated individually. An additional risk for aqueous latex systems at longer storage times is possible physical instability, resulting in changed properties of the coatings, and/or problems such as nozzle blockage during spraying.

### Redispersion of Anionic Polymer Powders

Eudragit L 100-55, Eudragit L 100, and Eudragit S 100 are spray-dried powders that consist of spray agglomerates. In order to process them as aqueous dispersions, they need to be redispersed in water to form nanosized latex particles (33). Redispersion is effected by adding small amounts of alkali or ammonia respectively to the aqueous suspension of the polymer powder; these partially neutralize the carboxylic groups and thus enhance deagglomeration and ensure formation of a latex dispersion. The polymer types require different alkali and processing times (Fig. 8). Owing to the influences of coating parameters and additional excipients in redispersed Eudragit L/S 100 coating formulations, the degree of neutralization and plasticizer quantities can be increased to the upper levels given in Figure 8 in order to enhance film formation. However, plasticizer levels of 70% calculated on dry polymer mass may increase sticking tendencies and possibly film permeability. Hence, increasing the neutralization level is the preferred approach. The particle size in redispersed latexes is around 100 nm, as in the commercial dispersions. The gastro-resistance and entero-solubility of the coatings, resulting from redispersed Eudragit L 100-55, are equivalent to those from the original latex Eudragit L 30 D-55 (34). Redispersed latexes can be used for gastro-resistant entero-soluble coatings in the same way as the commercial polymer dispersions.

For spray suspension preparation of Eudragit L/S 100, the plasticizer is added to the latex dispersion. As given in Figure 8, the plasticizer amounts are higher than for other formulations. The plasticizer has to be mixed with the polymer dispersion for at least 60 minutes before adding the antitacking agent and other excipients. In the case of Eudragit L 100-55, the resultant dispersion can be handled like the commercially available Eudragit L 30 D-55. The plasticizer and other excipients are homogenized separately and then added to the dispersion. Figure 9 shows two methods that can be used to incorporate pigments and glidants into an aqueous Eudragit dispersion.

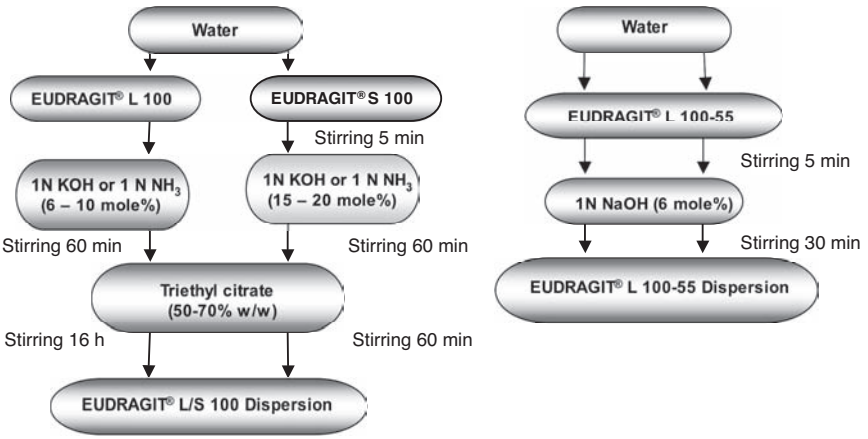



**Figure 8** Redispersion procedure of anionic poly(meth)acrylates: Eudragit® L/S 100 (*left*) and Eudragit L 100-55 (*right*).

For larger-scale redispersion, effective but slow-moving stirring equipment should be used. The stirrer should be equipped with a speed controller to adapt the stirring speed to the viscosity of the system, which normally means a higher speed for the higher viscosity in the beginning and a lower speed when the viscosity decreases near the end of the latex-forming process. Incorporation of air bubbles is to be avoided during all stages of the redispersion process.

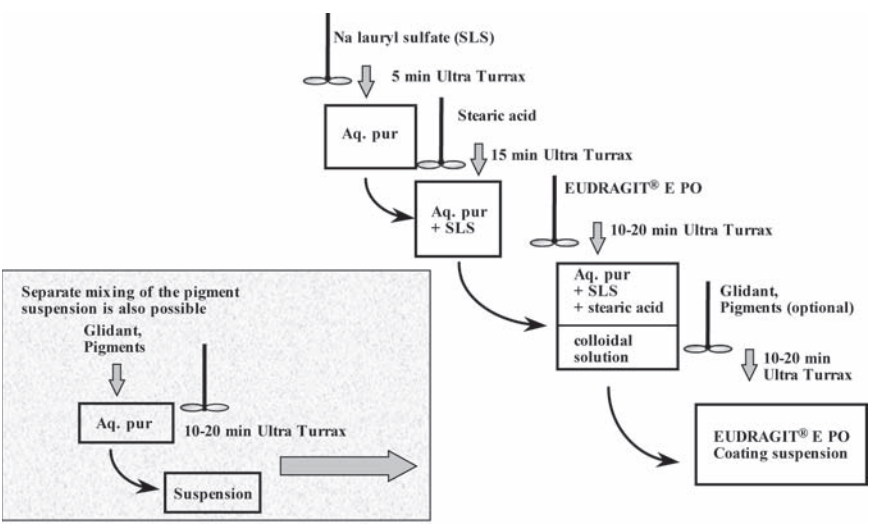



**Figure 9** Preparation procedure for Eudragit® E PO spray suspension: homogenization of glidants, pigments separately (*left*) or in line (*right*). *Abbreviation*: SLS, sodium lauryl sulfate.

**Mixtures of redispersed Eudragit L 100 and Eudragit S 100:** Both redispersions are conducted separately as described above using 1N $NH_3$. With moderate stirring, the Eudragit S 100 redispersion is poured into the redispersed Eudragit L 100. Stirring is continued for another 15 minutes before further excipients are added to prepare the spray suspension.

### Colloidal Solution of Eudragit E PO

Standard Eudragit E PO coating suspensions contain 10% sodium lauryl sulfate (SLS) as a wetting and dispersing agent and 15% stearic acid, which forms a soluble salt with the polymer. It is highly recommended to use stearic acid of powder grade quality for optimal processing and colloidal solution formation. With stearic acid and SLS in the dispersion, Eudragit E PO forms a colloidal solution in water that appears clear or pale yellow and shows the Tyndall effect. Since its viscosity is similar to that of water, it can be processed like the commercial Eudragit dispersions. Furthermore, shear stability is improved and hence high-shear homogenizers can be used for preparation. The preparation of Eudragit E PO spraying suspensions is simple and follows the scheme in Figure 9.

First the water is put into a vessel; SLS is added and dissolved while stirring. Then stearic acid and Eudragit E PO are added. Adding stearic acid before Eudragit E PO helps the polymer dissolve faster. Both regular propeller stirrers and homogenizers (e.g., Ultra Turrax or Silverson) can be used as stirring devices. However, due to the low efficiency of the conventional stirrer, colloidal solution formation takes four to six hours, whereas by using a homogenizer, it is finished within 30 minutes. An antitacking agent (preferably talc) and pigments can then be added to the colloidal solution or suspended separately, both while homogenizing. The preferred method is adding them as a suspension for ideal homogeneity. If talc is used as a glidant and a high-shear mixer is used to prepare the colloidal solution, it can directly be added to the colloidal solution with high-shear mixing. In the event of foam formation, antifoaming agents can be added.

## Process Parameters

Except for temperature, aqueous- and organic-based coating suspensions have the same processing conditions as long as the formulations are within the recommended solids content range in order to guarantee a low viscous coating liquid (60).

### Product Bed Temperature as a Main Control Parameter

To ensure appropriate film formation, the product temperature during spraying should be at least 10 K to 20 K above the MFT of the dispersion. Recommended product bed temperatures are 25ºC to 35ºC for aqueous coating processes and 20ºC to 30ºC for organic-based processes. Higher temperatures, especially in combination with turbulence, can lead to spray-drying effects. If spray-dried particles are incorporated into the coating, they may act as channelling agents and lead to increased permeability.

### Spray Rate

In aqueous processes, the main effort is to prevent the inclusion of water into the cores and any subsequent interaction with moisture-sensitive actives. To achieve good film formation under mild working conditions, the drug cores are heated to about 30ºC to 40ºC prior to coating. It is recommended to spray at a slower rate initially. For most substrates, it is useful to start with approximately 75% of the usual spray rate. After 30 to 60 minutes, the first latex layer forms a thin film, which isolates the core against water penetration. Later, the spray rate can be increased to the usual spray rate. Spraying too fast will cause overwetting, with sticking tendencies, and also may generate stability issues. If it is not completely evaporated, when stored at accelerated stability, the water in the core will plasticize the film (35) and hence cause sticking issues and changes in the permeability of the coating. Thicker coatings in particular will trap the solvent or water and severely hinder evaporation. Loss on drying as an in-process control is highly recommended.

### Atomization and Pattern Air Pressure

Aqueous latex formulations have very low viscosities and do not need high atomizing air pressure. The optimum level required to spray is 1 to 2 bar (14.1–28.0 PSI). When higher atomizing air pressure is applied, spray-drying of the coating suspension will occur, causing loss of coating material and functionality. In tablet coating, spray guns are usually designed with a second air channel to form the spray pattern. This pressure should usually not exceed the value of the atomizing pressure in order to generate an oval-shaped beam and to prevent the division of the spray zone into two sections ("lying eight"). Depending on the spray gun model and the air cap design, the ideal pressure for the pattern air can be between 50% and 100% of the atomizing air. It is useful to install flow meters for the atomizing air and pattern air on each spray gun, in order to indicate blocking tendencies during the coating process.

### Inlet Air Humidity

High inlet air humidity will slow down water evaporation. In this case, it is recommended to preferably reduce the spray rate or to increase the inlet air temperature moderately, in order to reduce the relative humidity. Installation of a dehumidification system guarantees reproducible conditions throughout the year. Exhaust air relative humidity is between 80% and 90% preferably.

### Drying Air Volume

Sufficient air volume effectively evaporates the water or solvent. The pan pressure should not exceed more than −150 Pa (~1.5 mbar, ~1.1 mm Hg, ~0.02 PSI). Higher pressure leads to poor cascading of tablets or capsules in the coating pan. A recommended drying air capacity in pan coating processes is 0.3 to 0.5 $m^3$/min/kg product. In fluid-bed coating equipment, the air volume must be adjusted to get

proper fluidization of the material. Depending upon the fluid-bed technique, the values may vary in a wider range.

### Pan Coater Setup

It is recommended to have a minimum distance of 10 cm (lab scale) to a maximum of 25 cm (production scale) between the spray nozzle and the bed at an angle of 90º in the upper third of the tablet bed. Shorter distances may lead to overwetting and inhomogeneous coatings, while longer distances lead to spray-drying effects, especially with turbulent air flow inside the pan. A "breakdown" of the tablet bed after a certain time at the beginning of the coating process may require readjustment of the nozzle positions. Uncoated tablets have a relatively rough surface and thus higher friction. The pan rotation speed must be optimized to ensure gentle movement of the tablets. Higher pan rotation speeds will increase mechanical stress and lead to chipping and cracking of the tablet edges and the film surface. Lowering the pan speed can lead to overwetting, since the tablets move more slowly in the pan and thus are exposed to the spray zone for longer periods of time. For comparable process conditions, the pan rotation is set slower in production scale equipment than in lab scale.

### Pump System

The spray suspension should be delivered by peristaltic pump to the spray nozzles using tubing with diameters as small as possible (down to 2 mm), in order to achieve a high flow speed, which prevents sedimentation. For the same reason, the tubing must be as short as possible. Aqueous latex systems in particular are sensitive to shear forces produced in gear pumps, airless systems, or vacuum pumps. In some cases, piston pumps or pressure vessels can be used instead.

## Postcoating Treatment

Residual traces of water can act as a plasticizer (35) and may have an influence on the coating permeability. Furthermore, unsuitable processing, i.e., excessive atomizing air pressure or high temperatures, can cause incomplete film formation during the coating process. Therefore, a validated drying process either in the coating equipment or in external drying facilities is recommended. Removal of water from the coated dosage forms may be significantly delayed if it has penetrated into the cores during coating because of high spray rates.

Curing enhances film formation from aqueous dispersions after coating by facilitating coalescence of the latex particles. Duration and processing requirements depend upon the polymer characteristics, plasticizer content, temperature, and environmental relative humidity (36). Furthermore, Zheng and McGinity (29) and Guiterrez-Rocca and McGinity (37) reported that curing duration varied by polymer combination. A standard postdrying of one hour at 40ºC is recommended. More intensive postcoating treatment is required for Eudragit RL/RS 30 D formulations, since they are not emulsion polymerization products. Conventionally,

curing has been performed on trays at 40ºC over 24 hours. However, curing can be done more efficiently in the coating equipment (38). Relative humidity, temperature, and process time have to be evaluated and optimized during product development, with consideration given to the specific product, equipment, and environmental conditions. The curing progress can be monitored by dissolution tests. The end-point and thus storage stability is reached when dissolution profiles become static with storage time. Mechanical stress should be kept at minimum levels in order not to damage the coatings.

### Multilayer Coatings

It is feasible to apply several coating layers onto a substrate in succession. Multilayer coatings become relevant when the addition of different functionalities is required or, as a simple application, in order to prevent interactions between substrate and the functional coating by the application of a separating subcoat. To reduce interactions between the different layers or to enhance the storage stability, it may be necessary to apply individual coating layers with an intermediate drying step in between. The drying process should be evaluated for each coating layer applied.

### Switch from Organic to Aqueous Formulations

Except for Eudragit FS 30 D and Eudragit NE 30 D, which are only available as aqueous dispersions, all other poly(meth)acrylates are formulated as both organic and aqueous systems. When an organic formulation is to be replaced by a bioequivalent aqueous one, specific distinguishing in vitro dissolution test methods need to be developed. Differences in film density and especially composition modifications may result in changed drug-release profiles and therefore require adaptation of the formulation. Usually the switch can easily be done for Eudragit RL/RS and Eudragit E coating formulations. When changing an organic enteric coating based on Eudragit L, Eudragit L 100-55, or Eudragit S to a redispersed aqueous system, an increased dissolution speed in buffer media may be observed, mainly caused by the higher plasticizer content (50–70% instead of 10% in the organic formulation) as well as by partial neutralization. Adaptation of the formulation needs to be done accordingly.

### Granulation Processes

Since poly(meth)acrylates provide excellent mechanical stability with remarkable flexibility, they can be used as binders in immediate-release formulations and in matrix formulations to provide controlled drug release. Both organic polymer solutions and aqueous latex dispersions can be applied alone or in combination with the polymer powders in order to increase process efficiency by reducing the solvent/dispersion volume. In contrast to coating processes, the addition of plasticizers is not required. However, plasticizers will increase the softness of

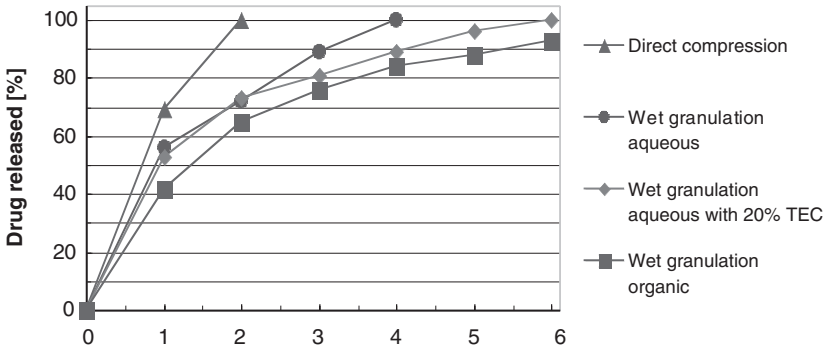



**Figure 10** Influence of processing technique on drug release from matrix tablets shown with diprophylline matrix tablets manufactured by different granulation techniques. *Abbreviation*: TEC, triethyl citrate.

the system and result in different matrix structures that usually are characterized by higher distribution and hence stronger retardation effects (Fig. 10). Due to the low viscosity of the latex dispersions, granulation can be performed in any common granulation equipment. Fluid-bed processes show advantages such as simultaneous drying and homogeneous distribution. Even dry granulation (e.g., roller compaction) can be used with the powdered Eudragit grades.

## FUNCTIONAL DOSAGE FORMS

### Taste Masking and Moisture Protection

The most efficient and simple approach to ensuring proper taste masking or protection against moisture uptake both for tablets and for particles is the application of film coatings. Among the different poly(meth)acrylates, the acid-soluble Eudragit E PO is most suitable. Eudragit L 30 D-55 and Eudragit RL 30 D can be used in thinner layers for this purpose as well, the latter possibly in combination with soluble cellulose ethers (31). Table 6 shows the usual application quantities for the various protection targets.

**Table 6** Protection Potential of Different Eudragit® Films Given as Weight Gain Dry Polymer per Unit Surface Area Substrate

| | Eudragit EP O ($mg/cm^2$) | Eudragit L 30 D-55; Eudragit L 100-55 ($mg/cm^2$) | Eudragit RL 30 D ($mg/cm^2$) |
|---|---|---|---|
| Sealing | ~1 | ~1 | ~1 |
| Taste masking | 1–2 | ~1 | ~1 |
| Moisture protection | 4–10 | ~1 | ~1 |

Since Eudragit E PO dissolves in the acidic stomach conditions, thicker coatings up to 10 mg/cm² can be applied without delaying drug release. For both Eudragit L 30 D-55 and Eudragit RL 30 D, not more than approximately 1 mg/cm² should be applied, in order to avoid modified release effects. Despite the advantages of Eudragit E PO for protective coatings, the use of Eudragit L 30 D-55 may become necessary for cationic drugs to avoid ionic interactions.

Aqueous Eudragit E PO coatings are highly flexible and can be applied to small particles including active pharmaceutical ingredient (API) crystals, granules, pellets, etc. The coated particles can be compressed into rapidly disintegrating tablets without damaging the film coating. Most pediatric formulations, such as dispersible or chewable tablets or single-use dry syrup formulations, can be designed using this polymer. Usually 1 to 2 mg/cm² of polymer application provides excellent taste-masking properties.

For taste-masking applications, an alternative to film coating is the neutralization of the bitter taste of basic drugs or salts thereof by targeted ionic interaction with acidic polymers. Powerful alkaline salts of basic drugs react with anionic poly(meth)acrylates, e.g., Eudragit L 100, and bind to the copolymer by ion exchange principles. The manufacturing process is a normal aqueous high-shear mixer granulation operation and can therefore very easily be integrated into pharmaceutical practice. The resulting polymer-active granules are often insoluble in water, which allows the formulation of liquid dosage forms such as dry syrups, and in many cases have almost neutral taste and odor. Furthermore, after binding to Eudragit L 100, chemically unstable active substances often show improved stability, with no further additives needed for stabilization even in liquid formulations. Suitable drugs should contain at least one basic functional group for reaction with the anionic groups of the polymer. Since the functional principle is based on molecular interactions, limitations for this process are high dose, high molecular weight of the active, and steric hindrance of the functional group in the active. The optimal drug/Eudragit L 100 mixing ratio must be experimentally determined for every product. Bitter drugs with a low-to-medium dose are preferred for this technique.

## Gastro Resistance and Gastrointestinal Targeting

For simple enteric coatings that quickly dissolve in the small intestine, Eudragit L 30 D-55, or redispersed Eudragit L 100-55, is typically used. If the drug is to be released in the lower sections of the small intestine, Eudragit L and Eudragit S can be used in mixtures to create a specific dissolution pH value (Fig. 1). For pharmaceutical forms that are to release the drug in the colon, Eudragit grades that dissolve above pH 7 (Eudragit S or the highly flexible Eudragit FS 30 D) are used. For the safe application of gastro-resistant formulations, it is important that the films remain largely impermeable in the acidic environment of the stomach. For particles, stomach transit times are typically in the range of 30 to 120 minutes, while for tablets, transit times can be up to several hours, depending on how much food is in the stomach and the core size (39). Anionic poly(meth)acrylate films

meet these requirements with minimum layer thicknesses of 40 to 50 μm (i.e., 3–5 mg dry polymer/cm$^2$). It is crucial that coatings of critical areas such as corners or edges conform to the required minimum layer thickness, since these areas, as sites of the lowest wall thickness, would otherwise contribute to the premature dissolution of the film. If thicker layers or polymers with higher dissolution pH are used, a delayed release in the small intestine can be achieved.

## Extended Release

The poly(meth)acrylates that are used for sustained-release film coatings and matrix tablets are Eudragit RL (highly permeable), Eudragit RS (low permeable), Eudragit NE, and Eudragit NM (both permeable). After contact with gastrointestinal fluids, the film coatings swell, independent of pH, and release the active by a diffusion-controlled mechanism. Eudragit RL and Eudragit RS can be mixed in any ratio in either organic or aqueous form to adjust permeability and obtain specific release patterns. Since the Eudragit RL features are dominant in these combinations, the amount of Eudragit RS polymer is usually much higher for extended-release effects. For typical ratios, see the section titled Poly(meth)acrylate Mixtures. Eudragit NE and NM have no reactive functional groups, since all carboxylic groups are esterified. Drug release here is mainly controlled by the coating thickness. Two-phase drug release can be designed by applying a drug-containing immediate-release top coat onto the controlled-release coating.

For preparation of controlled-release matrix formulations, both the pH-independent polymers, Eudragit NE 30 D, Eudragit NM 30 D, Eudragit RL, and Eudragit RS, and the anionic types, Eudragit L 30 D-55, Eudragit L, Eudragit S, and Eudragit FS 30 D, are used. Under physiological conditions, the Eudragit L polymers provide matrix tablets with higher pH effects than Eudragit S and Eudragit FS. Poly(meth)acrylates can be processed via all common granulation techniques. Also, direct compression can be used to manufacture poly(meth)acrylate matrix tablets (40,41). With higher degrees of distribution, increasing retardation effects are achieved (Fig. 10). Depending on drug solubility, usually 5% to 20% of dry polymer substance based on tablet weight is sufficient to control drug dissolution and release over a period of six to eight hours. In contrast to film coating, wet granulation with aqueous latex dispersions can be done without the addition of plasticizers. However, the addition of a plasticizer enhances the coalescence of the latex particles, therefore increasing the retardation effect.

In order to ensure extended drug release, matrix formulations should not contain strong disintegrants. The quantities necessary to achieve the desired effects of the polymer matrix on drug-release characteristics are significantly smaller in wet granulation than in direct compression of powders. Drug particles and granulating excipients are partially impregnated. During compression, they are embedded in a sponge-like network of thin polymer layers, which first control the penetration of digestive fluid into the matrix and later the diffusion of the dissolved drug through pores, channels, and capillaries in the matrix. Insoluble polymers such as Eudragit

NM 30 D form inert matrices. Their release mechanism is controlled by diffusion and gives straight lines in the plot of dissolved drug versus square root of time. However, when matrices from anionic poly(meth)acrylates start to dissolve at higher pH via salt formation, erosion effects increase drug release, whereas release is only based on diffusion at lower pH. Finally, complete dissolution or disintegration of the tablet is achieved. The highly effective films of aqueous poly(meth)acrylate latexes allow the production of sustained-release matrix tablets containing more than 80% active drug. In such formulations, the compression force normally has little influence on the release rate. The release pattern of poly(meth)acrylate matrixes can additionally be modified by a thin functional top coating, which will preferably reduce the release rate in the first phase and thus provide more linear release profiles (42).

## Multiparticulate Tablets

Fast-disintegrating multiunit tablets generally show superior biopharmaceutical behavior, with less variation in gastrointestinal transit time and less food effect compared to monolithic tablets. Besides the sufficient substrate hardness, the main precondition is high flexibility of the controlled-release coating in order to prevent cracking of films during compression. Among the different poly(meth)acrylates, Eudragit E, Eudragit FS 30 D, Eudragit NE 30 D, and Eudragit NM 30 D stand out for their excellent flexibility, whereas the anionic poly(meth)acrylates show more brittle characteristics (Table 3). As a point of reference, coating formulations with 100% elongation at break provide sufficient flexibility (11). The highly flexible polymers can be formulated without the addition of plasticizers, whereas the more brittle anionic types require the addition of plasticizers or mixing with soft Eudragit NE 30 D to achieve the required elasticity (Table 3).

Outer-phase excipients with plastic properties such as microcrystalline cellulose or lactose provide additional protective effects. In addition, the functions of the outer-phase excipients are to prevent direct contact of coating layers, reduce friction during compression, improve compressibility, and ensure rapid disintegration after application. The amount necessary to fill the intermediate spaces and to protect the coated particles during compression can be estimated by testing the tapped density of mixtures from particles and tableting excipients. Most useful mixtures should have the maximum tapped density. If the amount of the outer phase is less than 30%, excessive amounts of coated particles break during compression. During development, possible changes in dissolution profiles caused by mechanical stress during compression should be controlled thoroughly. Differences should be less than 10% in order to ensure reproducible drug release. Beckert (43) thoroughly investigated the different aspects of preparing multiparticulate tablets based on particles coated with poly(meth)acrylates.

## Drug Delivery Systems

Particular value to research and approved therapies is added by the development of drug delivery systems that provide optimized oral modified/controlled, dermal,

or transdermal delivery and transfection enhancement. The benefits are increasing therapeutic indices and improved patient compliance. These advantages support the development of new chemical entities, product life cycle extension, and conceptions of generics.

### Colonic Delivery Systems

Colonic delivery has gained importance for the treatment of local diseases but also for the oral delivery of proteins and peptides. Long transit times of dosage forms through the colon call for a targeted, time-controlled drug release in order to optimize therapeutic effects. Thus a novel multiunit delivery system was developed by combining the pH characteristics of anionic poly(meth)acrylates and diffusion-controlled kinetics. The multiunit dosage forms provide a relatively constant passage through the intestine and consist of a drug-layered pellet core coated with an inner layer of a pH-independent diffusion barrier from an aqueous coating of Eudragit NE 30 D or Eudragit RL/RS 30 D. This layer enables controlled drug release throughout the colon up to a 20-hour period. The outer layer of the pH-dependent Eudragit FS 30 D triggers the start of release at the ileo cecal junction. The particle core can be prepared by powder layering or extrusion and spheronization. In vitro proof of concept studies using 5-aminosalicylic acid (5-ASA) as the active compound and mixtures of Eudragit RL/RS 30 D as inner coatings confirmed the variability of the delivery system by statistical modulation using the central composite design (44,45). The "outer coating amount" (Eudragit FS 30 D dry polymer), "inner coating composition," and "inner coating thickness" were found to control drug release reproducibly within a 95% confidence interval and function as a basis for optimization (46).

A clinical study in healthy volunteers with dosage forms containing 200 mg of caffeine as a pharmacokinetic marker, which is well absorbed from both small and large bowel, and $^{13}$C-lactose-ureide for determining the oro cecal transit time demonstrated in vivo correlations. Plasma profiles of caffeine were significantly prolonged for the pH *and* timed delivery system compared to the pH-only based system (Fig. 11). Compared to the drug delivery systems used in currently marketed products approved for the treatment of ulcerative colitis (UC), drug release from the EUDRACOL™-based new multiunit dosage form with a double layer coating offers a new dimension for the oral treatment of mid-to-distal UC (47).

### Modulated Controlled-Release Systems

Certain diseases have predictable cyclic, circadian rhythms, and timing of regiments can improve therapies in selected chronic conditions of diseases such as bronchial asthma, arthritis, duodenal ulcers, cancer, diabetes, and neurological disorders. Thus, needs were identified, aimed at improved, time-programmed oral therapeutic systems (48). Conventional sustained-release systems provide release profiles following "first-order" or "square root of time" kinetics due to a constant diffusion barrier. The permeability modulation of coatings over time enables therapeutically optimized release profiles in vitro and in vivo.

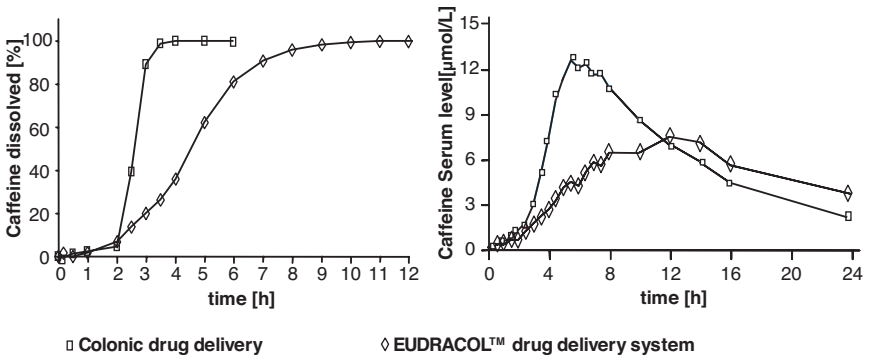



**Figure 11** In vitro (*left*) and in vivo (*right*) drug release of a conventional colonic release design (*squares*) and a pH-triggered diffusion-controlled delivery system EUDRACOL™ (*diamonds*) using caffeine as a model drug indicates in vitro–in vivo correlation.

The permeability of hydrophilic Eudragit RL and Eudragit RS coatings can be influenced by the interaction of anions with quaternary ammonium groups. Basic investigations confirmed that the mechanism of drug release involves an immediate penetration of water into the hydrophilic polymer layer followed by an instant exchange of chloride ions against anions present in the dissolution medium. Dependent on the attraction of the anions to quaternary ammonium groups,

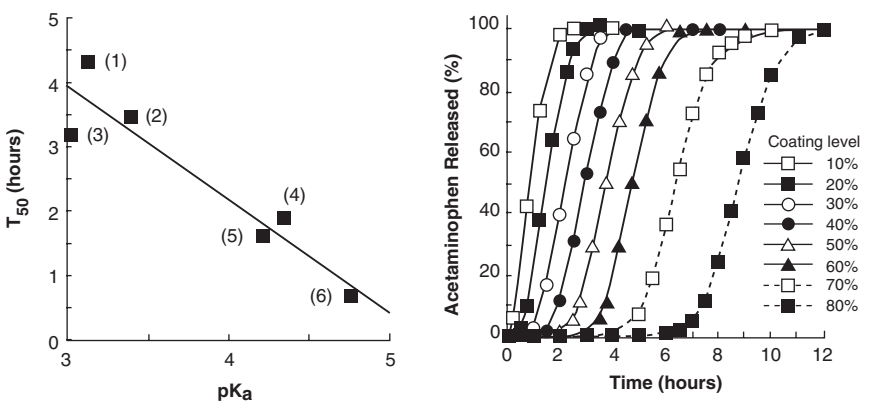



**Figure 12** Relationship between pK values of organic acids and $t_{50}$ of in vitro release profiles from sigmoidal release systems (*left*). Organic acids: citric acid (1), malic acid (2), tartaric acid (3), glutaric acid (4), succinic acid (5), acetic acid (6). The effect of Eudragit® RS 30 D polymer weight gain on acetaminophen pellets with 35% of succinic acid as a release modulator (*right*) formulated following the EUDRAPULSE™ delivery technology. *Source*: From Ref. 51.

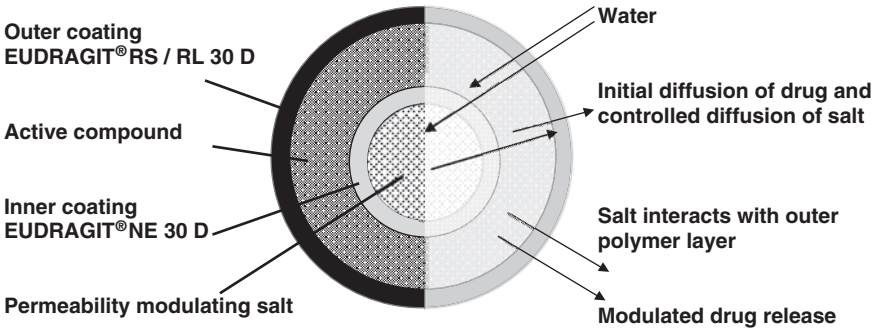



**Figure 13** Structure (*left*) and function (*right*) of a modulated-release particle, providing permeability modulation based on the EUDRAMODE™ technology.

permeability was influenced by exchanging anions. Strong attraction, reported for nitrate, sulfate, and citrate resulted in a low water flux and thus reduced coating permeability for drugs (49). Weak attractions typical for acetate and succinate ions induced a high water flux and thus accelerated drug diffusion (50). These effects were used for the development of sigmoidal or pulsed oral drug delivery systems (51). Using theophylline as a model drug, cores were prepared containing different amounts and types of organic acids and were finally coated with conventional Eudragit RS 30 D at 10% to 80% polymer weight gain.

Using succinic acid as a modulator, sigmoidal or pulsed release profiles were achieved, and lag time and slope could be controlled by the amount of organic acid in the core and coating thickness as shown in Figure 12. In vitro–in vivo correlation (IVIVC) was confirmed by several animal studies (52).

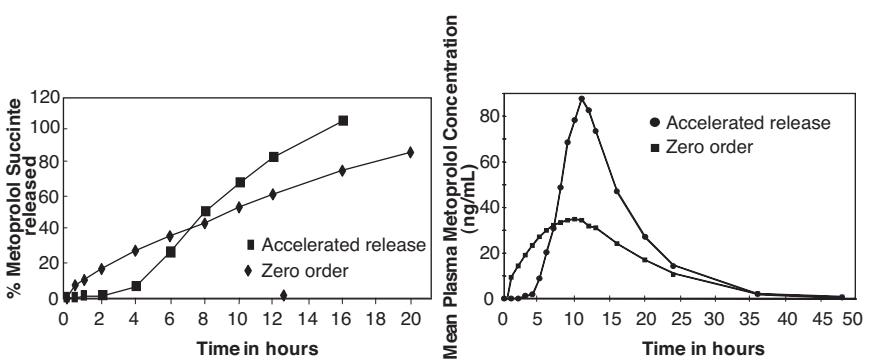



**Figure 14** In vitro (*left*) and in vivo release profiles (*right*) of a liner release system and an accelerated delivery system on metoprolol succinate. *Source*: From Ref. 54.

Based on the anion exchange at the quaternary ammonium groups in Eudragit RL 30 D and Eudragit RS 30 D, multilayered particles were developed that allowed the modulation of drug release from first-order kinetics to linear, zero-order or even accelerated profiles. The mechanism is based on kinetically controlling the ion exchange–induced permeability effects by separating the drug and the modulating ions or salts by an additional polymer layer acting as a diffusion barrier for the modulating anions. The systems, manufactured using conventional pharmaceutical processes and equipment, consist of Eudragit NE 30 D–coated salt cores that are further layered with the drug and finally coated with Eudragit RL/RS 30 D as shown in Figure 13. During release, the controlled flux of modulating salts allows for time-controlled permeability modulation of the outer Eudragit RL/RS layer.

Thus, a multiparticulate dosage form was developed that provided a linear release of terbutaline sulfate over a period of eight hours using trisodium citric acid crystals as cores. Citrate ions inhibit the hydration of the outer Eudragit RS film, controlling drug release to the desired diffusion pattern. In vivo studies in healthy, adult volunteers including statistical analysis confirmed biorelevant IVIVC on level A. The simulation of steady-state plasma concentrations did not show a significant difference compared to a commercial product (53).

Another multiunit dosage form was formulated that provided accelerated drug release of metoprolol succinate in vitro over a period of 16 hours as shown in Figure 14. In vivo plasma profiles confirmed significantly higher bioavailability than a commercial zero-order release product. Data processing by the numerical deconvolution method confirmed reliable IVIVC of level A, high predictability, and the value of statistics as a development tool for these delivery systems (54,55).

### Dermal and Transdermal Therapy Systems

In order to provide uniform blood levels over a period of up to several days, transdermal therapeutic systems have been developed, preferably based on matrix structures (56). Neutral and hydrophilic poly(meth)acrylate latex dispersions Eudragit NE 30 D and Eudragit RL/RS 30 D can be applied in combination with auxiliaries, i.e., plasticizers, by continuous blade or roller coating processes on foils. Thus, aqueous-based manufacturing processes are possible. Drugs incorporated as solutions or suspensions into the aqueous polymer dispersion get embedded in the polymer matrix upon drying and film formation. The final therapy systems may include the active compound in a dissolved or dispersed form.

The release kinetics of drugs embedded in insoluble methacrylate films follow Fick's second law of diffusion. The coefficients of diffusion were calculated in the range of $10^{-9}$ cm²/sec. Thus, release can be controlled by drug loading, i.e., concentration of the active in the polymer matrix, and layer thickness. Figure 15 reports the calculated diffusion data from model experiments in vitro, demonstrating controlled drug release of propranolol from different Eudragit RS layers by initial loading and matrix thickness.

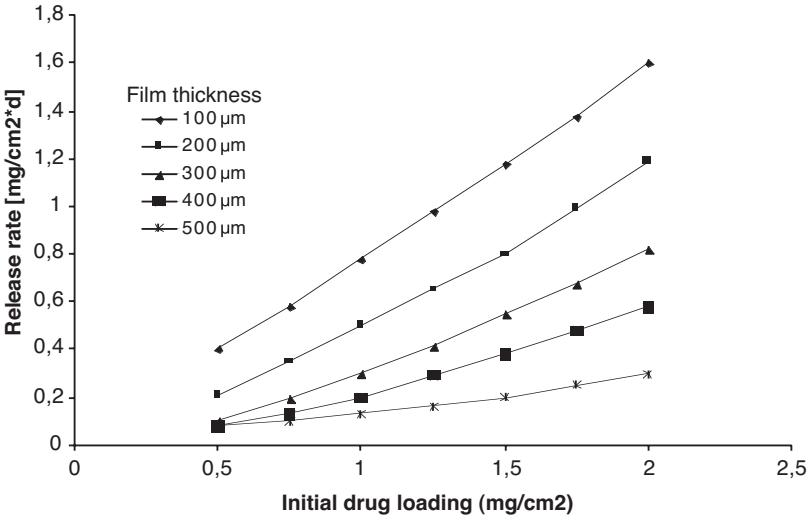



**Figure 15** Principle of release control from cast-free (meth)acrylate films, included in dermal or transdermal systems. Drug release per surface area is a linear function of drug loading and layer thickness.

Anionic dispersions such as Eudragit L 30 D-55 can be used for molecular entrapment of drugs, particularly in combination with the neutral Eudragit NE 30 D, to regulate the diffusion rate of drugs by their ionic influence on drug diffusion through the matrix (50). Further options to control diffusion of embedded drugs from patches to the skin are the addition of plasticizers and penetration enhancers.

Poly(meth)acrylate matrices proved high binding capacity for incorporated materials including drugs, pigments, fillers, or functional excipients. By absorbing water up to 60% of their own weight, they avoid influencing natural skin transpiration. Particularly, dried matrices of Eudragit NE 30 D have shown good clinical skin tolerance and were selected as a carrier for a line of transdermal formulations (57).

### Transfection Enhancement

Advanced therapeutic concepts for biopharmaceutics, such as oligonucleotides or siRNA, call for delivery systems that enable targeting and transfection. The intracellular delivery of active biomolecules from endosomes into the cytoplasm generally requires a membrane-disrupting agent. Since endosomes have a slightly acid pH of approximately 6, low-molecular-weight derivatives (Mw ~ 18.000g/mol) of anionic methacrylate copolymers, particularly MA:EA = 50:50, destabilize bilayer membranes by pH-triggered conformal changes in concentrations above 50 µg/mL (Fig. 16).

Human red blood cells served as endosomal membrane models (58). While no hemolysis occurred at neutral pH, nearly complete hemolysis was observed at

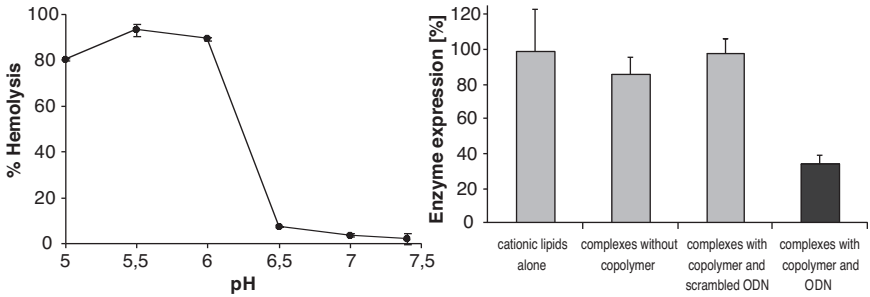



**Figure 16** pH-dependent RBC hemolysis induced by low-molecular-weight anionic methacrylate copolymers tested at 37ºC after 30 min incubation (*left*). Inactivating effects of ternary complexes on the activity of bladder tumor cell compared with individual complexes (*right*). *Source*: From Refs. 58 and 59.

pH 5.5, indicating pH-triggered conformal change and membrane destabilization at an endosomal pH of 5.0 to 6.5. The effect was confirmed in an activity assay using T24 bladder tumor cells. Only a liposomal complex of MA:EA = 50:50/ dileoyltrimethylammonium propane/antisense oligonucleotide (ODN) reduced the activity of bladder tumor cells to less than 50% after incubation in buffer at pH 7.4. Thus, the effect of the ODN could be increased significantly by the anionic polymer. Further investigations confirmed a wide therapeutic range and low cellular toxicity. The derivative poly-MA:EA:MAA = 35:35:30 turned out to be a good candidate for complexation in a drug delivery system due to its wider safety profile including lower cytotoxicity on macrophage-like cells (59).

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# 10

# Application of HPMC and HPMCAS to Aqueous Film Coating of Pharmaceutical Dosage Forms

**Sakae Obara and Hiroyasu Kokubo**

*Cellulose and Pharmaceutical Excipients Department, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan*

## INTRODUCTION

The first application of hypromellose, also known as hydroxypropyl methylcellulose (HPMC), for film coating appeared in a patent by Singiser (1) of Abbott Laboratories in 1962. Film coatings using HPMC have become popular, taking the place of the conventional sugar coating of tablets, because they give a superior appearance, act as protection for fragile tablets, and mask the unpleasant taste of drug substances. The main reason for the extensive use of HPMC as a film-coating polymer is that it is soluble in some organic solvents and also in water over the entire biological pH range. Film coating can therefore be done using an organic solvent system, and the film formed will dissolve in the digestive juices, leading to complete release of the active ingredients.

However, the lowest viscosity of HPMC available in the early 1960s was 50 mPa sec (viscosity of a 2% solution at 20°C). It was too viscous to prepare a coating solution having a high concentration of the polymer. Thus, the coating cost was relatively high. In 1965, low-viscosity types of HPMC (3, 6, and 15 mPa sec) were developed by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). This contributed significantly to the worldwide growth of film coating using HPMC in subsequent years. The use of an organic solvent system in film coating was long considered to be inevitable. The solvent systems most commonly used in film coating with HPMC were mixtures of a chlorinated hydrocarbon and an

alcohol. A typical solvent blend consisted of a mixture of methylene chloride and ethanol. However, the use of such organic solvents has been considered undesirable for the following reasons.

1. Solvents are difficult to remove completely from the coated preparations and may present a health hazard.
2. Regulations on the discharge of organic solvents into the atmosphere have become more severe as environmental concerns have increased in recent years.
3. Regulations on the exposure of factory workers to organic solvent vapors have become more stringent.
4. Economic considerations such as organic solvent cost and the provision of facilities to avoid the risk of explosion during film coating are also important.

The main reason for using organic solvents originally in film coating was to avoid possible decomposition of the active ingredients and problems such as "picking" or degradation of dosage forms during the coating operation, which might occur if water was used. Research in the mid-1970s demonstrated that the decomposition of active ingredients and possible coating difficulties were not a serious concern in the actual application of aqueous film coating using HPMC. The latent heat of evaporation of water (539 kcal/kg) is about three times higher than that of ethanol (204 kcal/kg) and this value raised concerns that a much longer coating time would be required in aqueous coating. This problem was largely overcome by equipment modifications including the side-vented coating apparatuses, which have a higher drying efficiency.

A point to which special attention should be paid in aqueous coating using HPMC is that the ideal ranges of coating conditions are somewhat narrow compared with those used in organic solvent coating, and improper coating conditions sometimes result in damage to coating batches, which makes them unsuitable for reprocessing. In the following sections, the properties of HPMC and fundamental aspects of the application of HPMC in aqueous film coating are discussed.

Enteric coating from aqueous systems has also been attractive to pharmaceutical manufacturers for the same reasons mentioned above. Because enteric materials are essentially insoluble in water, the use of an aqueous emulsion or suspension system seemed to be the best approach for aqueous coating. Hypromellose phthalate (HPMCP), an enteric polymer derived from HPMC, has long been used for solvent-based enteric coating. An approach to use this material for aqueous coating by suspending the micronized particles in water was studied. However, it was found that this material was not optimal for an aqueous system. An alternative material, hypromellose acetate succinate (HPMCAS), was subsequently developed. HPMCAS is also derived from HPMC and characteristically has good compatibility with plasticizers. It can dissolve over a wide range of pH values higher than 5.5 by controlling substitution in the polymer structure. This means that films having good gastric resistance can easily be produced in usual

coating operations, and HPMCAS can be used not only for enteric coating but for the preparation of prolonged-release preparations. Some results of basic and applied research on HPMCAS are presented in the second half of this chapter.

## PROPERTIES OF HPMC

### Types of HPMC for Film Coating

The chemical structure of HPMC is shown in Figure 1. HPMC is classified according to the content of substituents and its viscosity. Commercially available HPMC includes several substitution types such as those shown in Table 1, i.e., HPMC 1828, 2208, 2906, and 2910. Of the four digits in each number, the first two represent the median percent content of methoxy groups and the last two represent that of the hydroxypropoxy groups. The selection of proper substitution type is important for some pharmaceutical applications. The substitution affects the solubility–temperature relationship. Among the three grades 2208, 2906, and 2910, which have long been commercially available worldwide, 2910 has the best solubility in organic solvents, and so it has often been used for organic solvent–based coating. Even though aqueous coating has been replacing solvent-based coating and the solubility in organic solvents is of less importance, the 2910 grade is still widely used. Substitution grades other than 2910 are also applicable for aqueous coating, but there are few suitable commercial products of those substitution grades having low viscosity.

Another important parameter of HPMC is its molecular weight. Size exclusion chromatography (SEC) is commonly used to determine the molecular weight of water-soluble polymers. However, measuring the molecular weight by SEC is not a routine quality control for HPMC manufacturers due to difficulties in obtaining reproducible results and the fact that the SEC requires expensive apparatus. Since viscosity of the HPMC solution is directly correlated with its molecular

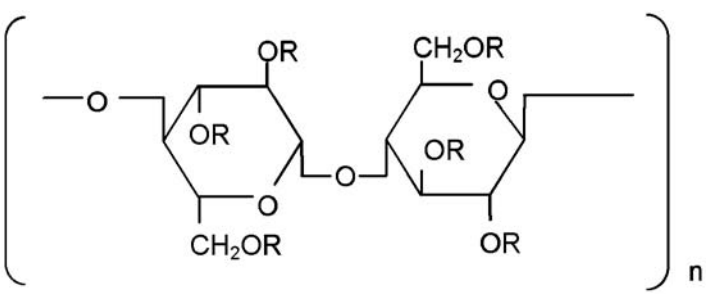



**Figure 1** Chemical structure of hydroxypropyl methylcellulose.

**Table 1** Standards on the Contents of Substituents of HPMC

| | Methoxy (%) | | Hydroxypropoxy (%) | |
|---|---|---|---|---|
| Substitution type | Minimum | Maximum | Minimum | Maximum |
| 1828 | 16.5 | 20.0 | 23.0 | 32.0 |
| 2208 | 19.0 | 24.0 | 4.0 | 12.0 |
| 2906 | 27.0 | 30.0 | 4.0 | 7.5 |
| 2910 | 28.0 | 30.0 | 7.0 | 12.0 |

weight, viscosity measurements are used for quality control as an alternative way of molecular weight determination. Labeled viscosity (nominal viscosity) is usually utilized as a parameter that represents viscosity grades. It is based on apparent viscosity of a 2% aqueous solution at 20°C. In the previous United States Pharmacopeia (USP) and Japanese Pharmacopeia (JP), the apparent viscosity was specified to be measured using a capillary viscometer, whereas the use of a rotational viscometer was the method in the European Pharmacopeia (Ph.Eur). The harmonization of the method for viscosity measurement for HPMC was discussed and the three pharmacopeias have reached an agreement to use the Ubbelohde viscometer to measure viscosity less than 600 mPa sec, and the Brookfield-type viscometer for 600 mPa sec and higher. This is based on a collaborated study, which found that one viscometer cannot cover the whole viscosity range of the current commercially available HPMC products with sufficient reproducibility. In this chapter, all labeled viscosities are based on the Ubbelohde viscosity, as only

**Table 2** Specifications of HPMC

| | 603 | 645, 606 | 615 |
|---|---|---|---|
| Substitution type | 2910 | 2910, 2910 | 2910 |
| Labeled viscosity | 3 mPa sec | 4.5 mPa sec, 6 mPa sec | 15 mPa sec |
| Appearance | | Fibrous or granular powder | |
| Color | | White to slightly off-white | |
| Apparent viscosity (2% solution at 20°C) | 2.4–3.6 mPa sec | 3.6–5.1 mPa sec, 4.8–7.2 mPa sec | 12.0–18.0 mPa sec |
| pH | | 5.5–8.0 | |
| Loss on drying | | Not more than 5.0% | |
| Residue on ignition | | Not more than 1.5% | |
| Methoxy content | | 28.0–30.0% | |
| Hydroxypropoxy content | | 7.0–12.0% | |

low-viscosity grades are discussed. A "6-mPa sec grade" means HPMC having a labeled viscosity of 6 mPa sec. Labeled viscosity does not mean the exact viscosity value of a product lot. In the compendial monograph, the apparent viscosity of a low-viscosity HPMC product is specified to be from 80% to 120% of the labeled viscosity. HPMC 2910 of low labeled-viscosity (3–15 mPa sec) is commonly used in film coating. The low-viscosity grades of HPMC are typically produced by depolymerization of high-viscosity grades. Examples of commercially available products of HPMC for film coating widely used throughout the world are Pharmacoat 603, 645, 606, and 615 (Shin-Etsu Chemical Co. Ltd., Tokyo, Japan) and Methocel E3, E5, E6, and E15 (Dow Chemical Company, Midland, MI). As an example, the specifications of Pharmacoat are summarized in Table 2.

## Characteristics of HPMC Aqueous Solution

Figure 2 illustrates the relationships between the concentration of various viscosity grades of HPMC and their solution viscosity. The required viscosity of a solution for aqueous film coating is commonly less than 100 mPa sec. The maximum concentrations of 3, 6, and 15 mPa sec grades, which can be used in film coating, are therefore approximately 14%, 7.5%, and 4.5%, respectively. Thus, the maximum concentrations available depend on the viscosity grade of HPMC used, although there are other factors that should be taken into consideration in practical

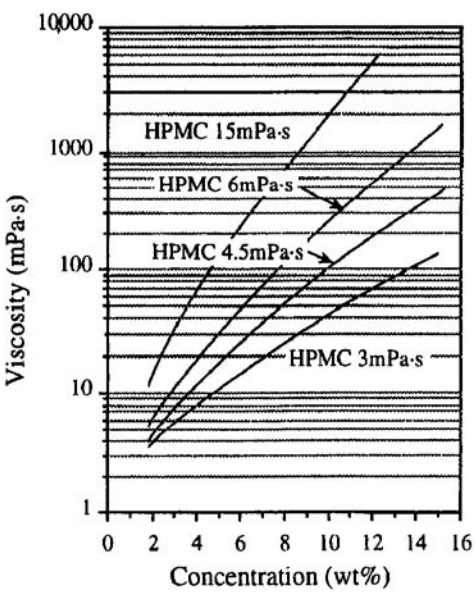



**Figure 2** Viscosity–concentration curve of HPMC.

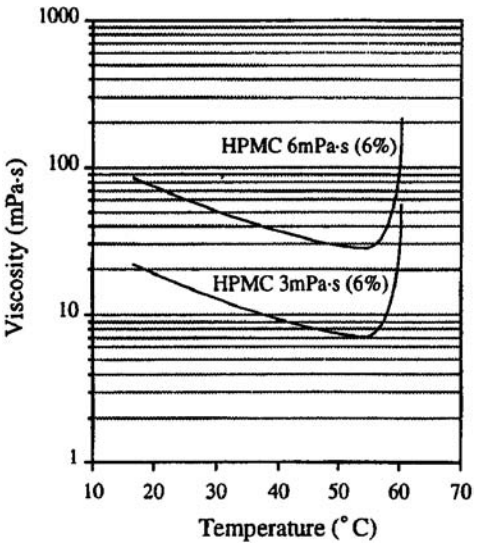



**Figure 3** Effect of temperature on the viscosity of aqueous solutions of HPMC.

applications. Aqueous solutions of HPMC gel upon heating. The thermal gelling temperature, which is close to the clouding point, depends on the level of substitution, and it is also affected by such factors as viscosity, concentration, heating rate, and the addition of salts. In Figure 3, the temperature–viscosity relationships of two 6% solutions of HPMC are shown. Dramatic increases in viscosity are observed at near 60°C, which indicates the occurrence of gelation. Problems

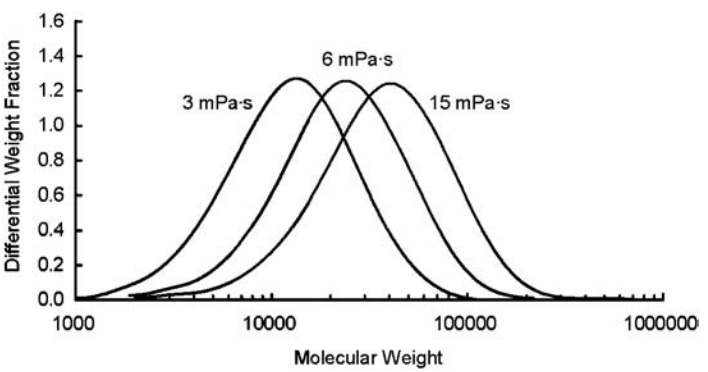



**Figure 4** Molecular weight distribution of HPMC using a SEC-MALLS technique. *Abbreviations*: SEC, size exclusion chromatography; MALLS, multiangle laser light scattering.

**Table 3** Molecular Weight of HPMC

| Sample | Mw[a] | Mw/Mn | Viscosity[b] (mPa sec) |
|---|---|---|---|
| Pharmacoat 603 | 16,000 | 2.0 | 3.0 |
| Pharmacoat 645 | 22,600 | 1.8 | 4.6 |
| Pharmacoat 606 | 35,600 | 1.6 | 6.0 |
| Pharmacoat 615 | 60,000 | 1.9 | 15.0 |
| Metolose 60SH-50[c] | 76,800 | 2.6 | 53.9 |

[a]Weight-average molecular weight measured by the SEC-MALLS method.
[b]Ubbelohde viscosity of 2% aqueous solution at 20°C.
[c]50 mPa sec grade of HPMC.
*Abbreviations*: SEC, size exclusion chromatography; MALLS, multiangle laser light scattering.

might be encountered if the solutions were at around this temperature. Preparation temperature of the coating solution should be less than 40°C for complete dissolution of HPMC particles.

## Molecular Weight and Its Distribution

Rowe (2) determined the molecular weight distribution of HPMC using SEC (also known as gel permeation chromatography or GPC). The data on molecular weight were represented based on polystyrene as a reference standard, and there is a possibility that molecular association occurred in dimethyl sulfoxide, which was used as the mobile phase, resulting in a very wide distribution; the ratio $M_w/M_n$ (weight-average molecular weight/number-average molecular weight) was greater than 10. Kato et al. (3) determined the molecular weight distribution by aqueous SEC based on the use of a series of polyethylene oxide standards. The weight-average molecular weights of HPMC of 3, 6, 15, and 50 mPa sec grades were 12,600, 29,400, 64,800, and 104,000, respectively. The ratio of $M_w$ and $M_n$ ranged from 4 to 5. Figure 4 and Table 3 show molecular weight data of HPMC using SEC with the multiangle laser light scattering (MALLS) technique. These results and previous reports indicate that molecular weight distribution is dependent on the measuring method and conditions.

## Physical Properties of HPMC Powder and Films

Callahan et al. (4) classified various pharmaceutical excipients according to their hygroscopicity by measuring equilibrium moisture content at 25°C. The results on HPMC and related cellulose derivatives are illustrated in Figure 5. According to their classification, HPMC is considered "very hygroscopic," which is defined as follows (4): "Moisture increase may occur at relative humidities as low as 50%. The increase in moisture content after storage for one week above 90% relative humidity (RH) may exceed 30%." Therefore, moisture absorption of

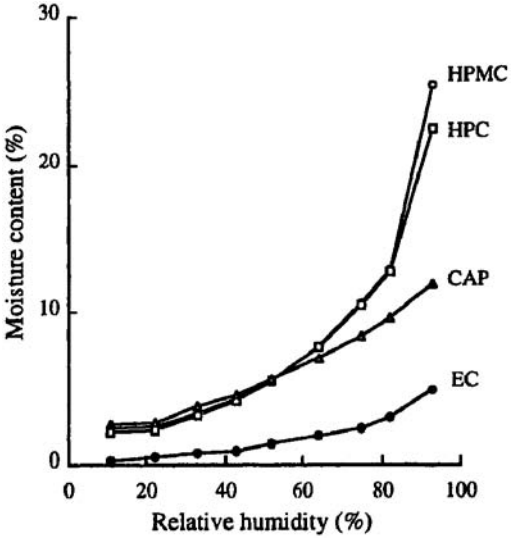



**Figure 5** Equilibrium moisture curves for HPMC and related polymers at 25°C. *Abbreviations*: HPC, hydroxypropylcellulose; CAP, cellacefate; EC, ethylcellulose. *Source*: From Ref. 4.

HPMC-coated pharmaceuticals may occur at very high humidity. In such cases, they should be packed in a moisture-proof material.

Various methods have been proposed for measuring water vapor permeability (WVP) of polymer films. Figure 6 shows a cell developed by Hawes (5) for measuring WVP. The WVP of various viscosity grades of HPMC and hydroxypropylcellulose (HPC) was measured and the results are shown in Table 4. Two kinds of film specimens were tested; one was a film prepared by casting an

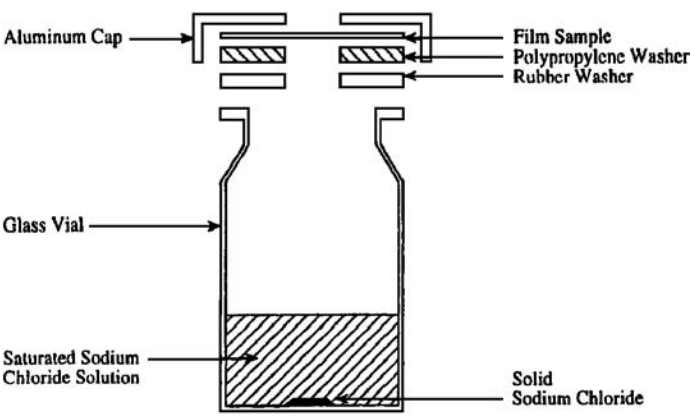



**Figure 6** Water vapor permeability cell. *Source*: From Ref. 5.

**Table 4** Water Vapor Permeability of HPMC and HPC Films

| Polymer, labeled viscosity | Sample | Water vapor permeability ($g/m^2$/24 hr) |
|---|---|---|
| HPMC, 50 mPa sec | Free film | 219 |
| HPMC, 15 mPa sec | Free film | 207 |
| HPMC, 6 mPa sec | Free film | 194 |
| HPMC, 6 mPa sec | Applied film | 273 |
| HPMC, 3 mPa sec | Applied film | 192 |
| HPC, 8 mPa sec | Free film | 106 |
| HPC, 8 mPa sec | Applied film | 202 |

*Abbreviations*: HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropylcellulose.

aqueous polymeric solution (free film) and the other was a film that was applied to tablets (applied film); both were 0.1 mm thick. Vials, each sealed by a sample of the film, were stored in a desiccator at 20°C with one side of the test film exposed to 0% relative humidity and the other to 75% RH. After an equilibrium period of 8 to 12 hours, the samples were weighed at intervals over a test period of 72 hours. The moisture permeability value of HPMC differed slightly depending on viscosity grade. The WVP tended to decrease as viscosity decreased. The WVP of applied films was always higher than that of free films, which might reflect higher porosity. HPC showed a tendency to have smaller WVP values than HPMC in both free and applied films.

Table 5 shows the mechanical properties of HPMC films. The properties vary with viscosity grade. Tensile strength and elongation of films (100 μm in thickness) prepared by casting of various viscosity grades of HPMC and HPC were measured using an Instron-type tensile tester at 20°C and 65% RH. Both tensile strength and elongation of HPMC films decreased as the viscosity decreased, and elongation of the 3 mPa sec grade showed an especially small value compared with that of 6 mPa sec grade. These observations suggest that the possibility of crack formation in coated films should be taken into consideration when an HPMC of lower viscosity grade such as 3 mPa sec is used. In contrast, HPC films exhibited very low tensile strength and comparatively higher elongation due to its plasticity.

**Table 5** Mechanical Properties of HPMC and HPC Films

| Polymer, labeled viscosity | Tensile strength (MPa) | Elongation (%) |
|---|---|---|
| HPMC, 50 mPa sec | 82.3 | 38.8 |
| HPMC, 15 mPa sec | 66.6 | 27.0 |
| HPMC, 6 mPa sec | 55.9 | 22.6 |
| HPMC, 3 mPa sec | 48.0 | 3.3 |
| HPC, 8 mPa sec | 10.8 | 35.5 |

*Abbreviations*: HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropylcellulose.

**Table 6** Dissolution Time of Films from Pharmacoat 606 in Various Fluids

| | Dissolution time (min)[a] | | |
|---|---|---|---|
| Test fluid | 20°C | 37°C | 50°C |
| JP 1st fluid (pH 1.2) | 2.0 | 2.1 | 6.2 |
| Water | 1.9 | 1.8 | 3.3 |
| 0.1 M Phosphate buffer (pH 7.5) | 2.3 | 3.8 | >60[b] |
| Kolthoff's buffer (pH 10) | 2.0 | 2.5 | 40–45 |

[a]Average of six measurements.
[b]Film remained in small fragments.

Table 6 shows the dissolution time of HPMC films (6 mPa sec grade, 80 μm in thickness) at various pH and temperature conditions. In film coatings soluble in gastric fluid, the dissolution properties of the films over the entire biological pH range directly influence the bioavailability of the active ingredients. There was no marked difference at 20°C. At 37°C, slight prolongation of the dissolution time was observed in 0.1 M phosphate buffer (pH 7.5) and Kolthoff buffer (pH 10). The dissolution time was dramatically delayed at 50°C. These changes are due to a salting-out effect. At 50°C, the temperature is close to the thermal gelling temperature so the film becomes less soluble and the films disintegrated, but remained in small fragments. From these data, it is expected that the films can be readily dissolved in the stomach at 37°C.

## APPLICATION OF HPMC TO FILM COATING OF PHARMACEUTICALS

HPMC forms transparent, tough, and flexible films from aqueous solutions. The films dissolve completely in the gastrointestinal tract at any biological pH, and HPMC provides good bioavailability of the active ingredients. The safety of HPMC has been proven by more than 40 years of application in the food and pharmaceutical industries. Animal toxicological studies of HPMC have been published since the 1950s. The most recent study was carried out under Good Laboratory Practice (GLP) (6).

### Effect of Moisture on the Stability of Active Ingredients

When aqueous coating first appeared in the pharmaceutical field, questions arose as to whether it could be applied to water-sensitive drugs and whether moisture absorption by the product during coating might degrade the drug. The results of studies on degradation of active ingredients, effect of moisture content, and long-term stability of aqueous film–coated tablets containing aspirin and ascorbic acid, both of which degrade in the presence of water, are given in Table 7. In these studies, almost no degradation of the active ingredients during coating was observed. The moisture content after coating was slightly lower than that before

**Table 7** Stability of Aspirin/Ascorbic Acid Tablets Coated with HPMC in an Aqueous System[a]

| Storage conditions | Items analyzed (%) | Tablet samples | After coating | After 30 days | After 90 days |
|---|---|---|---|---|---|
| 37°C, 75% RH | Salicylic acid | Uncoated | 0.07 | 0.23 | 0.56 |
| | | HPMC-coated | 0.09 | 0.24 | 0.53 |
| | Ascorbic acid | Uncoated | 8.55 | 8.27 | 8.25 |
| | | HPMC-coated | 8.46 | 8.39 | 8.28 |
| | Moisture | Uncoated | 0.49 | 0.92 | 0.90 |
| | | HPMC-coated | 0.18 | 1.16 | 1.21 |
| 37°C, in closed bottle | Salicylic acid | Uncoated | 0.07 | 0.11 | 0.27 |
| | | HPMC-coated | 0.09 | 0.13 | 0.22 |
| | Ascorbic acid | Uncoated | 8.55 | 8.56 | 8.54 |
| | | HPMC-coated | 8.46 | 8.46 | 8.56 |
| | Moisture | Uncoated | 0.49 | 0.45 | 0.41 |
| | | HPMC-coated | 0.18 | 0.20 | 0.21 |

Tablet formulation: acetyl salicylic acid (250 mg/tablet), ascorbic acid (27.5), microcrystalline cellulose (40.5), Talc (15.0), tablet weight (333 mg/tablet), tablet size (9.5 mm in diameter), Monsanto hardness (7–8 kg), disintegration time (1 min), coating amount (3%), apparatus (Hi-Coater HCF 100).
[a]Tablets were coated with Pharmacoat 603.
*Abbreviation*: RH, relative humidity.

coating in this case. Moisture present in the tablet can be partially removed by drying during the coating process. Although tablets often take up moisture to various extents during the coating operation, the moisture content can be restored to the initial level through postdrying.

A slight decrease was observed in the content of active ingredients during a storage test, as shown in Table 7, but there was no difference between coated tablets and uncoated tablets, so the coating operation did not affect the stability of the active ingredients.

## Selection of Viscosity Grade

Among the many viscosity types of HPMC, the 15, 6, 4.5, and 3 mPa sec grades are popular for aqueous film coating, with the 6 mPa sec grade being the most popular. The 3 mPa sec grade, having a low degree of polymerization, is capable of providing high-concentration polymer solutions, but film strength is quite inferior and peeling may occur during the coating operation if fragile tablets are used or if the pigment load is high. Thus, it is necessary to confirm, when using this viscosity grade especially, that such problems do not occur. In the case of 15 mPa sec grades, a high polymer concentration is difficult to use, and it is not economical. However, the film is so strong that it is sometimes useful for coating fragile tablets. The 4.5 mPa sec grade may be used to decrease the coating time without causing

a decrease in film strength. For pellet coating, a low-viscosity coating solution is more appropriate in order to prevent the pellets from sticking during the coating operation. Therefore, the 3 mPa sec grade is suitable for pellet coating.

## Selection of Additives

Plasticizers are not required when tablets with sufficient hardness and low friability are used and little or no pigment is contained in the coating formulation. If fragile tablets are coated or if large levels of pigment are added to the coating formulation, the film will adhere poorly to the tablet surface, and film peeling may occur or engraving on the tablets may not appear sharp. These problems may be avoided by the addition of plasticizers. Polyethylene glycol (PEG), especially a high molecular weight type such as PEG 6000, is a suitable plasticizer. Liquid type PEG such as PEG 400 is also applicable particularly for peeling and for avoiding logo-bridging. Although a greater effect is expected as the content of plasticizer increases, it should preferably be added at the minimum effective level (usually 20–30% with respect to the polymer). Excessive amounts of plasticizer may cause tablet tacking, plasticizer bleeding, color depletion, or interaction with the active ingredients. Propylene glycol is also effective as a plasticizer to some extent but tends to volatilize during the coating process and storage.

If titanium dioxide or a lake pigment is used, it is necessary to first disperse it in water in a ball mill or colloid mill. As interbrand differences are observed in the dispersion properties of titanium dioxide, switching to another brand is sometimes effective in improving the properties of the dispersion.

Lake pigments such as erythrosine aluminum lake powder are sometimes hard to wet. The addition of a small amount of alcohol to the pigments or the addition of surfactants to the water can aid dispersion. Water-soluble dyes have deep coloring effects but may color the tongue on oral administration of the coated preparations. The use of iron oxide pigments as coloring materials has become popular, but they are apt to precipitate in the coating solution, and comparatively strong agitation is required during the coating process.

To provide tablets with suitable slipping characteristics so that blister packaging can proceed smoothly, the addition of talc is also effective; 20% to 30% with respect to the polymer is sufficient for that purpose. In pellet coating, the addition of talc is effective for avoiding pellet tacking, but in this case more than 100% with respect to the polymer may be required to give the best performance.

## Preparation of the Coating Solution

A typical concentration of 6 mPa sec grade of HPMC is approximately 6% (this is not always reflected in the coating examples described below) to form a smooth surface film in tablet coating. The concentration may be increased to 8% to 10%. Higher concentrations than this are not recommended. If the active ingredient is highly water soluble and its content is very high, the active ingredient may dissolve

in the spray mists during the operation, resulting in the active ingredient being included in the film. This is often inconvenient, especially if the active ingredient has a bitter taste. Although a method to prevent this phenomenon completely has not yet been found for all cases, a fairly effective method is to keep the particle size of the spray mist small and to use a low spray rate to maintain a dry core surface.

To dissolve HPMC in water, the HPMC powder is first dispersed into a partial amount (half to one-third of the total amount used) of hot water, and then cold water is added. A clear solution is obtained after cooling. The temperature of the hot water should preferably be over 70°C to prevent lumping. On a production scale, moderate agitation is better than vigorous agitation while the powder is being added to the hot water since vigorous agitation may cause severe foaming, which may be difficult to remove. If the polymer concentration is less than 10%, even if the dispersion contains some powder aggregates, it will turn into a clear solution within a day on standing at room temperature. Therefore, if the coating solution is to be employed the next day, hot water does not always have to be used. Long-term storage of a coating solution may result in mold formation. Although no means of complete prevention of mold growth has yet been found, the addition of sorbic acid (final concentration 0.1%) is effective.

## Coating Equipment

Many types of equipment can be used for aqueous film coating. As a result of the high latent heat of water evaporation, the coating time depends on drying efficiency. A side-vented pan is most suitable for coating. For the spray equipment, an air-atomizing spray is recommended. In an airless spray system, which is useful for organic solvent coating, control of the spray rate is difficult and maintenance is time consuming. Coating equipment is described in detail in a separate chapter of this book.

## Coating Operation

In typical coating procedure with a commercial scale side-vented pan tablets are preheated, and spraying is initiated when the outlet temperature rises above 40°C. The feed rate of the coating solution is controlled so as to keep the outlet temperature over 40°C. If slight picking occurs due to overwetting as a result of improper operating conditions, the situation can be normalized by adjusting the conditions. However, extreme overwetting will damage the whole batch, so the entire operation must be carried out with great care.

When using extremely fragile tablets, the initial tablet temperature should be increased (e.g., to 50°C). Then pan rotation should be initiated at low speed and spraying started simultaneously. If the outlet temperature decreases and picking occurs, both pan rotation and spraying are stopped, and the tablets are reheated. These processes are repeated several times. After the film has developed to a reasonable strength, the operation is continued under normal conditions.

**Table 8** Formulation and Properties of Core Tablets

| Tablet formulation | |
|---|---|
| Spray-dried lactose | 79.5% |
| Cornstarch | 15.0% |
| L-HPC | 5.0% |
| Magnesium stearate | 0.5% |
| Total | 100.0% |
| **Tablet properties** | |
| Size | 7 mm in diameter, 9 mm R |
| Weight | 137.8 mg (CV = 1.68%) |
| Hardness | 6.9 kg |
| Loss on drying | 2.2% |
| Disintegration time | 3.3 min |
| Friability | 0.03% (Roche's friabilator, 25 rpm, 10 min, 20 tablets) |
| Surface roughness | R = 0.73 μm |

*Abbreviation*: L-HPC, low-substituted hydroxypropylcellulose.

Besides the side-vented pan a conventional pan can also be used for coating. If a continuous spray causes overwetting of the tablets in a conventional pan, intermittent spraying can be employed. In both cases, drying aeration should be continuous. When the tablets are fragile, the pan speed should not be increased until the film is partially formed. Tablets should be preheated to about 40°C and kept at this temperature during the coating operation. Picking may occur at lower temperatures.

The following examples of tablet coating illustrate the use of both laboratory-scale and production-scale machines.

### Dria Coater (Powrex Co., Ltd., Japan)

DRC-1200 (120 kg batch size) and DRC-500 (5 kg batch size) were used. The formulation and properties of the tablets used in the study are shown in Table 8. The operating conditions are shown in Tables 9 and 10. The evaluation was performed by determining the surface roughness of coated tablets and color variation. The results are shown in Figures 7 and 8. These data suggest that in the first 30 minutes, tablets were a mixture of coated and uncoated tablets.

### Hi-Coater (Freund Industry, Japan)

Vitamin $B_2$ tablets were coated with Pharmacoat 645 and 606 using a Hi-Coater. The operating conditions are shown Figure 9 shows the release profiles of vitamin $B_2$ from the coated tablets at various pH. No significant difference in drug release was observed for different pH values.

**Table 9** Operating Conditions (Dria Coater DRC-1200)

| | |
|---|---|
| Apparatus | DRC-1200 (Powrex, Japan) |
| Batch size | 120 kg |
| Spray gun | Devilbiss × 2, nozzle diameter 1.4 mm |
| Spray air | Atomizer 3.2 kg/cm$^2$ 250 L/min |
| | Pattern 3.4 kg/cm$^2$ 200 L/min |
| Gun distance | 25 cm |
| Drying air flow | 30 m$^3$/min |
| Spray rate | 220 g/min |
| Inlet air temperature | 75°C |
| Outlet air temperature | 51°C |
| Tablet temperature | 46°C |
| Pan speed | 8 rpm |
| Postdrying | 50°C, 30 min |

## Pellet Coating in a Fluidized Bed

For pellet coating using a fluidized bed, care must be taken such that the pellets do not adhere to each other during the coating operation. For this reason, a low-viscosity HPMC such as Pharmacoat 603 or Methocel E3 is better to use than a higher viscosity grade. To avoid tacking, an inorganic compound such as talc should be added to the formulation or an organic solvent should be employed.

A recent study has shown that methylcellulose (MC), rather than HPMC, is useful for pellet coating since it has less stickiness (7). MC is also water soluble and has similar characteristics to HPMC. A low-viscosity grade of MC such as Metolose SM-4 (Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) is commercially available for aqueous film coating. Figure 10 shows a comparison of agglomeration during pellet coating between MC and HPMC. The coating conditions are

**Table 10** Operating Conditions (Dria Coater DRC-500)

| | |
|---|---|
| Apparatus | DRC-500 (Powrex, Japan) |
| Batch size | 5 kg |
| Spray gun | Devilbiss × 2, nozzle diameter 1.4 mm |
| Spray air | Atomizer 3.2 kg/cm$^2$ 250 L/min |
| | Pattern 3.4 kg/cm$^2$ 200 L/min |
| Gun distance | 25 cm |
| Drying air flow | 3.5 m$^3$/min |
| Spray rate | 25 g/min |
| Inlet air temperature | 70 C |
| Outlet air temperature | 51 C |
| Tablet temperature | 43°C |
| Pan speed | 15 rpm |
| Postdrying | 50°C, 30 min |

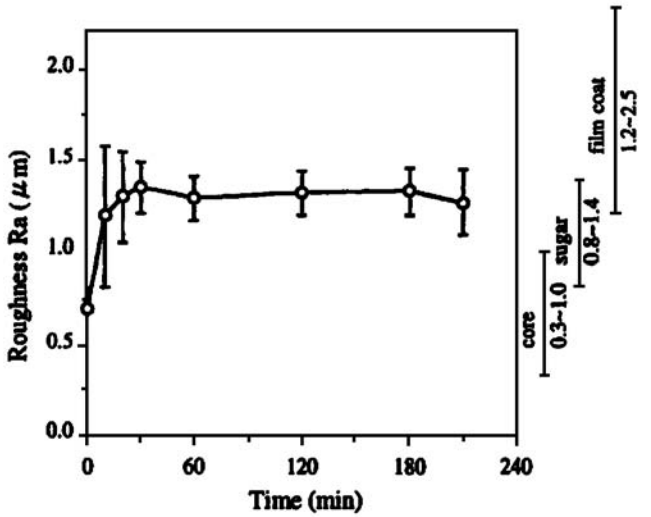



**Figure 7** Changes in surface roughness of tablets coated with Pharmacoat 645. Surface roughness of 10 tablets was measured using a surface-measuring instrument (Surfcom 554A, Tokyo Seimitsu Co., Japan) and average roughness (Ra: μm) was calculated. Error bars indicate standard deviation.

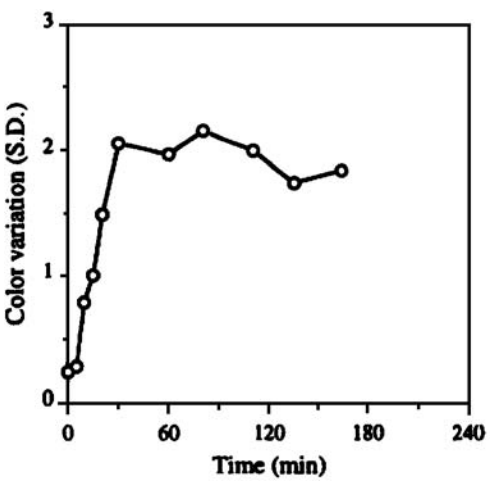



**Figure 8** Changes in color variation of coated tablets. Intertablet color variation of 20 tablets was measured using a color computer (SM-4, Suga Test Instruments, Japan), and the color variation was evaluated in terms of the standard deviation of ΔE (Hunter Lab).

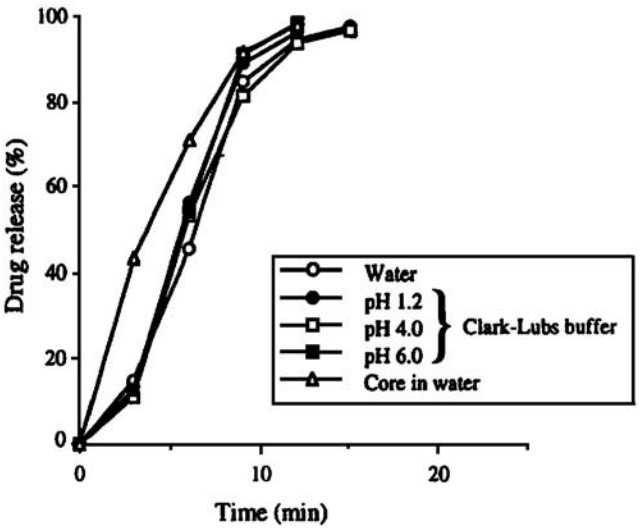



**Figure 9** Dissolution characteristics of coated tablets. The coated tablet (190 mg) contains 3.2 mg of riboflavin (vitamin $B_2$). Paddle speed: 100 rpm.

shown in Table 13. Using MC, the spray rate can be increased without granule agglomeration compared to HPMC.

## Possible Difficulties in Aqueous Coating Using HPMC

Various problems that arise during aqueous coating using HPMC can be attributed to an improper coating formulation or processing conditions. Some of the problems and suggestions to overcome them are discussed below.

### Picking

Picking is the removal of film fragments from the tablet surface. It is caused by insufficient drying or excessive spraying, and can be avoided by decreasing the spray rate and/or increasing the drying temperature or air flow. In some cases, a decrease in the concentration of the coating solution or the addition of sugar (over 10% with respect to HPMC) is effective. Some tablet formulations may suffer severe picking, and in these cases the use of a high-viscosity grade may overcome the problem.

### Cracking

Cracking can be observed during coating or storage of coated tablets. It occurs when the stress in the coating overcomes the tensile strength and adhesion of the coating film. The following suggestions, either alone or in combination, are effective in preventing cracking.

**Table 11** Operating Conditions (New Hi-Coater HCT-48N)

| | | |
|---|---|---|
| *Coating solution 1* | | |
| Pharmacoat 606 | 6% | |
| Water | 94 | |
| *Coating solution 2* | | |
| Pharmacoat 645 | 10% | |
| Water | 90 | |
| *Operating conditions* | | |
| Apparatus | | |
| Batch size | 5 kg | |
| Pan diameter | 480 mm | |
| Pan speed | 16 rpm | |
| Spray gun | ATF × 1, nozzle diameter, 1.2 mm | |
| Spray air | 150 L/min | |
| Spray air pressure | 2.0 kg/cm$^2$ | |
| Gun distance | 15 cm | |
| Spray rate | 30 g/min | |
| Air flow rate | 2.5 m$^3$/min | |
| Inlet air temperature | 70°C | |
| Outlet air temperature | 47°C | |
| Tablet bed temperature | 40°C | |
| Postdrying | 50°C, 30 min | |
| *Results* | | |
| | Pharmacoat | |
| | 606 | 645 |
| Coating time (3% coating-based tablet weight) | 83 min | 50 min |
| Coating solution consumption | 2490 g | 1500 g |
| Pharmacoat consumption | 3.6 mg/tab | |
| Disintegration time | | |
| Before coating | 2.5 min | |
| After coating | 3.9 min | |

- Add plasticizers such as PEG 6000 (over 20% with respect to HPMC).
- Use a higher viscosity grade of HPMC.
- Use tablets with less friability. Friable loss reduces the adhesive strength between film and tablet.

### Bridging

In the coating of engraved or scored tablets, the film often fails to follow the tablet contours. This occurs when the stress in the coating film overcomes the adhesive strength. Addition of PEG 6000 (20–30% with respect to HPMC) can prevent

**Table 12** Operating Conditions (New Hi-Coater HC-130N)

| | | |
|---|---|---|
| *Operating conditions* | | |
| Apparatus | HC-130N (Freund Industry, Japan) | |
| Batch size | 120 kg | |
| Pan diameter | 1300 mm | |
| Pan speed | 8 rpm | |
| Spray gun | AT × 3, nozzle diameter 1.2 mm | |
| Spray air | Atomizer 170 L/min | |
| Spray air pressure | 2.0 kg/cm$^2$ | |
| Atomizer + pattern | 250 L/min (at 5.3 kg/cm$^2$) | |
| Gun distance | 30 cm | |
| Spray rate | 70 g/min × 3 | |
| Air flow rate | 15 m$^3$/min | |
| Inlet air temperature | 80°C | |
| Outlet air temperature | 47°C | |
| Tablet bed temperature | 46°C | |
| Postdrying | 50°C, 30 min | |
| *Results* | | |
| | Pharmacoat | |
| | 606 | 645 |
| Coating time (3% coating-based tablet weight) | 286 min | 171 min |
| Coating solution consumption | 60 kg | 35.9 kg |
| Pharmacoat consumption | 3.6 mg/tab | |
| Disintegration time | | |
| Before coating | 2.5 min | |
| After coating | 3.9 min | |

this problem. It is also a good idea to adjust processing parameters to avoid overwetting.

### Mottling

Mottling is a nonhomogeneous distribution of color on the surface of the tablet. To avoid this problem, the pigment should be dispersed completely before preparing the coating solution.

### Orange Peel

Unsuitable formulation of the coating solution or coating operation frequently causes the surface of the coat to resemble the peel of an orange. Lowering the polymer concentration or decreasing the spray rate may prevent this problem. It can also be caused by an incorrectly adjusted coating apparatus, such as eccentric positioning of the needle in the gun nozzle or pulse pumping, which results in an unusual distribution of the spray mist.

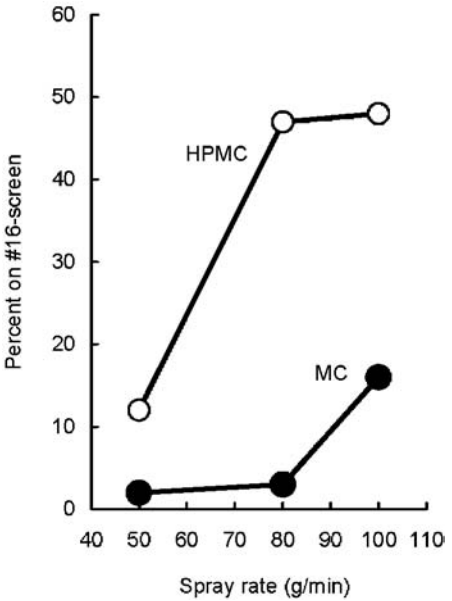
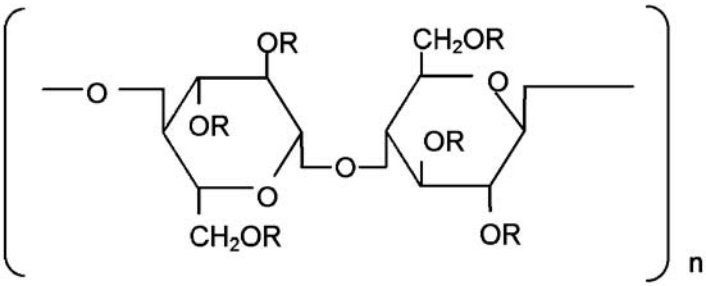



**Figure 10** Effect of spray rate on agglomeration of pellets. Comparison between HPMC (Pharmacoat® 603) and MC (Metolose® SM-4). Conditions are provided in Table 13. *Abbreviations*: HPMC, hydroxypropyl methylcellulose; MC, methylcellulose.

**Table 13** Operating Conditions for Pellet Coating

| | |
|---|---|
| *Core pellets* | |
| Spherical pellets containing theophylline (60%), 16-mesh pass | |
| *Coating solution* | |
| Pharmacoat 603 or Metolose SM-4, 7% aqueous solution | |
| *Operating conditions* | |
| Apparatus | FLO-5 (Freund Industry) |
| Batch size | 5 kg |
| Spray gun | Schlick 1.2 mm in diameter |
| Spray air pressure | 3.0 kg/cm$^2$ |
| Gun distance | 40 cm |
| Spray rate | 50, 80, 100 g/min |
| Inlet air temperature | 80°C |
| Outlet air temperature | 47, 39, 35°C |
| Bed temperature | 51, 44, 39°C |
| Coating amount | 8% |




R = -H, $-CH_3$, $-CH_2CH(CH_3)OH$,
$-COCH_3$, $-COCH_2CH_2COOH$,
$-CH_2CH(CH_3)OCOCH_3$, or $-CH_2CH(CH_3)OCOCH_2CH_2COOH$

**Figure 11** Chemical structure of hypromellose acetate succinate.

### Intertablet Color Variation

Intertablet color variation corresponds to intertablet variation of coating. Changing the formulation of the coating solution rather than altering the operating conditions is the best way to prevent it. For example, the addition of titanium dioxide or an increase in its content, or the use of a lake pigment instead of a water-soluble dye, is effective, although a slight change in the color tone may occur. These methods are based on reducing the dependency of color concentration on the coating amount.

**Table 14** Specification of HPMCAS (Shin-Etsu AQOAT)[a]

| Type | AS-LF | AS-MF | AS-HF |
|---|---|---|---|
| Acetyl content (%) | 5.0–9.0 | 7.0–11.0 | 10.0–14.0 |
| Succinoyl content (%) | 14.0–18.0 | 10.0–14.0 | 4.0–8.0 |
| Methoxyl content (%) | 20.0–24.0 | 21.0–25.0 | 22.0–26.0 |
| Hydroxypropoxyl content (%) | 5.0–9.0 | 5.0–9.0 | 6.0–10.0 |
| Viscosity[b] | | 2.4–3.6 cP | |
| Heavy metals | Not more than 10 ppm | | |
| Succinic acid | Not more than 1.0% | | |
| Loss on drying | Not more than 5.0% | | |
| Residue of ignition | Not more than 0.2% | | |

[a]Commercial name of Shin-Etsu Chemical Co., Ltd.
[b]2% in NaOH solution, Ubbelohde viscometer, 20°C.
*Abbreviation*: HPMCAS, hypromellose acetate succinate.

### HPMCAS: A Polymer for Aqueous Enteric Coating

Hypromellose acetate succinate, also known as hydroxypropyl methylcellulose acetate succinate (HPMCAS), is an enteric aqueous coating polymer developed by Shin-Etsu Chemical Co., Ltd. in Japan. This enteric polymer is soluble in aqueous media at a pH higher than 5.5, owing to the presence of carboxyl groups. The chemical structure of HPMCAS is shown in Figure 11.

This material was first approved in 1985 in Japan and has been listed in *Japanese Pharmaceutical Excipients* (JPE) since 1988, and in *the National Formulary* (NF) since 2005.

## PHYSICAL AND CHEMICAL PROPERTIES OF HPMCAS

HPMCAS for aqueous coating is a mechanically milled fine powder with an average particle size of approximately 5 μm that can be dispersed readily in water. The characteristics of HPMCAS are related to the level of two substituents, i.e., succinoyl and acetyl groups. Table 14 shows commercially available types of HPMCAS having different levels of content of substituents. There are three types—AS-LF, AS-MF, and AS-HF—depending on the ratio of succinoyl substitution to acetyl substitution (SA ratio). The SA ratio is highest in AS-LF, whereas AS-HF has the lowest SA ratio. Other specifications are also included in Table 14.

Figure 12 shows the equilibrium moisture content of HPMCAS at various humidities. Each type of HPMCAS differs in its equilibrium moisture content. These data indicate that the hydrophobicity of this polymer increases as the succinoyl content decreases or the acetyl content increases. The moisture content of AS-LF is similar to that of HPMCP under the same conditions. AS-MF and AS-HF exhibit lower equilibrium moisture contents.

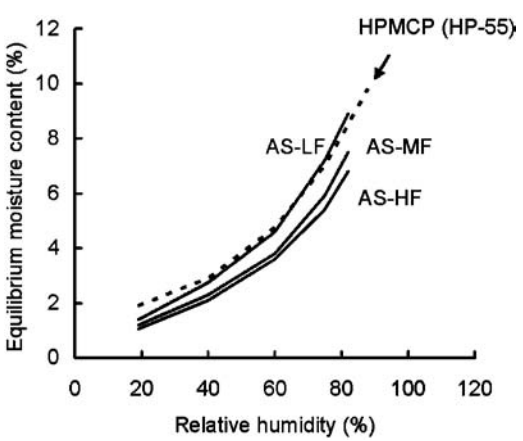



**Figure 12** Equilibrium moisture content of HPMCAS and HPMCP.

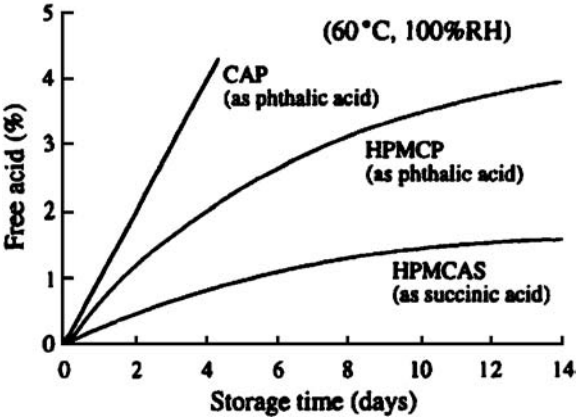



**Figure 13** Formation of free acid from enteric coating polymers.

Figure 13 shows the chemical stability of HPMCAS in comparison with other enteric polymers HPMCP and cellacefate, also known as cellulose acetate phthalate (CAP). As a measure of chemical stability, the formation of free acid from the polymers at 60°C, 100% RH was determined. The data indicate that HPMCAS is more stable than CAP and HPMCP.

Figure 14 shows the relationship between the dissolution time of HPMCAS films and substitution type. The polymer dissolves at the lowest pH for AS-LF, followed by AS-MF and AS-HF. The pH value at which the polymer dissolves depends

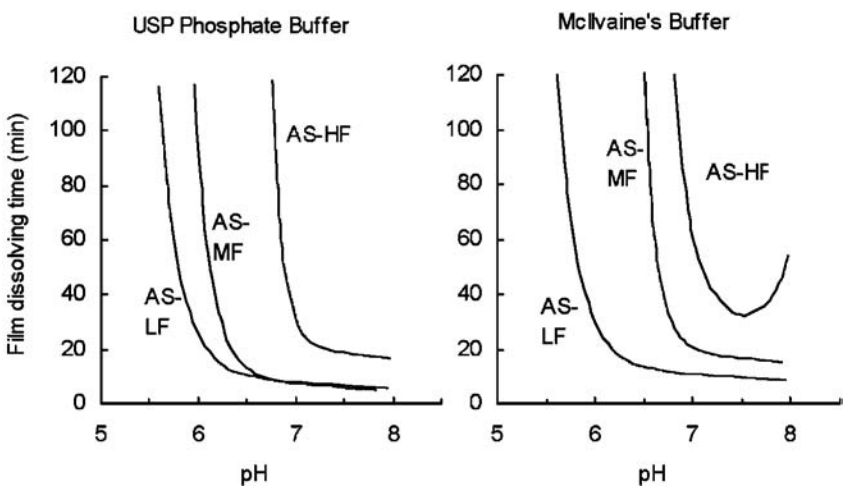



**Figure 14** pH-dependent dissolution patterns of films prepared from various types of HPMCAS in USP Phosphate buffer and McIlvaine's buffer. *Abbreviation*: HPMCAS, hypromellose acetate succinate; USP, United States Pharmacopeia.

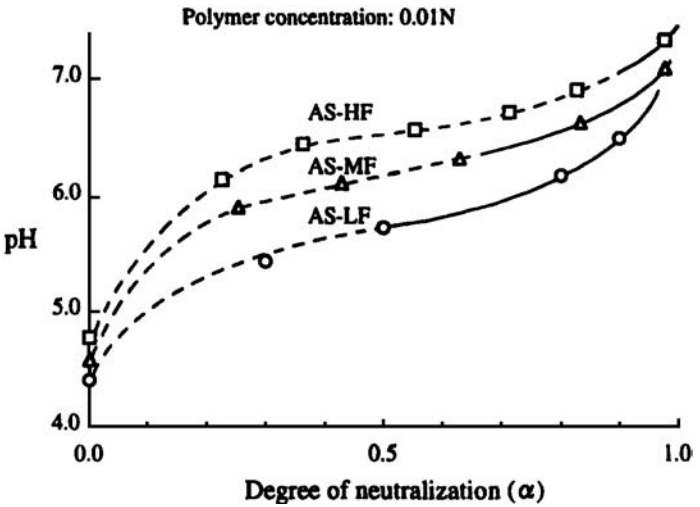



**Figure 15** pH titration curves of HPMCAS. *Abbreviation*: HPMCAS, hypromellose acetate succinate.

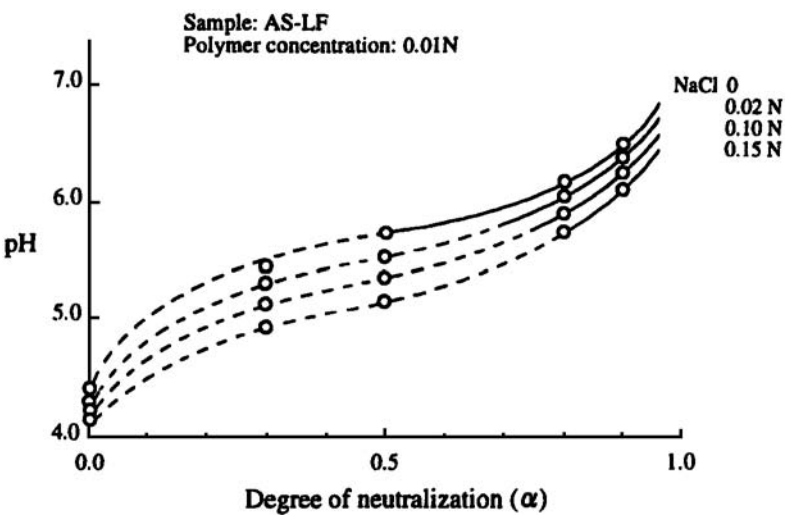



**Figure 16** Effect of NaCl on pH titration of HPMCAS. *Abbreviation*: HPMCAS, hypromellose acetate succinate.

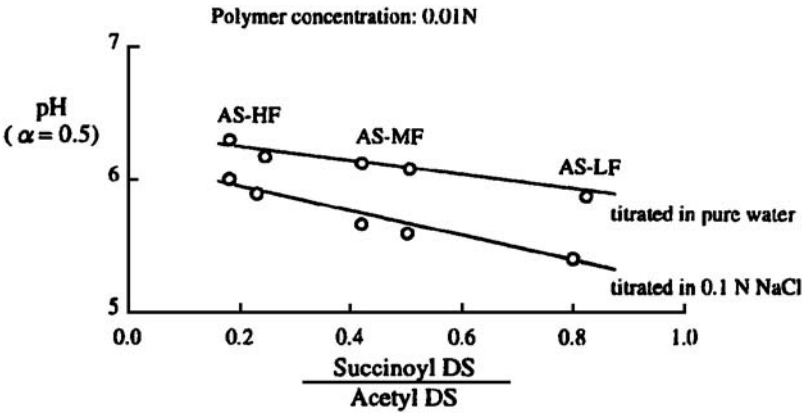



**Figure 17** Correlation of equilibrium pH at $\alpha = 0.5$ and SA ratio of HPMCAS.

on the buffer system but the order is not different. The ionic strength of the buffer seems to affect the dissolving profile. There is a unique phenomenon for the dissolution of AS-HF, where the time for the polymer to dissolve increases, as the pH increases above 7 in a high concentration buffer.

To further explain the mechanism of the pH-dependent solubility of HPMCAS, the electrolytic properties of carboxylic groups in the polymer were investigated. pH titration data provide some useful information on this matter. An aqueous dispersion of HPMCAS was directly subjected to pH titration. It took 3 to 4 minutes, however, to reach pH equilibrium, so continuous titration was not pos-

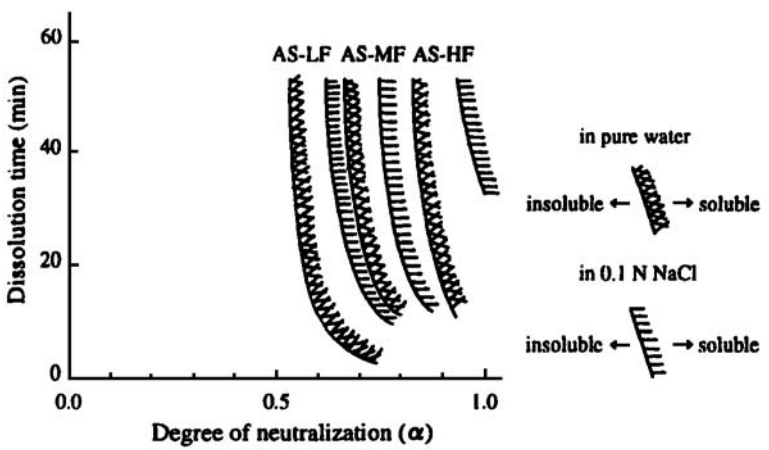



**Figure 18** Effect of neutralization and the addition of NaCl on the dissolution pattern of HPMCAS.

sible. Thus, the titration was carried out by adding a calculated amount of alkali to the polymeric dispersion to make a certain degree of neutralization (α) and measuring the pH of the dispersion at equilibrium. The results are shown in Figure 15. At α = 0.5, the equilibrium pH was the highest for AS-HF, followed by AS-MF and AS-LF, indicating that the nature of the dissociation is different. In the case of a monobasic weak acid, pH at α = 0.5 is equivalent to its p$K_a$. Assuming that this theory can be applied to HPMCAS, the results indicate that the dissociation constant is the highest for AS-HF, followed by AS-MF and AS-LF. In Figure 15, solid lines represent the regions in which the polymer is soluble.

Figure 16 shows the pH titration curves of HPMCAS (AS-LF) in the presence of NaCl. The pH at α = 0.5 was decreased as the salt concentration increased, which indicates greater dissociation at higher salt concentrations. Such a phenomenon is due to the difference in exchange of the sodium ion and the proton at the carboxyl group and is common to polyelectrolytes. Similar patterns were obtained with other types of HPMCAS.

Figure 17 shows the relationship between equilibrium pH at α = 0.5 and the SA ratio in the presence or absence of NaCl. As the SA ratio was increased, the pH decreased. These results suggest that dissociation increases as the number of carboxylic groups increases and that an increase in acetyl groups inhibits the dissociation at the succinoyl group.

Partially neutralized HPMCAS films, having various α values, were then prepared and their dissolution behavior in water or 0.1N NaCl solution was investigated. Figure 18 shows the dissolution time of the films as a function of the degree of neutralization. There were thresholds of degree of neutralization for

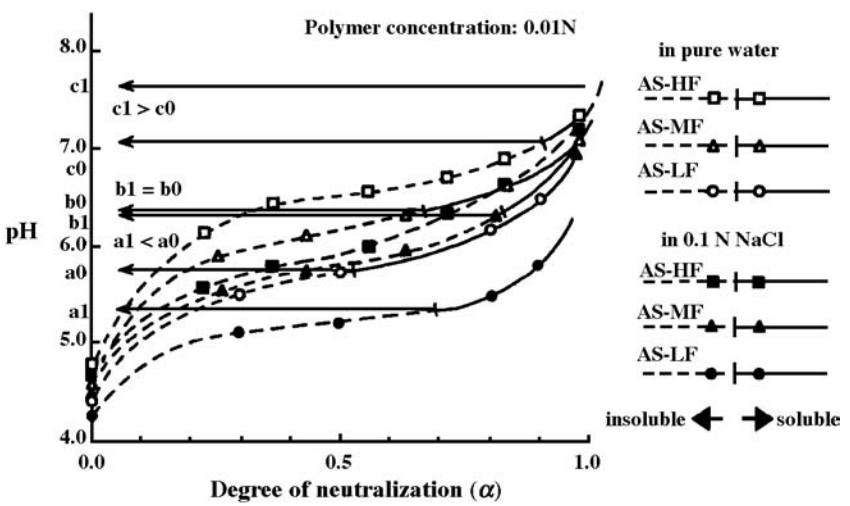



**Figure 19** Relationship between pH titration curve and dissolution of HPMCAS.

rapid dissolution of the films. It is suggested that as the polymer becomes more hydrophobic as the result of increasing the acetyl group content, a greater degree of neutralization is required for its dissolution. In the presence of NaCl, the threshold was shifted to high values for every polymer type, which was probably due to salting out.

Figure 19 shows the pH titration curves for all types of HPMCAS in the presence or absence of NaCl. At equilibrium, $\alpha$ defines (or reflects) the pH of the solution. Assuming that dispersed particles and films dissolve in the same manner, the dissolution pH of AS-LF films is predicted to be approximately 5.8 in the absence of NaCl. In the presence of NaCl, this value is decreased. On the contrary, the AS-HF films are predicted to dissolve at pH 7.0 in the absence of NaCl, and its dissolution pH in the presence of NaCl is more than 7.0. Thus, the pH at which HPMCAS dissolves depends on the SA ratio. This is due to the change in the degree of neutralization, and the type of buffer salts and ionic strength affect the dissociation nature of this polymer.

## FILM FORMATION OF HPMCAS FROM AQUEOUS MEDIA

### Selection of a Plasticizer

The selection of a suitable plasticizer is important for coating with aqueous dispersions of HPMCAS because the polymer will not form a film without being plasticized. Triethyl citrate (TEC) has been found to be a suitable agent for HPMCAS based on the results of experiments described below.

### Effect of Plasticizers on Film Appearance

Aqueous dispersions of HPMCAS and micronized HPMCP powder containing various plasticizers (20–100% based on polymer) were cast on a glass plate and dried at 40°C to form films. Clear films were obtained from dispersions containing TEC, triacetin, and propylene carbonate (Table 15).

**Table 15** Effect of Various Plasticizers on Film Formation from Aqueous Dispersions of HPMCAS and HPMCP

| | HPMCAS | | | | HPMCP | | | |
|---|---|---|---|---|---|---|---|---|
| Plasticizers | 20% | 30% | 50% | 100% | 20% | 30% | 50% | 100% |
| Dibutyl phthalate | N | N | N | T | N | N | N | N |
| Triethyl citrate | T | C | C | | T | C | C | |
| Triacetin | T | C | C | | T | C | C | |
| Ethylene glycol monoethyl ether | N | N | N | C | N | N | N | C |
| Propylene carbonate | T | C | C | | T | C | C | |

*Abbreviations*: HPMCAS, hypromellose acetate succinate; HPMCP, hypromellose phthalate; C, clear film formed; T, turbid film formed; N, no film formed.

**Table 16** Recovery of Plasticizers after Coating and Storage, and Gastric Resistance of Coated Tablets

| | Plasticizer | | |
|---|---|---|---|
| | Triethyl citrate | Triacetin | Propylene carbonate |
| Recovery after coating (%)[a] | 99 | 96 | 51 |
| Recovery after storage(%)[b] | 98 | 70 | – |
| Gastric resistance[c] | Good | Good | Poor |

[a]Tablets were coated with dispersion of the following formulation: HPMCAS (10%), plasticizer (3%), water (87%).
[b]40°C, 75% RH, 15 days.
[c]Tablets were subjected to disintegration test in simulated gastric fluid (the first fluid in Japanese Pharmacopoeia) to see if the tablets disintegrate (poor) or remain intact for 1 hr (good).
*Abbreviations*: HPMCAS, hypromellose acetate succinate; RH, relative humidity.

## Stability of a Plasticizer

Tablet coating was then performed by spraying the polymeric dispersions containing the plasticizers described above. The content of plasticizer was 30% with respect to the polymer. After coating, the amounts of polymer and plasticizer on the coated tablets were determined. The results are shown in Table 16. TEC and

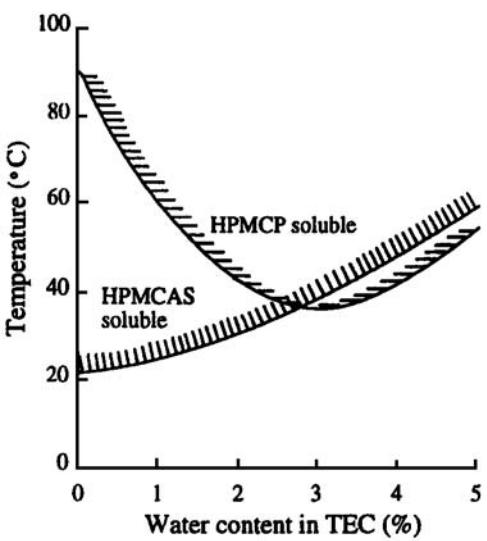



**Figure 20** Solubility of HPMCAS and HPMCP as a function of temperature and water content of TEC. *Abbreviations*: HPMCAS, hypromellose acetate succinate; HPMCP, hypromellose phthalate; TEC, triethyl citrate.

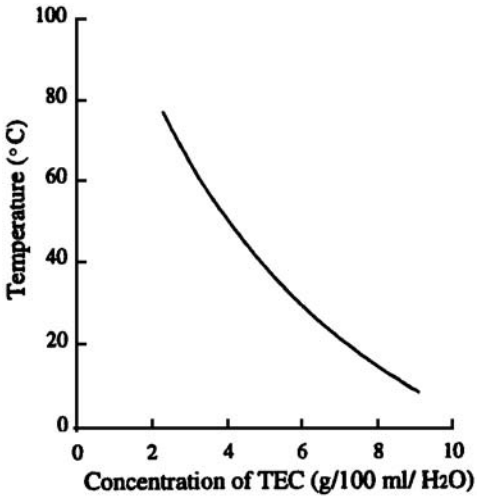



**Figure 21** Solubility of TEC in water. *Abbreviation*: TEC, triethyl citrate.

triacetin remained in the coated tablets in the same proportion as in the coating dispersions. Propylene carbonate remained to the extent of only 51%, as it evaporated during the spraying process. Tablets coated with HPMCAS plasticized with propylene carbonate showed insufficient gastric resistance. The content of TEC in the coated tablets was not changed after storage for 15 days at 40°C and 75% RH, whereas the content of triacetin decreased to 70%, probably due to degradation during the storage. Therefore, TEC was found to be the most suitable plasticizer for HPMCAS.

### Properties of TEC as a Plasticizer for HPMCAS

Figure 20 shows the solubility limits of HPMCAS and HPMCP in TEC as functions of temperature and water content of TEC. HPMCAS dissolved in anhydrous TEC at 23°C, and, as the water content was increased, this temperature limit of solubility shifted upward. HPMCP dissolved at 90°C in anhydrous TEC, but the curve showed a minimum at a water content of 3%. Since the usual temperature for tablet coating is 30 to 40°C, the solubility range of HPMCAS is wider than that of HPMCP, so that films from HPMCAS form more readily than from HPMCP. Figure 21, which covers TEC concentrations in the coating dispersion, shows that the solubility of TEC in water increased at lower temperatures.

### Film Formation

The mechanism of film formation in aqueous latex systems has been suggested by several researchers. The particles get closer during the drying process and the

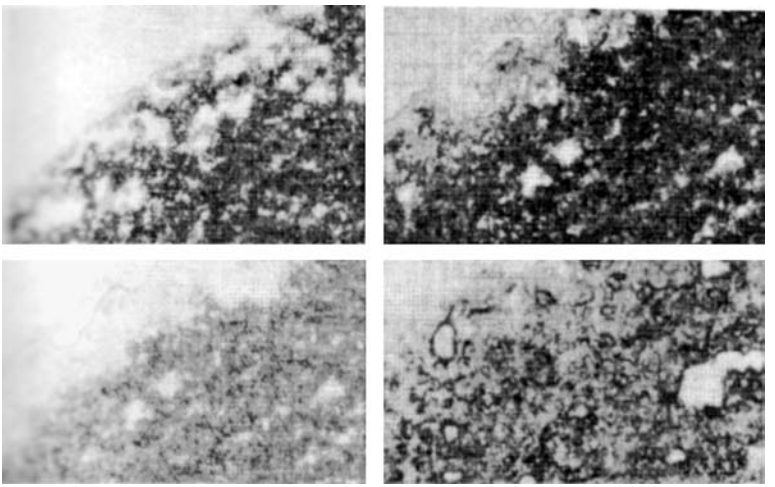


**Figure 22** Microscopic views of film formation from HPMCAS aqueous dispersion.

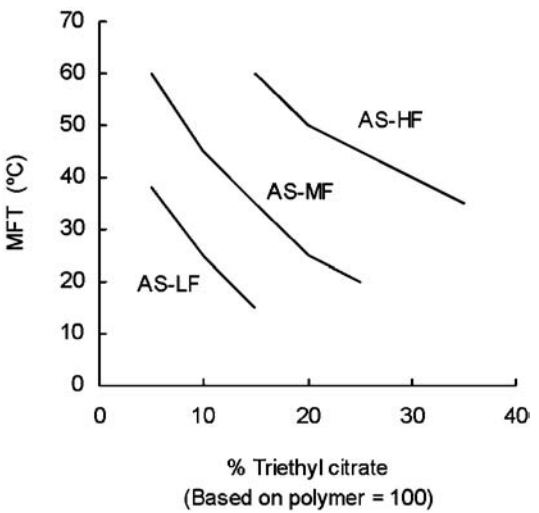



**Figure 23** Minimun film formation temperature of HPMCAS at various plasticizer content.

**Table 17** Mechanical Properties of Enteric Polymeric Films

| Polymer | Plasticizer | Tensile strength (MPa)[a] | Elongation (%)[a] |
|---|---|---|---|
| HPMCAS AS-LF | Triethyl citrate 20% | 15.4 ± 1.0 | 2.8 ± 0.2 |
| AS-MF | Triethyl citrate 28% | 16.2 ± 0.7 | 2.9 ± 0.2 |
| AS-HF | Triethyl citrate 30% | 13.4 ± 0.9 | 3.4 ± 0.2 |
| HPMCP HP-55[b] | None | 18.5 ± 1.0 | 5.4 ± 0.8 |
| CAP (Aquateric)[c] | Diethyl phthalate 35% | 6.7 ± 1.4 | 9.2 ± 2.0 |
| Eudragit L 30 D-55[d] | Triethyl citrate 20% | 25.4 ± 5.0 | 2.3 ± 0.6 |

[a]Mean ± SD of at least five experiments.
[b]Cast film from organic solution.
[c]Cellacefate commercially available from FMC Corporation. Films were prepared by spraying aqueous dispersion.
[d]Acrylic resin commercially available from Evonik-Degussa GmbH. Films were prepared by spraying aqueous dispersion.
*Abbreviations*: HPMCAS, hypromellose acetate succinate; HPMCP, hypromellose phthalate; CAP, cellulose acetate phthalate.

capillary force makes the particles eventually coalesce with each other. It is considered that this theory can be applied for the film formation of HPMCAS, but due to its larger particle size compared with other latex emulsions, the mechanism can be slightly different. A suggested theory of film formation from the aqueous dispersion of HPMCAS is that the plasticizer is separated from the water phase during the drying process and it dissolves or gelates the particles of HPMCAS. The particles then fuse to each other to form a film. Figure 22 shows microscopic views of film formation. At the beginning of drying, particles dispersed in water are observed (upper left). As the water evaporates, the particles are pulled together (upper right) and an increase in temperature causes TEC to separate from water. In the lower left panel, separated TEC can be seen surrounding aggregates of particles. At the end of drying, TEC fuses the polymer and film formation is completed (lower right). Figure 23 shows the minimum film formation temperature of HPMCAS at various plasticizer contents.

## Mechanical Properties of HPMCAS Films

Table 17 shows the mechanical properties of free films of enteric polymers. Except for HPMCP, the films were prepared by spraying the dispersion onto a Teflon sheet, under a controlled spray rate and temperature (8). The cast method, which is commonly used for film preparation, is difficult to apply for aqueous dispersions of HPMCAS. In this method, the dispersed particles settle during the drying process, resulting in heterogeneous film formation (9).

## AQUEOUS ENTERIC COATING USING HPMCAS

### Preparation of Coating Dispersions

Table 18 gives a typical example of an enteric coating formulation using HPMCAS. The optimum content of plasticizer (TEC) depends on the type of HPMCAS; 20% based on polymer weight is suitable for AS-LF, 28% for AS-MF, and 35% for AS-HF.

Figure 24 shows how to prepare the coating dispersion. Prior to adding ingredients, temperature of the water should be below 25°C (A). Under stirring, dissolve TEC and sodium lauryl sulfate in the water first (B). After TEC is completely dissolved, add the powder of HPMCAS and talc gradually (C). After the powder is uniformly dispersed, the coating fluid is ready to use (D). The dispersion should be gently stirred throughout the coating process so that the dispersed particles do not settle. It is also recommended that the dispersion be kept at a temperature below 25°C to avoid coagulation of polymer and plasticizer. When the dispersion is pumped to a gun nozzle at high temperature, coagulation sometimes happens inside the nozzle, which will lead to a gun blockage. This drawback has recently been improved by using an alternative method, which will be discussed later.

### Tablet Coating

There are several key points to be noted for coating processes using HPMCAS:

1. The spray gun needs to be closer to the tablet bed surface than for an organic solvent coating.
2. The following "two-stage" coating is recommended. In the initial stage, which uses approximately 25% of the total coating dispersion, spray slowly and keep the tablet surface relatively dry. The conditions in this stage are similar to those used in coatings with HPMC. A thin layer of polymer surrounds the cores and protects the tablet surface from overwetting in the next stage. After a weight gain of 2% has been applied, double the spray rate. The outlet product temperatures should be approximately at 40°C.

**Table 18** A Typical Coating Formulation

| | |
|---|---|
| HPMCAS (Shin-Etsu AQOAT) AS-MF | 7.0% |
| Triethyl citrate | 1.96% |
| Talc | 2.1% |
| Sodium lauryl sulfate | 0.21% |
| Water | 88.73% |
| Total | 100.0% |

*Abbreviation*: HPMCAS, hypromellose acetate succinate.

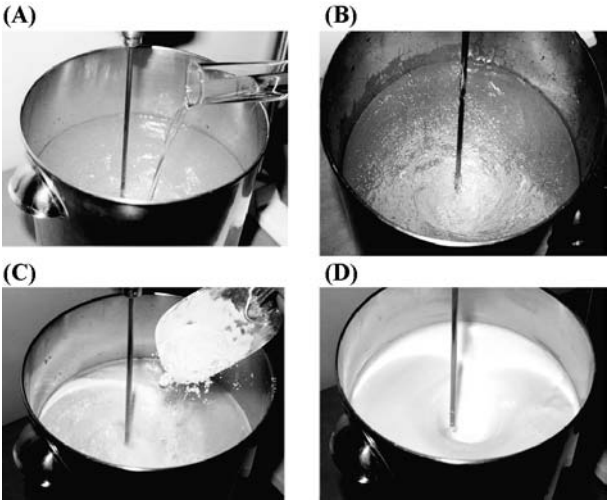



**Figure 24** Preparation of coating dispersion.

3. Once the desired amount of coating has been applied, the tablets must be dried to complete the coalescence. This typically takes about 30 min at an inlet temperature of 70°C, until the outlet temperature reaches 50°C.

Table 19 shows characteristics of core tablets in this example. Core tablets should have low friability to remain intact during aqueous coating. If defective tablets are found in the coating process, a subcoating with HPMC is recommended.

The process conditions for lab-scale and production-scale machines are shown in Tables 20 and 21, respectively. Figure 25 shows coating amount and gastric resistance. After enteric coating, additional "overcoating" is often effec-

**Table 19** Formulation and Properties of Core Tablets (Placebo)

| | |
|---|---|
| Lactose | 73% |
| Corn starch | 18% |
| Povidone (K30) | 3% |
| L-HPC (LH-11) | 5% |
| Mg stearate | 1% |
| Total | 100% |

Diameter: 8 mm; thickness: 4 mm; radius: 12 mm; weight: 200 mg; hardness: 100N; disintegration time: 3 min; friability: 0.05%. *Abbreviation*: L-HPC, low-substituted hydroxypropylcellulose.

**Table 20** Conditions for Tablet Coating at Laboratory Scale

| Apparatus | New Hi-Coater HCT-48N (Freund Industry, Japan) | |
|---|---|---|
| Batch size | 5 kg | |
| Spray gun | ATF × 1 | |
| Nozzle diameter | 1.8 mm | |
| Nozzle distance | 16 cm from bed surface | |
| Spray air pressure | 200 kPa | |
| Spray air flow | 150 L/min | |
| | Initial stage | Second stage |
| Pan speed | 16 rpm | 20 rpm |
| Inlet air temperature | 75°C | 79°C |
| Inlet air flow | 2.5 $m^3$/min | 3.0 $m^3$/min |
| Outlet air temperature | 42°C | 40°C |
| Spray rate | 25 g/min | 45 g/min |
| Spray time | 35 min | 89 min |
| Coating amount—weight gain | 0–2% | 2–11% |
| Final coating amount—weight gain | | 11% |
| Total spraying time | | 124 min |
| Postdrying | | Inlet 75°C, 30 min |

tive for the prevention of tacking during accelerated testing under high temperature and humidity.

## Fluid-Bed Coating

Table 22 shows the formulation of pellets used in the study. Table 23 shows processing conditions for granule coating using fluid-bed coating machines. In the fluid-bed coating, the spray gun needs to be set in a closer position as mentioned in the tablet coating, but two-step coating is not necessary. Figure 26 shows gastric resistance at various coating amounts. Figure 27 shows the release of vitamin $B_2$ at various pH in comparison with HPMCP.

## Aqueous Coating with a Concentric Dual-Feed Spray Nozzle

Since HPMCAS reached the marketplace, several pharmaceutical manufacturers have launched their products successfully using it. It should be pointed out, however, that this product has a major drawback, i.e., the requirement for cooling. Increase in temperature of the coating dispersion causes coagulation of the polymer and plasticizer, which sometimes leads to gun blocking. Therefore the temperature of the dispersion during the coating process has been recommended to be below 25°C, preferably less than 20°C.

**Table 21** Conditions for Tablet Coating at Production Scale

| Apparatus | New Hi-Coater HCF-100N (Freund Industry, Japan) | |
|---|---|---|
| Batch size | 60 kg | |
| Spray gun | ATF × 2 | |
| Nozzle diameter | 1.8 mm | |
| Nozzle distance | 20 cm from bed surface | |
| Spray air pressure | 400 kPa | |
| Spray air flow | 160 L/min | |
| | Initial stage | Second stage |
| Pan speed | 16 rpm | 20 rpm |
| Inlet air temperature | 70°C | 80°C |
| Inlet air flow | 13 $m^3$/min | 15 $m^3$/min |
| Outlet air temperature | 41°C | 40°C |
| Spray rate | 110 g/min | 220 g/min |
| Spray time | 80 min | 233 min |
| Coating amount—weight gain | 0–2% | 2–11% |
| Final coating amount—weight gain | | 11% |
| Total spraying time | | 313 min |
| Postdrying | | Inlet 80°C, 30 min |

Recently a new method was developed to overcome this drawback (10). Since the coagulation occurs by strong binding of the polymer and plasticizer at high temperature, in the new approach the plasticizer is sprayed separately to avoid coagulation. Using this technique, nozzle clogging does not occur and it is not necessary to chill the coating dispersion. Moreover, the polymer can be applied in greater concentrations than in the conventional method. Therefore, shorter processing times can be achieved.

Figure 28 shows the whole scheme of this coating method. The plasticizer (TEC) and the polymeric dispersion without plasticizer are separately sprayed using a newly developed "concentric dual-feed spray nozzle." Figure 29 shows the structure of the spray nozzle. Currently this type of nozzle is commercially available from Spraying Systems Co., Japan. This nozzle has a triple layer tip, consisting of an inner nozzle tip for the polymer dispersion without plasticizer, a middle one for the plasticizer, and an outer one for the atomizing air. Two pumps are required and each of them should be set to a proper speed to supply materials in a desired ratio. Table 24 shows processing parameters in tablet coating. The polymer concentration can be increased up to 15%, whereas the conventional aqueous dispersion coating can only use 7% at maximum. Figure 30 shows gastric resistance at various coating amounts in comparison with the conventional and the dual-feed method. Since gastric resistance is better at a lower polymer

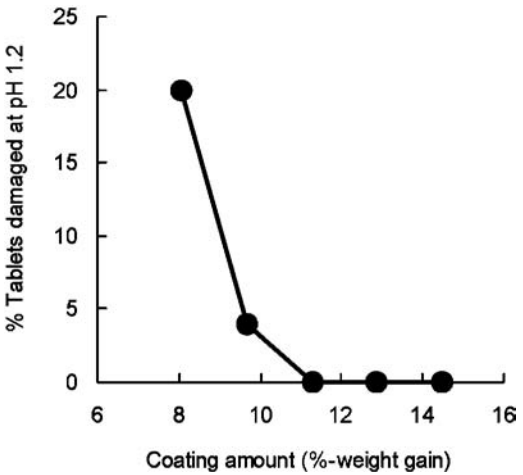



**Figure 25** Gastric resistance of tablets coated with HPMCAS (AS-MF). One hundred tablets were treated with a simulated gastric fluid (pH 1.2) containing a red dye, which colored defective positions of the coated surface. Data represents the number of defective tablets.

concentration, the dual-feed method requires slightly more coating to obtain sufficient gastric resistance. However, since the polymer concentration is higher, the processing time is significantly shorter.

## Application for pH-Dependent Sustained Release Dosage Form

Enteric coatings are used for the protection against digestive enzymes and also can be used for sustained release dosage forms by combination with uncoated components. The pH-dependent sustained release dosage forms are less popular due to the patient-to-patient variation in gastric pH; however, these systems have

**Table 22** Formulation and Properties of Core Pellets (Digestive Enzyme)

| | |
|---|---|
| Pancreatin | 60.0% |
| Lactose | 25.6% |
| Corn starch | 6.4% |
| Hydrated silicone dioxide[a] | 5.0% |
| HPC[b] | 3.0% |
| Total | 100.0% |

Pellet diameter: 0.8 mm; shape: cylindrical; disintegration time: 11 min.
[a]Carplex®, Shionogi, Japan.
[b]Hydroxypropylcellulose Type L, Nisso, Japan.

**Table 23** Conditions for Pellet Coating with a Fluidized-Bed (Laboratory Scale)

| | |
|---|---|
| Apparatus | Flow Coater FLO-1 (Freund Industry, Japan) |
| Batch size | 1.5 kg |
| Spray gun | Schlick × 1 |
| Nozzle diameter | 1.8 mm |
| Nozzle distance | 12 cm from bed surface |
| Spray air pressure | 200 kPa |
| Spray air flow | 120 L/min |
| Inlet air temperature | 80°C |
| Inlet air flow | 2.5 $m^3$/min |
| Outlet air temperature | 36°C |
| Product temperature | 34°C |
| Spray rate—polymer dispersion | 60 g/min |
| Spray time | 71 min |
| Coating amount—weight gain | 32% |
| Postdrying | Inlet 75°C, 30 min |

been extensively used for antibiotics because these dosage forms have few bioavailability problems.

Figure 31 shows a typical blood concentration curve of a pH-dependent sustained release formulation. It consists of uncoated pellets and enteric-coated pellets in a certain ratio. Although the uncoated components rapidly release the active ingredient, the coated component is emptied from the stomach over a wide

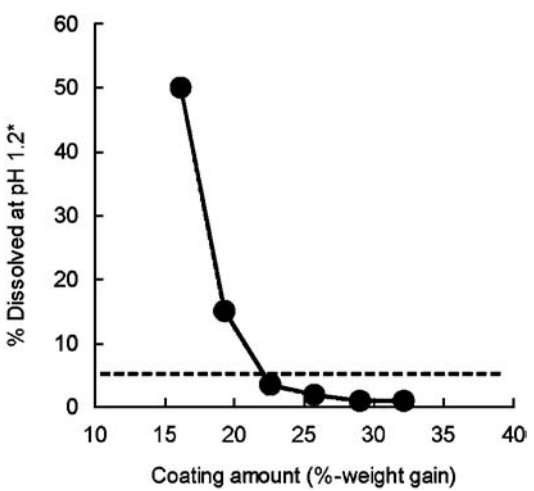



**Figure 26** Gastric resistance of pellets coated with HPMCAS (AS-MF). *Percent dissolved in a simulated gastric fluid (pH 1.2) at 2 hours.

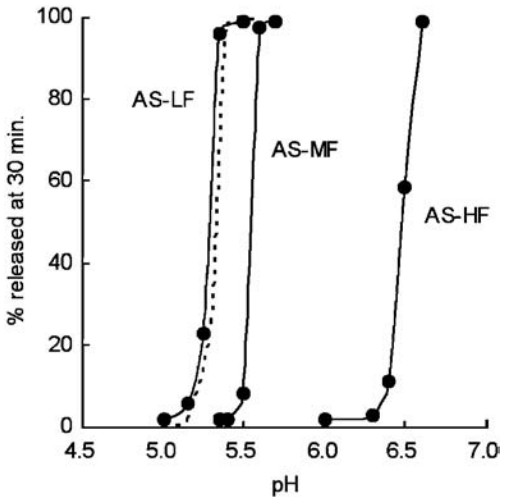



**Figure 27** Dissolution of vitamin $B_2$ at 30 min from granules coated with HPMCAS at various pH. Dotted line represents granules coated with HPMCP (HP-55) for comparison. *Abbreviations*: HPMCAS, hypromellose acetate succinate; HPMCP, hypromellose phthalate.

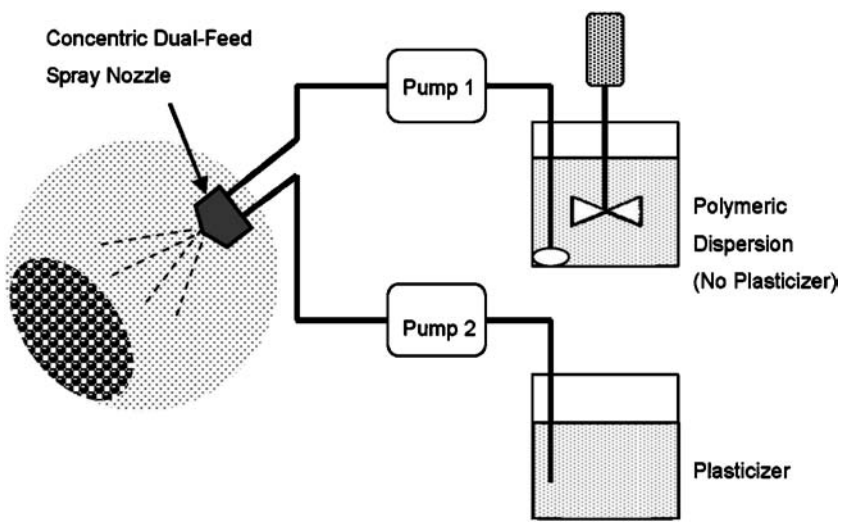



**Figure 28** Aqueous coating of HPMCAS using a concentric dual-feed spray nozzle.

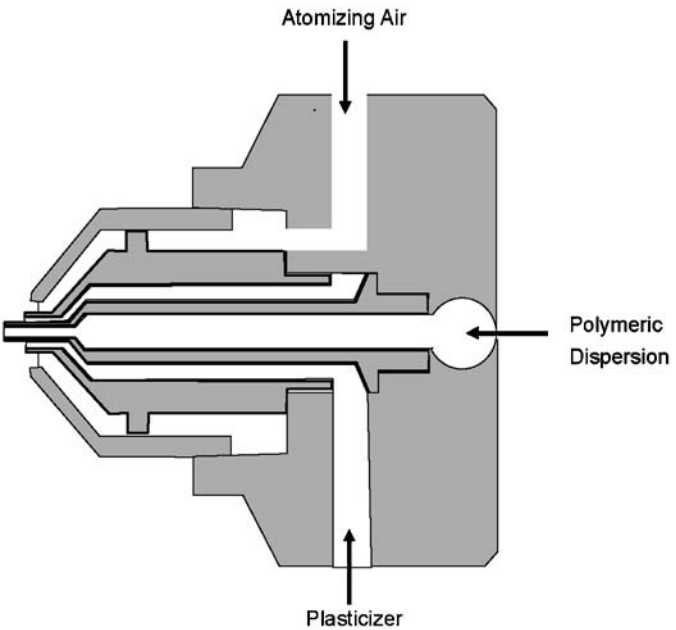



**Figure 29** Concentric dual-feed spray nozzle.

time span. The coated pellets release the active ingredient at a certain pH in the small intestine. As the emptying time of each pellet is variable, the blood concentration profile exhibits a broad curve. To get a desired release pattern, it is important to design the ratio of the uncoated and coated pellets and to select a polymer type that has a suitable dissolution pH.

The following is an example of a pH-dependent sustained release dosage form of cephalexin, a widely used antibiotic, coated with HPMCAS. The cephalexin pellets were prepared by an extrusion-spheronization process, and HPMCAS was coated on the pellets using a fluidized bed. The coating amount was 25% (polymer basis) with respect to the core pellets. Three types of coated pellets were prepared using AS-LF, AS-MF, and AS-HF.

An in-vitro evaluation was performed using a dissolution test (Japanese Pharmacopoeia, rotary basket method). The results are shown in Figure 32. The graph represents the relation between the dissolution at 30 minutes ($D_{30}$) and pH of the test fluid. A difference was seen in the dissolution pH of each substitution type.

The pellets were then administered to human volunteers and urinary samples were collected to determine the urinary excretion rate of cephalexin. The results in Figure 33 represent the urinary excretion rate–time curve of the core pellets and coated pellets. AS-HF had the most delayed peak compared with the other grades. This type was then used as an enteric polymer for this dosage

**Table 24** Conditions for Tablet Coating Using a Concentric Dual-Feed Spray Nozzle at Laboratory Scale

| | |
|---|---|
| *Coating formulations* | |
| Polymer dispersion | |
| HPMCAS (AS-MF) | 15.0% |
| Talc | 4.5% |
| Sodium Lauryl Sulfate | 0.15% |
| Water | 80.35% |
| *Plasticizer* | |
| Triethyl citrate | 28% with regard to HPMCAS |
| *Operating conditions* | |
| Apparatus | New Hi-Coater HCT-48N (Freund Industry) |
| Batch size | 5 kg |
| Spray nozzle | ATFM concentric dual spray nozzle × 1 |
| Nozzle distance | 6 cm from bed surface |
| Spray air pressure | 300 kPa |
| Spray air flow | 100 L/min |

| | Initial stage | Second stage |
|---|---|---|
| Pan speed | 16 rpm | 20 rpm |
| Inlet air temperature | 70°C | 75°C |
| Inlet air flow | 2.4 $m^3$/min | 2.8 $m^3$/min |
| Outlet air temperature | 43°C | 38°C |
| Spray rate—polymer dispersion | 25 g/min | 50 g/min |
| Spray rate—plasticizer | 1.05 g/min | 2.10 g/min |
| Spray time | 13 min | 47 min |
| Coating amount—weight gain | 0–1.6% | 1.6–13% |
| Postdrying | | Inlet temperature 75°C, 30 min |
| Final coating amount—weight gain | | 13% |
| Total processing time | | 60 min |

*Abbreviation*: HPMCAS, hypromellose acetate succinate.

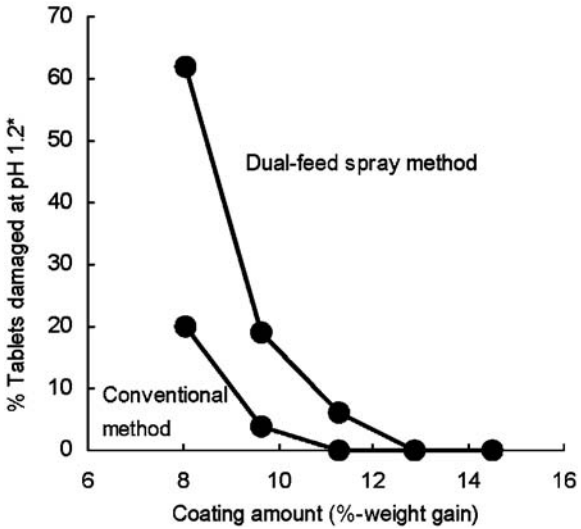



**Figure 30** Gastric resistance of tablets coated with HPMCAS (AS-MF) using a concentric dual-feed spray nozzle. *One hundred tablets were treated with a simulated gastric fluid (pH 1.2) containing a red dye, which colored defective positions of the coated surface. Data represents the number of defective tablets.

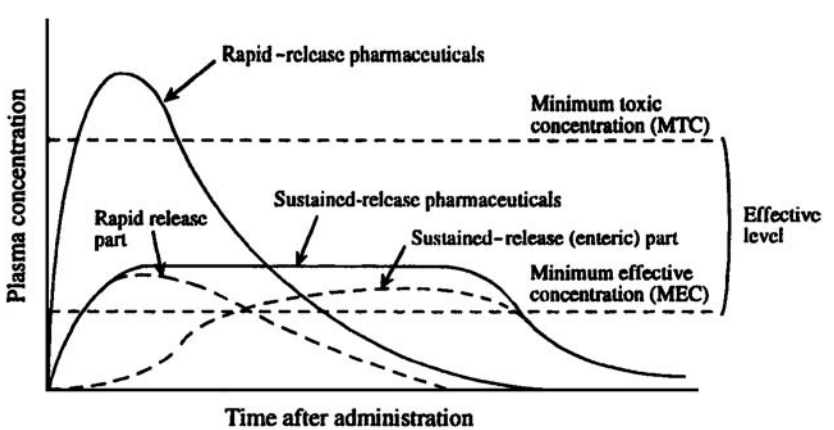



**Figure 31** Blood concentration–time curves after administration of sustained-release pharmaceutical dosage forms.

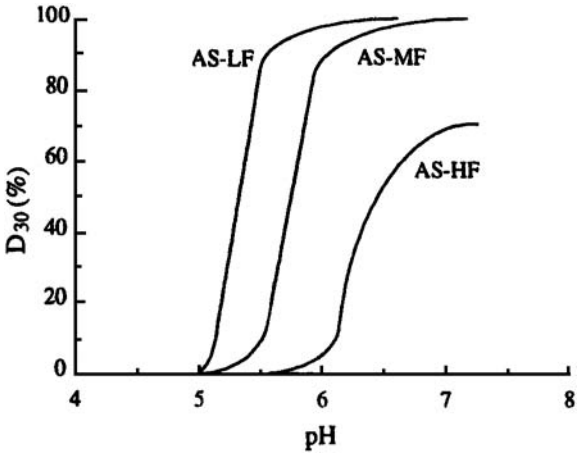



**Figure 32** Dissolution profiles of cephalexin pellets coated with HPMCAS.

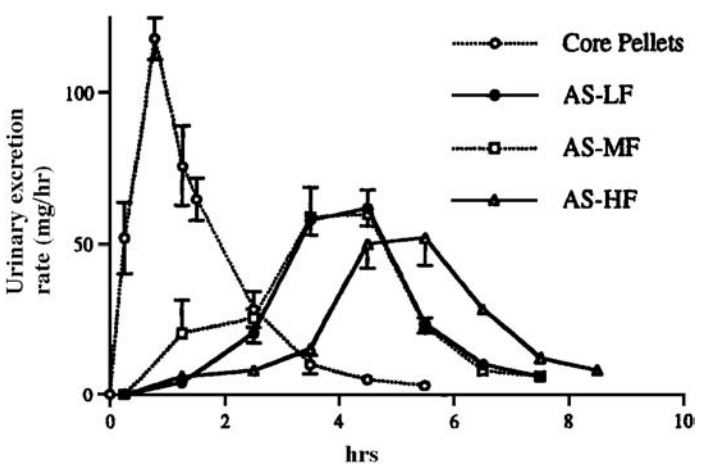



**Figure 33** Urinary excretion rate–time curve of cephalexin pellets uncoated or coated with HPMCAS. Pellets (0.5 g cephalexin) were administered to healthy volunteers after a light meal. Data represent mean ± standard error (n = 3).

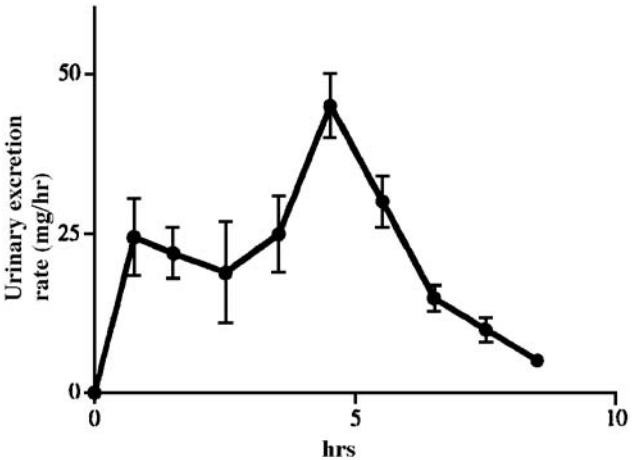



**Figure 34** Urinary excretion rate–time curve of pH-dependent controlled release cephalexin pellets using HPMCAS (AS-HF). Uncoated:coated = 3:7. Pellets (0.5 g cephalexin) were administered to healthy volunteers after a light meal. Data represent mean ± standard error (n = 3).

form. The coated pellets and core pellets were blended in a mixture at a ratio of 3:7. This form was next administered to the volunteers and the urinary excretion rate of cephalexin was determined. The results in Figure 34 indicate that sustained absorption was achieved. As a control, pH-independent sustained release pellets were prepared to compare bioavailabilities. The pellets were prepared by coating the pellets with ethylcellulose. Three samples, having different release rates, were prepared and administered to healthy volunteers. Table 25 shows the $T_{max}$ (time

**Table 25** Total Urinary Recovery and $T_{max}$ of Drug after Oral Administration of Cephalexin Pellets Coated with HPMCAS or Ethylcellulose

| Coating material | $T_{max}$ (hr) | Total urinary recovery (%)[a] |
|---|---|---|
| Uncoated | 0.75 | 94 |
| HPMCAS | | |
| AS-LF | 4.5 | 99 |
| AS-MF | 4.5 | 99 |
| AS-HF | 5.5 | 91 |
| Ethylcellulose | | |
| 15% | 1.5 | 98 |
| 20% | 2.5 | 75 |
| 25% | 3.5 | 40 |

[a]The amount of cephalexin in urinary samples was determined by high-performance liquid chromatography.

at the peak of blood drug concentration) and total urinary recovery of cephalexin, from the pH-dependent type and the pH-independent type. The total urinary recovery was decreased as the $T_{max}$ was delayed, but the pH-dependent type had significantly higher urinary recovery, which is equivalent to bioavailability in this case, than the pH-independent type with a longer $T_{max}$. This difference is considered to be due to cephalexin having a narrow absorption window in the upper area of the small intestine (11), and time-dependent release pellets tend to pass the absorption window before drug release has been completed.

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# 11

# The Applications of Formulated Systems for the Aqueous Film Coating of Pharmaceutical Oral Solid Dosage Forms

**Ali R. Rajabi-Siahboomi and Thomas P. Farrell**
*Colorcon, West Point, Pennsylvania, U.S.A.*

## INTRODUCTION

Aqueous coating technology remains the main option for film coating of oral solid dosage forms. This is irrespective of the purpose of the film-coating applications, i.e. for conventional and modified-release film coatings. The main reasons for its continued popularity are the environmental limitations of organic solvents used, recent advances in the formulation of aqueous film–coating materials, as well as major improvements made in the coating machines and their ancillaries.

This chapter provides a review of the use of formulated aqueous coating systems for

- conventional film-coating systems (immediate release),
- enteric film-coating systems (delayed release), and
- barrier membrane controlled release film-coating systems (extended release).

In the previous edition of this book, both formulated immediate release (Opadry®) and modified release (Surelease® and Sureteric®) aqueous film coatings were reviewed (1). This chapter serves to summarize advances made in the formulation and application of both immediate and modified release film coatings since 1997.

## AQUEOUS FILM COATING FOR IMMEDIATE RELEASE FORMULATIONS

As detailed in the prior edition of this book, the original Opadry formulations, introduced in late 1970s comprised low viscosity hypromellose (HPMC), plasticizers, and pigments. These fully formulated Opadry formulations provided numerous advantages versus the use of individual raw materials including the reduction of the number of raw materials for QC testing, reduced dispersion preparation time, consistent color-matched formulations, good processibility, excellent appearance on tablets, and good mechanical film properties. Opadry formulations have enjoyed widespread, successful use globally and are still found on a great variety of marketed products. However, one drawback of the Opadry formulations is that dispersion solids must be kept in the range of 10% to 15% by weight in water to achieve processible dispersion viscosities of 300 to 600 centipoise. In order to increase productivity, by decreasing coating time and/or increasing spray rate, the Opadry II family of products comprising HPMC and polysaccharides was introduced in the 1980s. With Opadry II, processible dispersions can be obtained at 20% rather than 10% to 15% solids, which allows for the productivity increase as well as increased adhesion.

Although HPMC-based Opadry II formulations have also been very successful commercially, unmet needs of the pharmaceutical industry emerged in the last two decades for which additional fully formulated film-coating options were required. Given the advent of direct-to-consumer advertising for both over-the-counter (OTC) and prescription pharmaceutical products globally and especially in the United States, coatings providing enhanced aesthetic characteristics (e.g., gloss and pearlescence) were sought to establish unique brand identity. In addition, "functional attributes" (e.g., moisture and oxygen protection) were also sought within immediate release film coatings in order to preserve labile active pharmaceutical ingredients. In response, over the last 10 years, film coatings were developed that improve aesthetic characteristics of dosage forms and provide functional benefits.

The most significant recent advances in the development of fully formulated aqueous film coatings have been the introduction of new film coatings based on polyvinyl alcohol (PVA) and sodium carboxymethylcellulose (NaCMC). Film coatings comprising these polymers offer the formulator the same or greater production conveniences afforded to them when using Opadry formulations containing HPMC and also provide functionality previously unrealized. PVA-based films are known to have relatively low moisture vapor and oxygen permeability (Table 1). On the other hand, NaCMC-based films have low oxygen permeability but relatively high water vapor permeability. Another important feature of NaCMC-based films is that, when formulated and applied properly, they are very glossy. NaCMC-based film coatings therefore offer the possibility of both enhanced functionality and aesthetics.

## PVA-BASED FILM COATINGS

Opadry aqueous moisture barrier (AMB) and Opadry II 85 series are two proprietary families of PVA-based products that were commercialized in the mid-

**Table 1** Moisture and Oxygen Permeability of Pure Polymeric Films (Film Thickness = ~100 μm)

| Polymer | MVTR (25°C/80% RH) (grams $H_2O$/100 $in^2$/day) | $O_2$TR (25°C/60% RH) ($cm^3$ $O_2$/100 $in^2$/day) |
|---|---|---|
| NaCMC | 96 | 0.04 |
| HPMC | 30 | 10.0 |
| HPC | 15 | 11.0 |
| PVA | 10 | 0.04 |

*Abbreviations*: MVTR, moisture vapor transmission rate; NaCMC, sodium carboxymethylcellulose; HPMC, hypromellose; HPC, hydroxypropylcellulose; PVA, polyvinyl alcohol.

to-late 1990s. The Opadry AMB formulation was optimized to provide the lowest moisture vapor transmission rate (MVTR) possible while still affording all the conveniences of fully formulated film-coating systems. It is supplied as a color-matched system and can be readily dispersed into water at the 20% solids level. Owing to the inherent tackiness of the PVA polymer, the maximum achievable spray rates obtained with Opadry AMB are not as high as those of HPMC-based Opadry II film coatings. The Opadry II 85 series family of products was developed to address this. Opadry II 85 series products offer MVTR almost as low as Opadry AMB but can be applied at significantly higher spray rates.

## Formulating and Coating Moisture-Sensitive Products

Even though PVA-based films have inherently low MVTR does not guarantee that dosage forms coated with film coatings comprising PVA will be stable in moisture-rich environments. The ultimate stability of moisture-sensitive products is dependent on both formulation and processing variables including (*i*) core excipients, (*ii*) film-coating formulations, (*iii*) film-coating process parameters, and (*iv*) packaging materials. Core excipients possessing low water activity are preferred in the development of moisture-sensitive formulations, because they can preserve an active from hydrolytic degradation by tightly binding moisture in the core. One example of an excipient with low water activity is Starch 1500®, which has been shown to reduce the hydrolytic degradation rate of acetylsalicylic acid and ranitidine hydrochloride (2–4).

The preservation of dosage forms from the deleterious effects of water by coating with a PVA-based film coating also has been demonstrated. In one case, the hydrolytic degradation rate of acetylsalicylic acid was decreased (5). In another, the stability of a powdered Echinacea extract, which normally liquefies within a few hours at ambient conditions, was dramatically extended to 18 months by layering the Echinacea powder onto nonpareil beads and then coating with an Opadry II 85 series formula (6).

The ultimate moisture content of coated tablets is also significantly influenced by coating process parameters. In recent work, coating process parameters were systematically studied through a carefully constructed design of experiments. Spray rate, air flow, and inlet temperature were found to significantly influence both moisture content and aesthetics of coated products (7). Most importantly, it was found that the moisture content of a dosage form could be maintained or even decreased during an aqueous film–coating process. Depending on the air flow and inlet temperatures utilized, the moisture content of the coated multivitamin varied between 0.6% and 2.7% versus the starting moisture content of 1.4% in the uncoated core. Therefore, it is possible to coat moisture-sensitive products using aqueous film–coating processes and avoid the use of potentially hazardous organic solvents, which historically have been selected in this type of application. In a separate study, the use of a predrying step was also found to significantly impact the final moisture content of coated tablets (8).

## NaCMC-BASED FILM COATINGS

Although NaCMC has been used in core formulations and as a secondary film former in film-coating formulations for several decades, its commercial use as a primary film former in film coatings did not begin until the early 2000s. Capitalizing on the inherent glossy nature of NaCMC-based films, the proprietary Opaglos® 2 family of products was developed to impart gloss to dosage forms using standard, aqueous film–coating equipment. Opaglos 2 is provided as either a clear formulation or color-matched to a wide spectrum of colors. The gloss levels achievable with Opaglos 2 are on par with those achieved using the more time-consuming and labor-intensive sugarcoating process and approximate those obtained using more expensive processes such as gel dipping and gel enrobing.

NaCMC is also the primary film former in the related, proprietary Opadry fx film-coating system. Opadry fx contains pearlescent pigments, and, optionally, standard dyes and lakes as colorants. Pharmaceutically approved pearlescent pigments are titanium dioxide platelets and mica platelets coated with titanium dioxide. Pearlescent pigments are optical filters that refract specific wavelengths of light to create color effects that vary depending upon the viewing angle. Although the nature of the colorants is different, both Opaglos 2 and Opadry fx are applied under similar process conditions. To account for the relatively viscous nature of NaCMC and achieve maximum gloss values, Opaglos 2 and Opadry fx film-coating dispersions are applied at the 7.5% solids level and at conservative spray rates.

## COATING OXYGEN LABILE DOSAGE FORMS

Although Opaglos 2 and Opadry fx are most often selected because of their ability to enhance the aesthetic characteristics of dosage forms, both film coatings also possess excellent oxygen barrier properties. These properties have been demon-

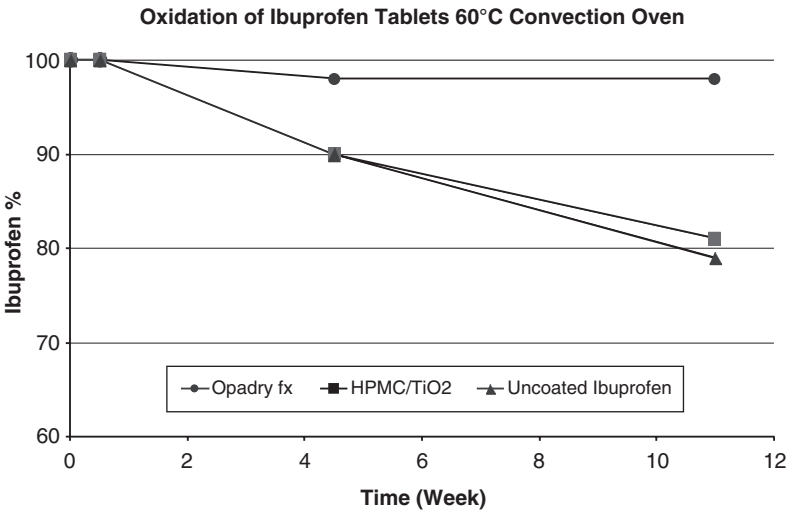


**Figure 1** Oxidation of ibuprofen tablets: ibuprofen tablets uncoated, coated with a standard Opadry film coating comprising hypromellose and titanium dioxide, or coated with Opadry® fx. Film coatings applied to 3% weight gain.

strated both in the measurement of oxygen transmission rates (9) and in the preservation of ibuprofen under conditions known to result in oxidation of the active (10). In the latter study, the ibuprofen assay of uncoated cores and cores coated with an HPMC-based Opadry coating (3% weight gain) was only about 80% after storage in a convection oven at 60°C for 11 weeks. In contrast, the ibuprofen assay of cores coated with Opadry fx (3% weight gain) was still about 99% under the same conditions (Fig. 1).

## CONCLUSIONS FOR IMMEDIATE-RELEASE FORMULATED FILM-COATING SYSTEMS

Film coatings based on PVA and NaCMC offer the formulator new functional benefits. It is now possible to coat moisture-sensitive cores, using aqueous coating processes, and preserve them through the use of PVA-based coatings. NaCMC-based coatings provide demonstrable oxygen barrier properties and also excellent aesthetic characteristics.

## FILM COATING FOR MODIFIED-RELEASE FORMULATIONS

The applications of aqueous modified release film-coating formulations depend on the type of polymers used, the majority of which are water insoluble (at low pH media for enteric polymers). Therefore, aqueous polymeric dispersions in the

form of a latex or pseudolatex are used for pharmaceutical functional film-coating systems.

## Formulated Aqueous Enteric Film-Coating Systems

Enteric coating systems are part of modified release film coatings, which are intended to remain intact (and thus prevent any drug from being released or any acidic media being absorbed) for different periods after ingestion, but ultimately to dissolve in order to permit the drug to be rapidly released thereafter. These formulations are also referred to as delayed release systems, where the delay in the onset of drug release, after ingestion, will depend on the type of the polymer used in the film coating and the transit of the dosage form through the gastro-intestinal tract. Although the United States Pharmacopoeia has set forward specific disintegration and dissolution testing for enteric coated tablets (USP 29-NF 24), it does not quantitatively measure the acid media that may have been absorbed into the tablet core (i.e., acid-uptake) while residing in the stomach. This is especially important to measure when an acid labile drug is in the core formulation, therefore a reproducible method to measure percent (%) acid taken up (absorbed) by an enteric coated tablet is described.

### Method for Acid-Uptake Measurement

Accurately weigh 6 to 50 tablets ($W_0$) and expose to the acid media (0.1N HCl or pH 4.5 acetate buffer) for two hours at 37°C in a disintegration apparatus. The tablets should remain intact if enteric coating is successful. Then remove the tablets, pat dry to remove surface moisture and reweigh ($W_t$). From the differences in weights before and after exposure to acid media, the percent acid uptake may be calculated as shown in Equation 1:

$$\% \text{ acid uptake} = \frac{W_t - W_0}{W_0} \times 100 \cdot \quad (1)$$

The lower the % acid uptake, the more effective the enteric coating will be in protection of the drug in the core. However, values of up to 10% acid uptake have been shown to be acceptable for protecting highly acid labile drugs such as proton pump inhibitors (PPIs) (11).

The highly functional nature of enteric coatings dictates that some film characteristics are extremely important, including possession of:

- good mechanical properties that guarantee reproducibility and ruggedness (toughness) in performance,
- permeability characteristics of the film to ensure that the quantities of drug released through intact films are low and meet compendial requirements, and
- good polymer chemical stability (a characteristic that also helps to ensure that predictable product performance is achieved). Therefore, performance of the product does not change with time of storage.

## COMMERCIALLY AVAILABLE AQUEOUS ENTERIC SYSTEMS

There are two formulated enteric systems available from Colorcon Inc. for aqueous enteric coatings of oral solid dosage forms: tablets, granules, pellets, and capsules. Enteric coating of capsules is more challenging due to potential migration of plasticizer leading to a brittle film; however, there are examples where capsules have been successfully enteric coated (12). One system uses polyvinylacetate phthalate, PVAP (Phthalavin®), as the enteric polymer and is called Sureteric and another uses methacrylic acid copolymer type C (Eudragit® L 100-55) called Acryl-EZE®. Details of Sureteric coating systems have been discussed previously in the last edition of this book (1). Here in this chapter the dispersion characteristics and applications of Acryl-EZE systems will be discussed.

### Acryl-EZE Formulated Aqueous Enteric Systems

Acryl-EZE is a family of products developed and patented by Colorcon Inc. (U.S. patent number 6,420,473 B1). These systems are all available in dry powder form, ready for dispersion in water, and are formulated using the enteric polymer methacrylic acid copolymer type C (Eudragit L 100-55). Formulations may contain a plasticizer, neutralizing agent, flow aid, surfactant (wetting agent), detackifier, and pigment blends. The presence and level of each ingredient depend on the formulation, which is prepared on a case by case basis to meet the requirements of specific application. These requirements may vary from color matching to pH trigger point that is the pH of the media at which the film starts to dissolve rendering the dosage form for disintegration, deaggregation, and finally dissolution of the medicament.

Acryl-EZE powder is reconstituted to 20% w/w solids dispersion and applied on tablets at a weight gain range of 7% to 10% for enteric performance, depending on the tablet size (surface area) and mechanical and other surface properties.

The recommended storage conditions for the Acryl-EZE family of products are below 30°C/65% relative humidity, which provide a 12-24 month retest interval from the date of manufacturing.

#### Preparation of Typical Acryl-EZE Dispersions

- Determine the amount and weigh the Acryl-EZE powder and water required to make a dispersion with 20% w/w solids, based on the quantity of tablets to be coated and the target coating weight.
- Stir the water to form a vortex using a propeller stirrer and add the Acryl-EZE powder to the center of the liquid vortex in a slow steady stream, avoiding clumping and maintaining a vortex.
- Continue stirring for 20 min and then pass the dispersion through a 250 micron sieve to remove any undispersed powder agglomerates or large particles prior to the coating process. This will prevent potential spray nozzle blockage during the coating process.

- Start the coating process and continue stirring the dispersion while the coating is ongoing, to prevent settlement of suspended material.

Note: If a high shear mixer is used to prepare the dispersion, only 10 min of stirring is required and an antifoam emulsion, such as 30% emulsion of simethicone (at 0.5% w/w of the Acryl-EZE solids) should be added to water prior to the preparation.

### Coating Process Recommendations

In order to maximize coating efficiency and prevent spray drying, a product bed temperature range of 30 to 32°C is recommended, keeping the atomization pressure low (typically 1.5–2.0 bar). Examples of typical coating process parameters and enteric performance of Acryl-EZE applications are shown in the case studies below.

### Case Study 1: Enteric Coating of 81 mg Aspirin Tablets Using Acryl-EZE

In this case study, tablet formulation, coating processes, and enteric performance of 81 mg aspirin tablets are demonstrated. The tablet formulation comprising 81 mg aspirin, partially pregelatinized corn starch (Starch 1500®), microcrystalline cellulose (Emcocel® 50M), and stearic acid were prepared (170 mg tablet weight and 7.0 mm diameter, standard convex). The tablets were then enteric coated with pigmented Acryl-EZE 93O 92052 (20% coating dispersion), taking samples at 5, 6, 7, 8, 9, and 10% theoretical weight gains. The tablet coating (pan load of 130 kg) was carried out in a 48-inch side-vented pan (Accelacota-150, Manesty) equipped with four spray guns with individual peristaltic pumps. The coating process parameters used during the enteric coating are shown in Table 2. The total coating process time was 3.65 hr.

The tablets were tested for acid uptake and enteric performance (*European Pharmacopoeia* third edition 2001) after manufacture and three months storage at 40°C/75% RH (85 cc foil sealable HDPE bottles). Table 3 shows that the acid uptake for 81 mg aspirin enteric coated tablets was less than 5% when the tablets had 6% or more coating weight gains. There was no drug release in 0.1N HCl acid

**Table 2** Coating Process Conditions for Enteric Coating of 81 mg Aspirin Tablets with Acryl-EZE

| Process parameter | Values |
|---|---|
| Average inlet temperature (°C) | 52.70 |
| Average exhaust temperature (°C) | 36.24 |
| Average tablet bed temperature (°C) | 30.00 |
| Average spray rate (g/min) | 343.00 |
| Atomizing air pressure (bar) | 3.0 |
| Fan air pressure (bar) | 2.5 |
| Pan speed (rpm) | 7 |
| Airflow ($m^3$/hr) | 2600 |

**Table 3** Enteric Performance of 81 mg Aspirin Tablets Coated with Acryl-EZE

| Theoretical weight gain (%) | Acid uptake (%) | Released in 0.1N HCl after 2 hr (%) | $T_{80\%}$ in phosphate buffer (pH = 6.8) |
|---|---|---|---|
| 6 | 4.05 | 0.0 | <30 min |
| 7 | 2.76 | 0.0 | <30 min |
| 8 | 2.37 | 0.0 | <30 min |
| 9 | 2.56 | 0.0 | <30 min |
| 10 | 2.34 | 0.0 | <30 min |

phase for two hours and successful drug release in pH 6.8 phosphate buffer phase, meeting the USP 24 requirements for delayed release aspirin tablets (Table 3).

Dissolution and free salicylic acid content testing on the coated tablet after three months of storage at 40°C/75% RH indicated excellent stability results and passed the USP delayed release requirements (13).

## Enteric Coating of PPIs

PPIs are used in the treatment of acid-related gastro-duodenal disorders by reducing gastric acid secretion. Proton Pump Inhibitors (PPIs) are substituted benzimidazoles and both share a similar core structure and mode of action, but differ in substituent groups (14,15). The type of substituents affects the chemical properties of the compounds that directly influence their rates of reactions and therefore their stability in different media (16). The stability of PPIs in aqueous media is a function of pH with an increased rate of degradation as the pH decreases. Consequently, most oral dosage forms of PPIs are formulated as enteric coated granules, tablets, and multiparticulates. Table 4 shows the current PPIs available in tablet and capsule forms in United States.

Multiple dose treatment of patients with PPIs results in a decrease in their gastric acid secretion with a subsequent elevation in gastric pH (17,18). Due to the rise in gastric pH, the enteric coated dosage form when administered will be subjected to a higher pH environment than is typically found in a healthy, fasted stomach (simulated in-vitro utilizing 0.1N HCl, USP). Therefore, in the following two case studies, different acid phases, 0.1N HCl (pH 1.2) and/or pH 4.5 acetate buffer (USP), have been investigated for acid uptake, enteric protection testing, and subsequent drug release to better simulate the gastric environment of patients who are administered multiple doses of this class of medicament.

### Case Study 2: Enteric Coating of 20 mg Rabeprazole Sodium Tablets with Acryl-EZE

Tablets of 20 mg rabeprazole sodium (Na) were prepared (total weight 146 mg, 6.3 mm diameter) by an organic wet granulation method and seal coated with alcoholic ethylcellulose/magnesium oxide 1:1 %w/w (theoretical weight gain of

**Table 4** Delayed Release Solid Oral Dosage Forms of PPIs Available on the U.S. Market

| PPI | Proprietary name (U.S.) | Solid dosage form | Strength (mg) |
|---|---|---|---|
| Omeprazole | Prilosec | Capsule | 10, 20, 40 |
| Lansoprazole | Prevacid | Capsule, MUPS tablet | 15, 30 |
| Rabeprazole sodium | Aciphex | Tablet | 20 |
| Pantoprazole sodium | Protonix | Tablet | 20, 40 |
| Esomeprazole magnesium | Nexium | Capsule | 20, 40 |

*Abbreviation*: PPI, proton pump inhibitor.

1.37% or 1.5 mg/cm$^2$) as described by Saeki et al. (19). The enteric coating was applied using Acryl-EZE 93F19255 at various weight gains of 8.1, 10.1, 12.1, and 14.1% in a partially perforated coating pan (LDCS5, Vector Corporation). Table 5 shows the coating process parameters used in this case study.

The percent acid uptakes for the enteric coated rabeprazole sodium tablets were 4.3% in 0.1N HCl and 5.4% in an intermediate pH 4.5 acetate buffer. Visual inspection of the tablets after two hours in each media indicated no signs of rabeprazole sodium degradation. Any degradation of rabeprazole leads to a yellow or purple discoloration of the tablet, film layer, or dissolution medium.

Drug release profiles of Acryl-EZE coated rabeprazole Na tablets are shown in Figures 2 and 3 with less than 10% drug release in 0.1N HCl acid or pH 4.5 acetate buffer and more than 80% dissolved after 45 min in pH 7.8 phosphate buffer. Visual observation showed no signs of degradation in the dissolution vessel

**Table 5** Coating Process Parameters Used for Enteric Coating of Rabeprazole Tablets with Acryl-EZE

| Parameter | Values |
|---|---|
| Pan volume (L) | 1.3 |
| Pan charge (kg) | 1 |
| Inlet temperature (°C) | 63 |
| Outlet temperature (°C) | 35 |
| Fluid delivery rate (g/min) | 12 |
| Process air flow (CFM/CMH) | 40/68 |
| Pan rotational speed (rpm) | 25 |
| Atomization air pressure (psi/bar) | 18.5/1.3 |

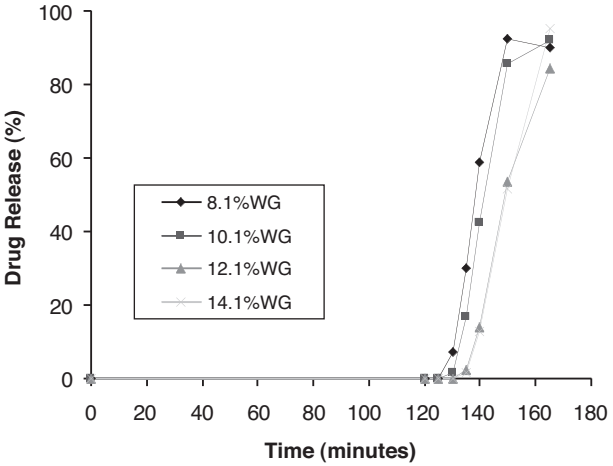


**Figure 2** Drug release profiles of rabeprazole sodium tablets in 0.1N HCl acid, followed by phosphate buffer, pH 7.8.

and HPLC chromatograms did not indicate any degradant peaks for the assayed tablets (20). Figures 2 and 3 also show that the release profiles of enteric coated rabeprazole Na tablets could be modulated by varying the Acryl-EZE coating weight gain.

### Case Study 3: Enteric Coating of Lansoprazole Pellets

Lansoprazole delayed release multiparticulates have been shown to have better absorption properties compared with an enteric tablet (21). As a result, enteric coated multiple unit formulations of lansoprazole have been developed. It has been

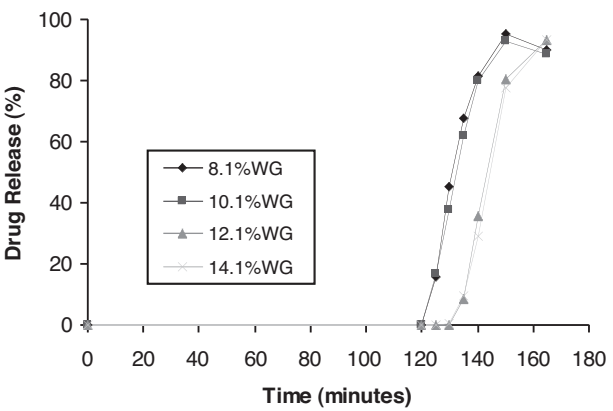


**Figure 3** Drug release profiles of rabeprazole sodium tablets in acetate buffer, pH 4.5, followed by phosphate buffer, pH 7.8.

reported that application of binder solutions to prepare drug layered lansoprazole pellets or extrusion-spheronization of lansoprazole formulation causes degradation of the drug (22). In contrast, dry powder layering has been shown to provide a stable manufacturing method for acid labile drugs such as lansoprazole (23).

In this study, delayed release multiparticulates were prepared by dry powder layering of lansoprazole on to nonpareil (840–1000μm) pellets, as described by Makino et al, 1991 (24), using a centrifugal fluid-bed granulator (Glatt, GPCG-1). The parameters used for the powder layering application are listed in Table 6. The drug layered pellets were screened (16 mesh, 1190 μm) prior to enteric coating in an Aeromatic Strea-1 fluid-bed coating machine with Acryl-EZE 93F19255 to 26% theoretical weight gain. The coating processing parameters are listed in Table 7. The pellets were manually filled in size 1 gelatin capsules (Capsugel, Morris Plains, NJ) (15 mg/255 mg pellets) for further analysis.

Dissolution testing was performed in a USP apparatus II (VanKel VK7000) at 75 rpm, 37.0 ± 0.5°C. The delayed-release dissolution testing ($n = 6$) was performed in 500 ml of acid phase followed by phosphate buffer USP (pH 6.8) as described in USP (25). Similar to rabeprazole sodium tablets, enteric coated lansoprazole pellets were also tested in two different acid media, 0.1N HCl (pH 1.2) and pH 4.5 acetate buffer (USP).

Figure 4 shows that lansoprazole pellets coated with Acryl-EZE 93F19255 (26% theoretical weight gain) exhibited enteric protection in both acid phases, followed by rapid drug release in the buffer phase. The results showed no drug release in the acid phase (0.1N HCl or pH 4.5) after one hour, followed by 80% release within 20 min in pH 6.8.

## Scale-Up of Coating Processes

Successful acid resistance of enteric coated solid dosage forms requires careful selection of coating processes on small laboratory and large-scale coating facilities. A major challenge and time-consuming process for new product-development

**Table 6** Dry Powder Layering Parameters Used to Layer Lansoprazole on Pellets

| Parameters | Value |
|---|---|
| Batch size (g), 840–1000 μm nonpareils | 2250 |
| Rotor speed (rpm) | 200 |
| Binder spray rate (g/min) | 20 |
| Powder addition rate (g/min) | 15 |
| Inlet air temperature (°C) | 55 |
| Outlet air temperature (°C) | 45 |
| Bed temperature (°C) | 45 |
| Atomization air pressure (bar) | 1.5 |
| Air flap (%) | 20 |
| Air flow ($m^3$/hr) | 68–80 |
| Total processing time (min) | 113 |

**Table 7** Fluid-Bed Coating Parameters Used for Enteric Coating of Lansoprazole Pellets with Acryl-EZE

| Parameters | Value |
|---|---|
| Batch size (g), 1190 μm drug layered pellets | 500 |
| Coating spray rate (g/min) | 4.5 |
| Inlet air temperature (°C) | 44 |
| Outlet air temperature (°C) | 33 |
| Bed temperature (°C) | 32 |
| Atomization air pressure (bar) | 1.2 |
| Total processing time (min) | 144 |

relates to successful transfer of technology from the laboratory scale to the production scale. A successful technology transfer will depend on (*i*) a robust product (for the core to be coated and the coating formulation to be applied) and (*ii*) identification of critical processing parameters and tolerance ranges for those parameters. Table 8 shows the process parameters established for the applications of Acryl-EZE for typical coating machines from small to large scale (26).

### Other Factors to Consider When Enteric Coating with Acryl-EZE

**Seal-coat:** Most robust core formulations with high mechanical strength do not require a seal-coat (also called sub-coat). However, core formulations

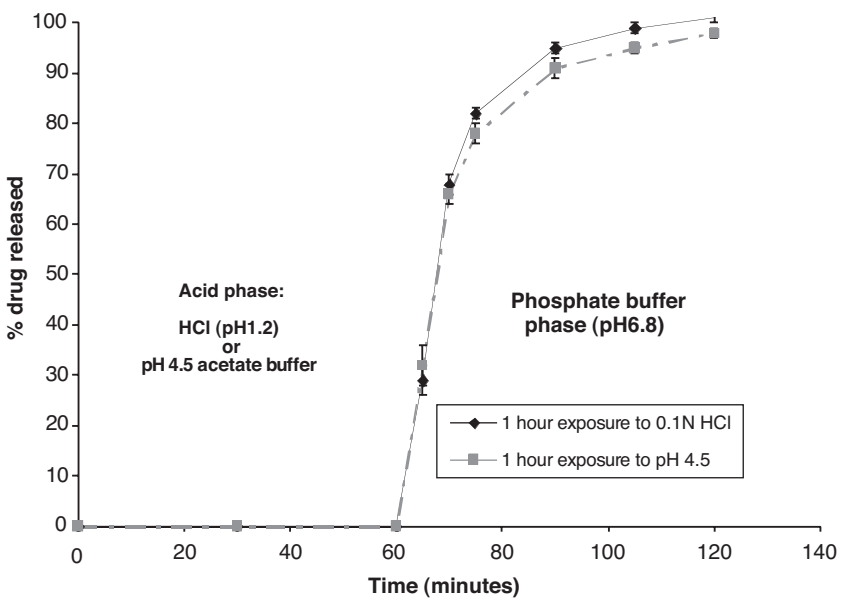


**Figure 4** Drug release profiles of lansoprazole pellets (in gelatin capsules) in 0.1N HCl acid or acetate buffer (pH 4.5) for one hour followed by phosphate buffer (pH 6.8).

**Table 8** Coating Process Parameters Used for Medium to Large Scale Acryl-EZE Enteric Coating of Tablets in Different Coating Machines

| Coating Parameter | O'Hara 48" Pan | Accela 150 | Accela-60 DXL | GS-300 | Glatt GC-1000 | HCT 130-XL | Bamtri BGB-150E |
|---|---|---|---|---|---|---|---|
| Solids content (%w/w) | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Theoretical weight gain (%) | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Tablet charge (kg)[a] | 140 | 120 | 360 | 180 | 75 | 245 | 140 |
| Inlet air temperature (°C) | 53 | 53 | 54 | 60 | 65 | 70 | 55 |
| Drying air volume ($m^3$/hr)[b] | 2600 | 2600 | 6800 | 1800 | 1500 | 2040 | N/A |
| Tablet bed temperature (°C) | 29–32 | 29–35 | 29–36 | 35–37 | 32 | 34 | 34 |
| Exhaust air temperature (°C) | 34–38 | 36–38 | 37–40 | 32–37 | 40 | 32 | 37 |
| Pre-warm tablet bed (°C) | 34–36 | 34–36 | 34–36 | 38 | 38 | N/A | N/A |
| Spray equipment | 4 X SSVAU | 4 x Manesty | 5 X JAU | 3 X Graco | 3 x ABC | 8 x Freund | 3 x Bamtri |
| Fluid nozzle (mm) | 1.5 | 1.2 | 1.5 | 1.4 | 1.2 | 1.2 | 1.2 |
| Air cap (mm) | 3.3 | 4 | 3.4 | #4 | N/A | 3.0 | N/A |
| Atomizing air pressure (bar)[c] | 2.8 | 3.0 | 5.1 | 2.5 | 3.5 | 145 (slpm) | 2.1 |
| Pattern air pressure (bar)[c] | 2.1 | 2.5 | N/A | N/A | 3.5 turns | 60 (slpm) | N/A |
| Gun-to-bed distance (cm) | 21–23 | 23–24 | 25–30 | 25 | 20 | 20 | 17 |
| Spray rate (g/min) | 350 | 340 | 500–600 | 230–330 | 120–180 | 600 | 250 |
| Baffles | 4 | 4 | 4 | 6 | N/A | N/A | 2 |
| Pan speed (rpm) | 6-8 | 7 | 3.5–4.5 | 10–11 | 13 | 6 | 6.5 |

[a]Maximize pan charge
[b]Air volume may be decreased to prevent edge chipping
[c]Adjust to maximize efficiency

containing acid-sensitive drugs, such as PPIs, may require a seal-coat to prevent degradation of the drug by the acid polymer in the enteric film coat.

The seal-coat should provide mechanical strength, be inert and not interfere with the drug or the enteric polymer. For example, it has been reported (27) that polyethylene glycol, used as a plasticizer in the seal-coat, may interact with the aspirin in an enteric coated tablet and on storage lead to dissolution failure. However, when an Opadry sub-coat formulated with triacetin was used, no such interaction was observed. Acryl-EZE and Opadry systems are compatible with no issues for transferring the liquid feed line from sub-coat to Acryl-EZE dispersion during the coating process. For general applications of a seal-coat, Opadry YS-1-7027 and O3K 19229, at 2% to 3% weight gain, are recommended.

**Use of pumps:** Acryl-EZE aqueous-enteric coatings can be applied successfully using various types of coating equipment; however, use of gear pumps should be avoided. A major limitation of gear pumps in the application of aqueous polymeric dispersions (including latexes and pseudolatexes) is the sensitivity of the dispersion to the shear generated inside the gear pumps. This may result in agglomeration (or coagulation) of the polymer system, due to significant wear of the pump mechanism, which in turn will lead to the dispersed material (polymer and pigments) penetrating between the gear surfaces and the pump housing, causing the pump to seize up.

**Tablet shape:** Tablet shape may have a significant effect on the performance of applied functional films including enteric coatings. Shallower shapes are more prone to edge attrition and may result in a nonuniform film coverage on the edges of the tablet. If the core characteristics are such that a large weight gain of enteric coating is necessary, 1% to 2% sub-coat can be used to strengthen and smooth the core edges. In addition to enhancing enteric protection, the sub-coat may allow for a much reduced level of enteric coating. This can result in enhanced product performance, as well as time and cost savings (28).

## EXTENDED-RELEASE AQUEOUS FILM–COATING SYSTEM: SURELEASE

Organic solvent–based coating of ethylcellulose has been employed in the formulation of extended release oral solid dosage form. However, the use of aqueous coating systems is preferred whenever possible due to environmental concerns and operator safety. The film-forming processes of organic and aqueous coatings of ethylcellulose are different, with the latter being a result of coalescence of the ethylcellulose particles in the dispersion when sprayed on the surface of the substrate (29).

Surelease is a family of fully formulated, aqueous dispersion products, manufactured by Colorcon (30), designed specifically for modified drug release such as extended release, programmable release, and taste masking applications. Using ethylcellulose, a water insoluble polymer, as the rate controlling excipient in Surelease, there are major technological benefits along with the reproducible

release profiles that are achieved. The compositions of various types of Surelease are summarized in Table 9.

## Applications of Surelease

### Dispersion Preparation

Surelease is supplied as a 25% (w/w) solids dispersion, which is recommended to be diluted with water to 15% (w/w) solids before use. Before dilution, the container of Surelease is required to be agitated to ensure homogenization of solids in the dispersion. Then the dispersion is diluted by adding two parts of purified water to three parts of Surelease and stirred with a low shear mixer for approximately 15 min. It is advisable to continue gentle agitation throughout the coating process to prevent potential sedimentation of solid particles.

### Coating Process Recommendations

In order to maximize coalescence and prevent spray drying, a product bed temperature range of 40 to 42°C is recommended, keeping the atomization pressure around 1.5 to 2 bars. Some typical process conditions established with Glatt fluid-bed coating machines are shown in Table 10.

### Extended Release Coating of Multiparticulates

Surelease is applied onto drug layered nonpareils, extruded spheres, granules, drug crystals, and mini-tablets preferably using fluid-bed coating technology. Top spray coating may be used for small particulates such as drug crystals; however, a Würster process (bottom spray) is generally recommended.

Drug release from Surelease coated multiparticulates is mainly controlled by the coating film thickness (theoretical weight gain) as shown in Figure 5 for chlorpheniramine maleate layered on nonpareil beads.

**Table 9** Composition of Surelease Product Range (Surelease®-E-7-x)

| Ingredient | Function | x-19020 | x-19030 | x-19040 | x-19050 |
|---|---|---|---|---|---|
| Ethylcellulose | Polymer | ✓ | ✓ | ✓ | ✓ |
| Fractionated coconut oil | Plasticizer | | | ✓ | |
| Dibutyl sebacate | Plasticizer | ✓ | ✓ | | |
| Ammonium hydroxide (28%) | Stabilizer | ✓ | ✓ | ✓ | ✓ |
| Oleic acid | Stabilizer/ plasticizer | ✓ | ✓ | ✓ | ✓ |
| Purified water | Vehicle | ✓ | ✓ | ✓ | ✓ |
| Colloidal $SiO_2$ | Flow aid | | ✓ | | |
| Hypromellose | Stabilizer | | | | ✓ |

**Table 10** Typical Process Parameters Used for Application of Surelease® to Drug-Layered Pellets for Bottom Spray Würster Systems

| | Coating process conditions | | |
|---|---|---|---|
| Process parameter | Glatt GPCG-3 | Glatt GPCG-60 | Glatt GPCG-200 |
| Batch size (kg) | 3 | 70 | 200 |
| Spray gun | Schlick 970 | Schlick HS | Schlick 940 |
| Fluidizing air volume ($m^3$/hr) | 83–107 | 800–900 | N/A |
| Inlet air temperature (°C) | 64–67 | 60–66 | 72–75 |
| Exhaust air temperature (°C) | 40–45 | 39–41 | 47–51 |
| Product bed temperature (°C) | 41–47 | 40–46 | 43–46 |
| Atomizing air pressure (bar) | 1.5 | 2.0 | 2.0 |
| Spray rate (g/min) | 25–28 | 210–306 | 500–650 |

In addition, the aqueous solubility of the drug has a major influence on the drug release rate as shown in Figure 6, where four drugs with different water solubilities have been layered on nonpareil pellets and then coated with Surelease E-7-19040 (16% theoretical weight gain). A highly water soluble drug such as guaifenesin is released faster than less soluble drugs with no lag-time. However, amlodipine, a poorly soluble drug, is released very slowly and with a considerable lag-time (Fig. 6).

In the case of poorly water soluble drugs, a low theoretical weight gain (thin film) of Surelease may be sufficient to achieve the desired release profile. However, low weight gain on multiparticulate systems (very large surface area) may lead to batch to batch inconsistency. Altering the permeability of the Surelease film by incorporating a hydrophilic additive will enable the user to apply higher

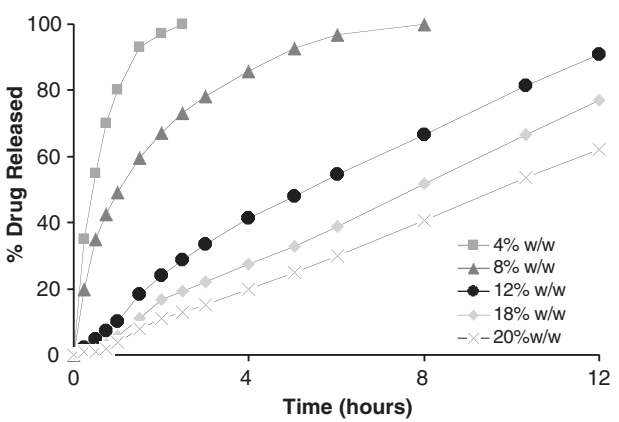


**Figure 5** Effect of theoretical coating weight gain of Surelease E-7-19040 on chlorpheniramine maleate released profiles.

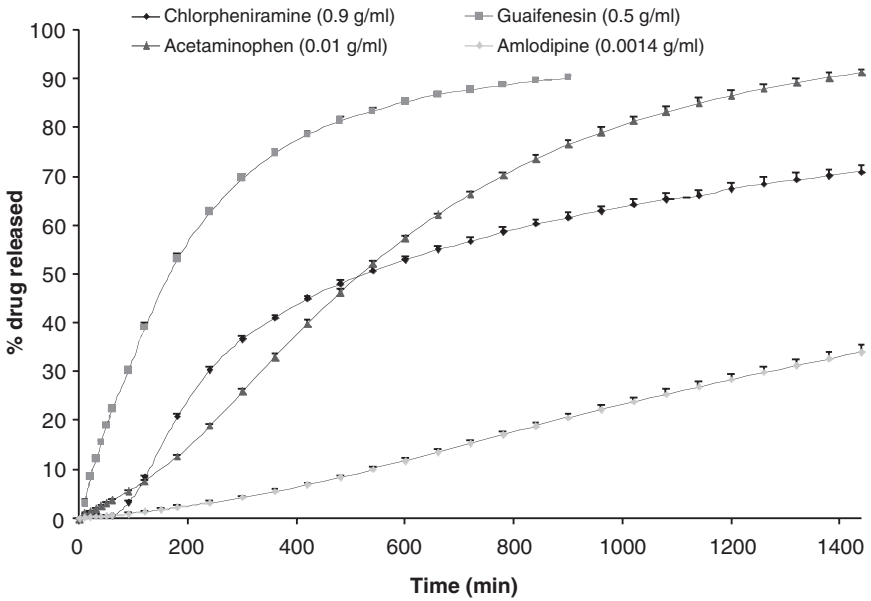


**Figure 6** Effect of aqueous solubility on drug release rate from beads coated with 16% w/w Surelease®.

theoretical weight gain, reduce lag-time, and ensure consistent faster release profiles for drugs with low aqueous solubilities (31). Figure 7 shows the inclusion of hypromellose (Methocel E5) in Surelease E-7-19040, as a permeability enhancer (11% theoretical weight gain) and its effect on drug release profiles.

### Extended Release Coating of Tablets

Hydrophilic matrix tablets formulated with highly soluble drugs are often characterized by an initial rapid burst release of drug, prior to adequate gel layer formation. Surelease has been utilized to film coat matrix tablets to inhibit the burst release, as well as a method for modulating drug release rate (32).

### Matrix Granulation

Undiluted Surelease may be used as a binder in high shear, low shear, or fluid-bed granulation. The granules are then compressed into tablets in order to generate an extended drug release profile.

### Film Curing

The majority of extended release (ER) barrier membrane coating systems require thermal postcoating treatment ("curing") in order to achieve reproducible and storage-stable drug release characteristics. For example, FMC literature recom-

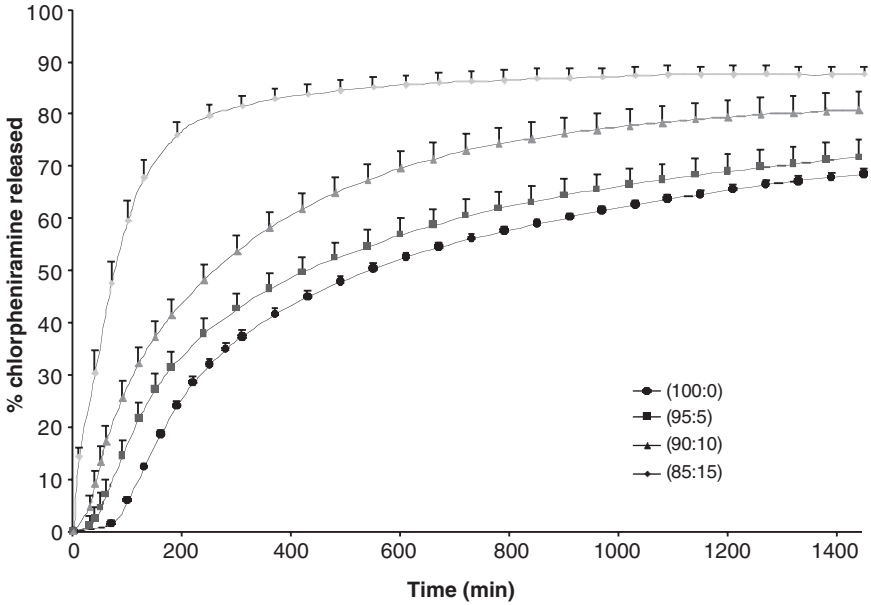


**Figure 7** The influence of a permeability enhancer on chlorpheniramine maleate release from pellets coated with different Surelease E-7-19040: Methocel E5 ratios (theoretical weight gain 11%).

mends that multiparticulates coated with Aquacoat ECD are incubated in a tray dryer at 60°C for two hours postcoating, to promote complete coalescence of polymer particles in the film.

Surelease family of products is fully formulated, optimally plasticized systems and as a consequence of plasticization of the polymer during manufacture, generally Surelease films do not require a curing step. However, it is advisable to test for the occurrence of incomplete polymer coalescence during coating by placing the Surelease-coated products at 50 to 60°C for 2, 12, and 24 hr, and comparing the release profiles from these units with "uncured" beads. A curing effect may be noted if the elevated temperature incubation results in a decrease in the rate of drug release. The need for a curing step may be eliminated through optimization of the coating process.

## SUMMARY OF AQUEOUS FILM COATING FOR MODIFIED RELEASE FORMULATIONS

In this section of the chapter, examples of applications of Acryl-EZE and the Surelease family of products to achieve enteric (delayed) and extended release profiles, respectively, are provided. Typical process conditions and performance of the products were highlighted as guidelines for formulators and production personnel.

The successful application of these products will require careful consideration of drug properties, condition of the equipment utilized, and in depth understanding of the technology selected. Both Acryl-EZE and Surelease provide various product options for delayed and extended release formulation as well as ease of application, to help the formulators develop their products in a timely manner and ensure consistent production performance when in the market.

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# 12

# Particle Design Based on Aqueous Coating for Controlled Drug Release

**Hirofumi Takeuchi and Yohei Hoashi**
*Gifu Pharmaceutical University, Gifu, Japan*

**Yoshiaki Kawashima**
*Department of Pharmacy, Aichi-Gakuin University, Nagoya, Japan*

## INTRODUCTION

Controlled-release matrix tablets have become the simplest and least expensive method to control drug release. During the past two decades, many polymers, waxes, gums, and clays have been reported in the literature as retardant materials in this system (1–7). The retardant materials have been introduced into the formulation, using direct compression, wet granulation, and recompression techniques. The majority of controlled delivery systems for the oral route release the active agent into the gastrointestinal juices by dissolution, diffusion, or a combination of both mechanisms. The selection of both drug and retardant polymers along with the other filler excipients will impact the mechanism and rates of drug release from monolithic systems.

Cellulose derivatives and acrylic resin polymers comprise the group of polymers that are presently available as aqueous coatings for pharmaceutical dosage forms. These polymers in the dry state have been utilized in matrix-type tablet formulations by directly compressing the powdered mixtures of polymers with drugs (5–9). Small microparticulates have also been coated with polymer solutions and dispersions and then compressed into matrix tablets. This method imparts more precise and predictable control on drug release from the resultant tablet, since the particles are coated with films of known permeability, thickness,

and solubility. This process has been used to mask undesirable tastes of drugs, improve drug stability, and also to physically separate components that are incompatible in the solid state.

In looking at the recent development in tablet design, rapidly disintegrating tablets (RDTs) in the mouth have received much attention as a patient-friendly dosage form. These tablets can be taken with a small amount of water or without water, which leads to better compliance especially for children or elderly patients who have difficulty swallowing conventional tablets or capsules. In designing RDTs, it is important to prepare coated drug particles suitable for taste masking.

In this chapter, several technologies relating to aqueous polymeric coating are presented. Following an overview of materials and equipment used for aqueous coating, the preparation of polymeric nanosphere dispersions and the characterization of the films are discussed as well as the properties of novel aqueous-coating systems prepared by a fluidized bed coater. The preparation of drug-containing microparticles with polymers by spray drying and coating of drug particles for RDTs are also discussed.

## MATERIALS AND EQUIPMENT FOR AQUEOUS-BASED COATED GRANULES

Polymers for aqueous film coating may be grouped into cellulose ether derivatives and acrylic resins. Commercially available cellulose ethers include hypromellose 2910, 2208 (TC-5, SB-4, Shin-Etsu Chemical Corp., Tokyo, Japan), methyl cellulose (Metolose® SM-4, Shin-Etsu Chemical Corp., Tokyo, Japan), hydroxypropyl methylcellulose acetate succinate (AQOAT® AS, Shin-Etsu Chemical Corp., Tokyo, Japan), ethylcellulose (EC) (Aquacoat® ECD, FMC Corp., Philadelphia, PA; Surelease®, Colorcon, Inc., West Point, PA), and cellulose acetate phthalate (CAP) (Aquacoat CPD. FMC Corp., Philadelphia, PA). Hypromellose is used as an aqueous solution. Methyl cellulose is a water soluble polymer for the preparation of granules. Hydroxypropyl methylcellulose acetate succinate is used as an aqueous dispersed enteric film-forming polymer. Aquacoat ECD is a 30% w/w aqueous dispersion of EC with sodium lauryl sulfate and cetyl alcohol as stabilizers. Surelease is a 25% w/w aqueous dispersion of EC as the rate controlling polymer plasticized with ammonium oleate and dibutyl sebacate. Aquacoat CPD is a 30% w/w aqueous dispersion containing CAP for enteric coating.

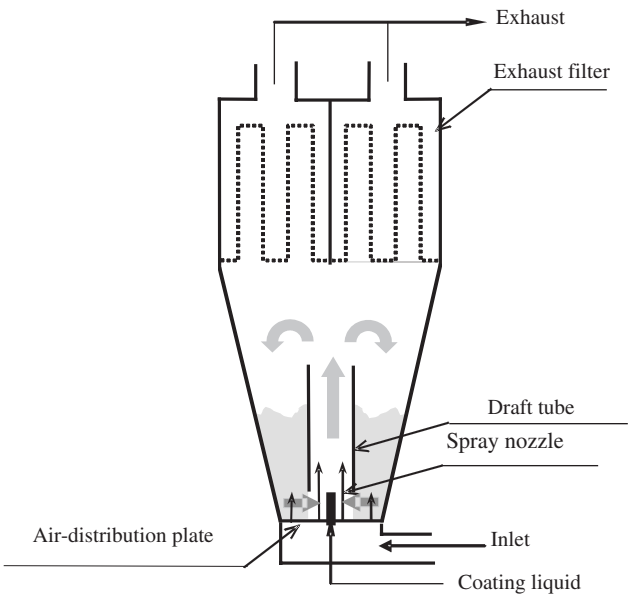
The acrylic resin derivatives are available as 30% w/w poly(metha) acrylate latices (Eudragit® RL 30 D, RS 30 D, NE 30 D, NE 40 D, L 30 D-55, and FS 30 D, Röhm Pharma, Darmstadt, Germany). The ammonium groups in Eudragit RL 30 D and Eudragit RS 30 D are present as salts and make the polymers permeable. Eudragit RL 30 D forms a readily permeable film, whereas Eudragit RS 30 D films are sparingly permeable. By varying the composition of a polymer blend of Eudragit RS 30 D and RL 30 D, the permeability of a combination film can be controlled. In addition, the permeability of Eudragit RL/RS films is independent of the pH. Eudragit NE 30 D is quite permeable and is generally used in conventional dosage forms. Eudragit NE 40 D is aqueous dispersion identical to

Eudragit NE 30 D with 40% solid particles. Eudragit L 30 D-55 and Eudragit FS 30 D are anionic copolymers soluble in intestinal fluid from pH 5.5.

Other valuable aqueous-coating agents commercially available from BASF include the Kollicoat® family of products: IR, Protect, SR 30D, MAE 30DP, and MAE 100P (BASF, Ludwigshafen, Germany). Kollicoat IR is polyvinylalcohol-polyethylene glycol graft-copolymer with excellent film-forming properties for an instant release coating. Kollicoat Protect is a solid solution of Kollicoat IR and polyvinyl alcohol (PVA) for moisture protection and taste masking effects. Kollicoat SR 30D is a 30% aqueous dispersion of polyvinylacetate stabilized with povidone and sodium lauryl sulfate for sustained release coating and taste masking. Kollicoat MAE 30DP and MAE 100P are two different grades of a methacrylic acid/ethyl acrylate copolymer (1:1) supplied as 30% aqueous dispersion and as a powder, respectively, for enteric coatings. Studies comparing Kollicoat MAE 30D with commercial cellulose derivatives for enteric coating were published by Scheiffele et al. (10).

For the preparation of discrete solid particles coated with aqueous-based polymers, the conventional coating pan, fluidized bed, or spray-drying equipment has been used. For aqueous film coating, the drying efficiency of the equipment is important to control, in order to avoid erosion of the core, agglomeration of particles, penetration of moisture into the core, and decomposition of moisture-sensitive active ingredients. The coating pan does not appear to produce an optimal aqueous film coating, although the modified coating pan (e.g., perforated coating pan) has been reported to improve the drying efficiency (11). The fluidized bed process is a popular technique for the coating of fine or intermediate-size particles. The fluidized bed process varies with the spraying system, i.e., top-spray, bottom-spray, and tangential-spray. These processes have been discussed in detail in Chapter 3. In the top-spray process, the coating solution is sprayed downward onto the particles fluidized by the air from below. The Wurster coater utilizes the bottom-spray system, in which the coating is applied from the bottom at the same time and in the same direction as the flow of the particles through a chamber. With the tangential-spray method, the coating solution is sprayed tangentially in the same direction, as the particles rotate homogeneously in a spiral motion. Rapid evaporation of the solvent is a characteristic of a fluidized bed system, which helps avoid the penetration of the solvent into the core. Mehta and Jones (11) suggested that the Wurster coater provides ideal conditions for the complete coalescence of the polymer particles, with little or no penetration of water into the core. In a later study, Mehta et al. (12) found no significant differences in the drug release behavior of aspirin granules enterically coated with Eudragit L 30 D, using the three spray systems. The demand to coat fine particles having a diameter even smaller than 100 μm has increased, as new microparticulate delivery systems are developed, although fluidization of such fine particles is extremely difficult due to their aggregating tendency. A new compounded type of fluidized bed system installed with a bottom tapered draft tube and a screen impeller to deaggregate agglomerates was recently developed to coat such discrete fine particles, as shown in Figure 1 (13). A hybrid type of fluidized bed system having two functions of

**(A)** Wurster type fluidized bed coater




**(B)** Newly developed fluidized bed device

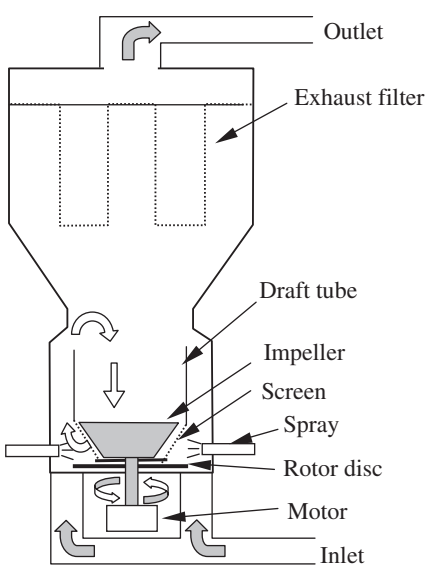



**Figure 1** Schematic diagram of fluidized bed system: (**A**) Wurster type fluidized bed coater and (**B**) newly developed fluidized bed device.

spray drying and fluidized bed system was developed by spray drying the solution or slurry of the drug with a polymer, followed by forming soft agglomerates of primary coated particles by fluidization, as shown in Figure 2 (14). The resultant agglomerates can readily disintegrate into the original coated particles and these systems have applications in dry powder inhalation systems (15).

The spray-drying method can produce discrete particles coated with an aqueous-coating solution or dispersion from spray droplets of the aqueous solutions or suspensions of drug and coating polymer when sprayed into a drying chamber. Spray-drying equipment may utilize at least one of three contact and mixing mechanisms for spray droplets and air in the drying in chamber, including concurrent flow, countercurrent flow, and mixed flow dryers (Fig. 3). In the concurrent flow dryer, spray droplets and air pass through the dryer in a concurrent flow pattern, which is widely used for heat-sensitive materials. In the countercurrent flow dryer, spray droplets and air enter at opposite ends of the dryer. This dryer can produce high-density products, which should meet requirements for drugs that are not sensitive to heat. The mixed flow dryer can handle coarse sprays in restricted volume chambers. For heat-sensitive materials, this equipment is not recommended, since the products are in contact with hot air. The formation of a spray (atomization) is important for achieving the optimal conditions. The atomization is achieved with rotary atomizers or nozzles. With a rotary atomizer,

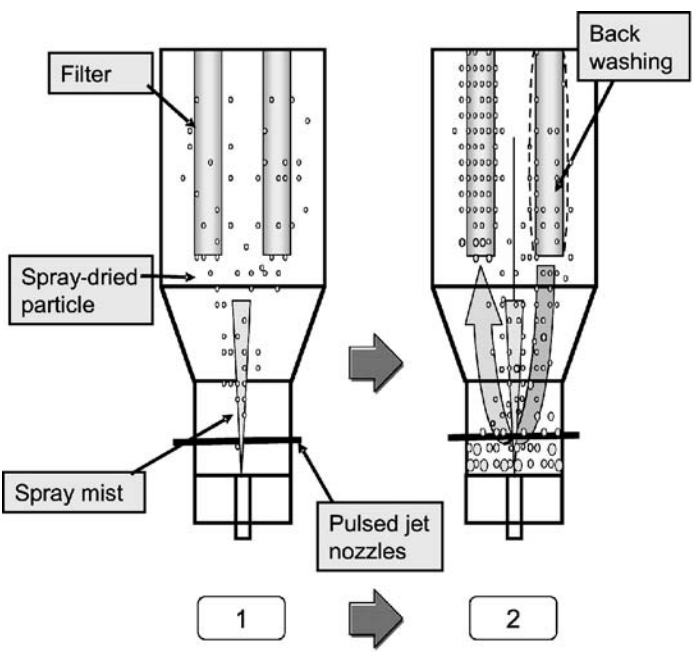



**Figure 2** Hybrid type fluidized bed system.

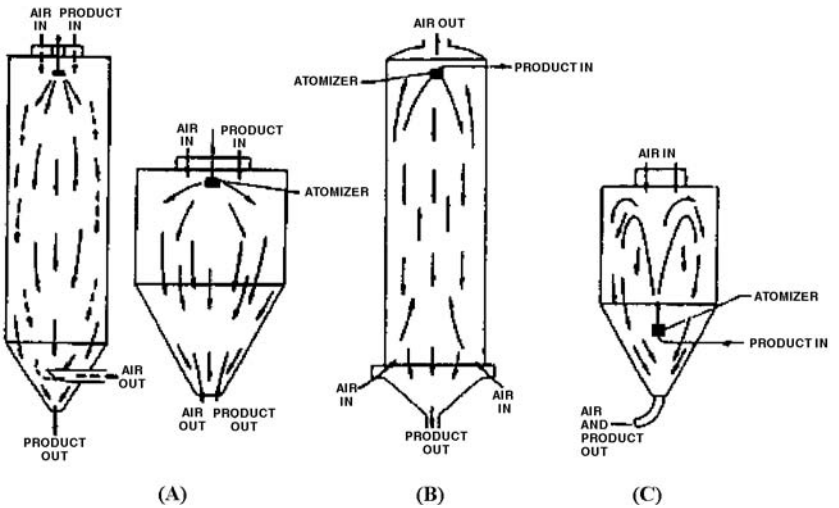



**Figure 3** Product air flow in spray dryers: (**A**) concurrent flow dryer, (**B**) countercurrent flow dryer, and (**C**) mixed flow dryer.

a wheel or disc atomizer is used. There is a wide range of nozzle sizes and designs, which are mainly classified according to the required pressure and nozzles that may employ two fluids. Generally, rotary atomizers are used to produce a fine- to medium-coarse product (10–150 mm), whereas coarse products (150–300 mm) are produced by using a nozzle atomizer. The general criteria for the selection of the atomizer and the dryer system have been described by Masters (16).

## DEVELOPMENT OF NEW POLYMERIC NANOSPHERE SYSTEMS FOR AQUEOUS COATING

Film formation from an aqueous polymeric colloidal dispersion is composed of four stages: (*i*) an aqueous colloidal dispersion, (*ii*) a close compacted array with water filled interstices, (*iii*) a densely packed array of deformed particles, and (*iv*) a continuous film without internal solid–solid interfaces. The transition from *iii* to *iv* is closely correlated to the glass transition temperature ($T_g$) of the polymer and to the minimum film-forming temperature (MFT) of the latex. $T_g$ is an intrinsic property of the material. The MFT is the minimum temperature above which a continuous and clear film is formed during drying. This temperature is determined by various physicochemical parameters, including $T_g$, latex morphology, and particle size. $T_g$ is also influenced by additives, including the plasticizer as well as the polymer water content (17). For the formation of strong films, a strong interaction and coalescence between particles would be required, which are also influenced by the above-mentioned parameters. Among those parameters, the reduction of particle size into the nanometer range is a key parameter to enhance the coales-

cence of particles due to an increase in surface energy, specific surface area, and coordination number of packed particles into a unit surface area. In this section, methods to prepare polymeric nanospheres for aqueous coating are discussed, including the polymeric spherical crystallization method developed by the authors. In addition, the physicochemical characterization of the film prepared with the resultant nanospheres is described.

The methods of polymeric nanoparticle preparation have been divided into two groups, i.e., a chemical method with polymerization of monomers and a physicochemical method using a readymade polymer. In the former, polyacrylamide and polymethyl methacrylate nanoparticles were prepared by the emulsion and dispersion polymerization methods, respectively (18,19). Biodegradable polymeric nanospheres were prepared by Couvreur et al. (20) with polymerization of alkylcyanoacrylates used as a surgical glue. In this process, polymerization of monomers was carried out in an o/w emulsion system with an acidic aqueous phase. In the physicochemical method, biodegradable nanospheres with polylactic acid were prepared by Gurny et al. (21). Other physicochemical preparation methods for the preparation of nanospheres include salting out and gelation (22,23). We have developed an emulsion solvent diffusion method as one of the polymeric spherical crystallization processes to prepare biodegradable polymeric nanospheres with poly lactic acid glycolic acid (PLGA). In Figure 4, the scheme to prepare an aqueous PLGA nanosphere dispersion with the emulsion solvent diffusion process is

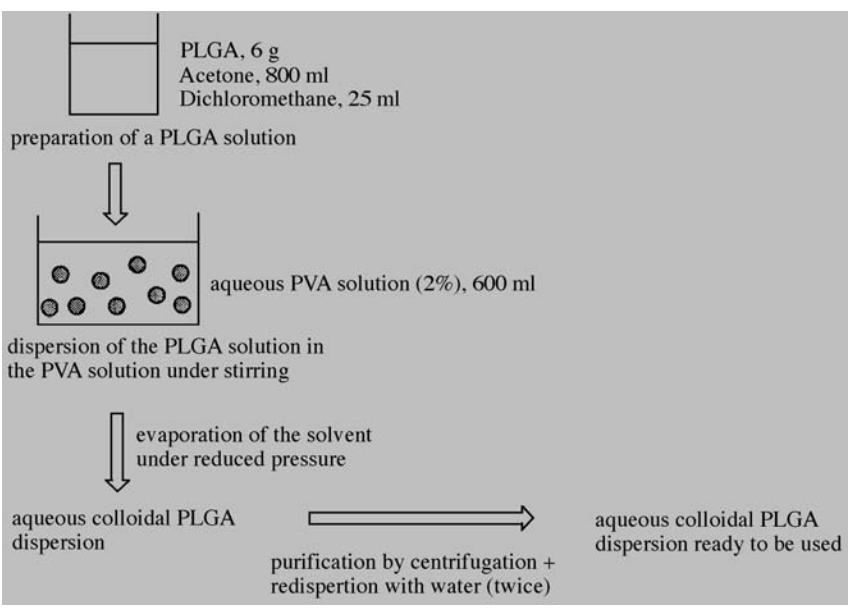



**Figure 4** Schematic for the preparation of an aqueous PLGA nanosphere dispersion by the emulsion solvent diffusion process. *Abbreviation*: PLGA, poly lactic acid glycolic acid.

illustrated. The PLGA dissolved in a mixture of acetone and dichloromethane (97:3) was dispersed in an aqueous PVA solution under stirring. Diffusion and evaporation of the solvent under reduced pressure induced solidification (crystallization) of the polymeric emulsion droplet, resulting in the formation of an aqueous PLGA nanosphere dispersion. The dispersed PLGA nanospheres were sedimentated by ultracentrifugation, followed by removal of the aqueous supernatant to yield the resultant PLGA nanospheres. The sedimented nanospheres were redispersed in distilled water under stirring. This cleaning process was then repeated. The average particle size of the redispersed PLGA nanosphere was 355 nm (SD: 21 nm), which did not change during storage for 10 days at 4°C (24).

An investigation of the physicochemical properties, such as the mechanical and transport properties of the free film produced with aqueous colloidal polymer dispersions under various preparation conditions, is useful to find an optimized formulation and preparation condition as well as to evaluate coating performance.

Transport properties of films for water vapor and substances dissolved in liquid were measured by a serum bottle method and a diffusion cell method, respectively. In the serum bottle method, the weight change of a serum bottle containing a supersaturated salt solution (e.g., sodium chloride) to maintain a constant internal relative humidity (e.g., 75.28% at 25°C), with a film sealing the opening, is measured periodically after the bottle is placed in a desiccator. The water vapor permeability is calculated using Equation 1:

$$P_{\mathrm{WV}} = -\frac{dM}{dt}\left(\frac{h}{A \cdot \Delta_P}\right) \tag{1}$$

where $P_{wv}$ is the water vapor permeability coefficient, d$M$/d$t$ the rate of weight change of the serum bottle with time, $h$ the thickness of polymer film, $A$ the area of the opening of the serum bottles, and $\mathbf{\Delta}_{\mathrm{p}}$ the vapor pressure gradient across the film.

In the diffusion cell method, a standard diffusion cell, such as a side-by-side diffusion cell, is employed. The polymer film is placed between each half of the diffusion cell and clamped in place. The drug dissolved in solution is introduced to the donor side of the cell, while dissolution medium is added to the receiver side, thus producing a concentration gradient. In both chambers, side cell magnetic stirrers are placed to continually mix the dissolution medium. The concentration of drug in the receiver cell is monitored. The drug permeability of the film is calculated by Equation 2:

$$-\frac{dM}{dt} = P_{\mathrm{B}} \cdot A \cdot \Delta C \tag{2}$$

where $P_{\mathrm{B}}$ is the drug permeability of the film, $A$ the surface area of the film in contact with the solution, $\Delta C$ the drug concentration difference between the two diffusion cells, and $d$M/$d$t the rate of weight change of drug with time in the receiver cell.

It has been found that the mechanical properties of the film are well correlated with $T_g$, which can be measured by either a thermomechanical analyzer (TMA) or a differential scanning calorimeter (DSC). By using TMA, creep compliance behavior of the film, defined as the ratio of the relative creep extension of the film to the applied stress, can be measured. By observing this property, it is possible to predict how the plasticizer added to the formulation will modify the coating. We observed the effects of plasticizer in PLGA films prepared from aqueous PLGA nanospheres using both TMA and DSC (24). To prepare an ideal film, the PLGA dispersion with average diameter of 355 nm was dropped slowly on a Teflon film, stuck to a horizontal glass plate to obtain a very smooth surface. The film was dried in a desiccator for three days at ambient temperature. In order to obtain PLGA films with better mechanical and pharmaceutical properties, various plasticizers were mixed in the colloidal PLGA dispersion. It was found that polyethylene glycol 1500 and triethyl citrate had good plasticizing effects, decreasing significantly the $T_g$ of the PLGA latex films. The $T_g$ value determined via TMA was higher than that measured using DSC, as seen in Figure 5. It was suggested that DSC might be useful to detect the mobility of plasticizer molecules, whereas TMA could be helpful in detecting the changes in the mechanical properties of films induced by heat.

A new aqueous polymeric enteric-coating system was developed with the aqueous dispersion of hydroxypropyl methylcellulose phthalate (HPMCP) nanoparticles prepared by the emulsion solvent diffusion method (25). Briefly, an aqueous

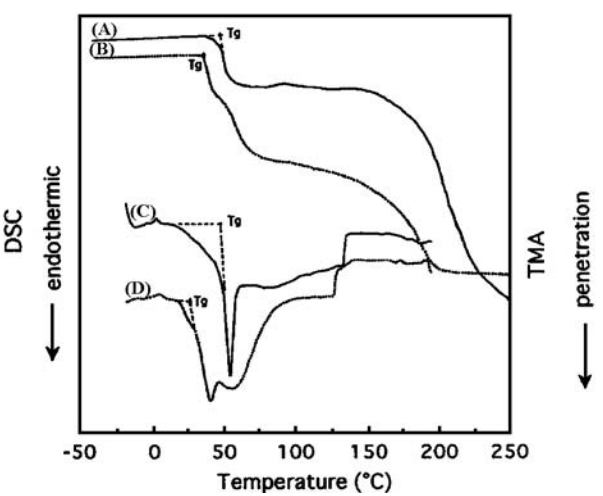



**Figure 5** Comparison between the TMA and DSC chart of PLGA latex film: (**A**) TMA chart of a pure PLGA film, (**B**) TMA chart of a PLGA film containing 30% PEG 1500, (**C**) DSC chart of a pure PLGA film, and (**D**) DSC chart of a PLGA film containing 30% PEG 1500. *Abbreviations:* TMA, thermomechanical analyzer; DSC, differential scanning calorimeter; PLGA, poly lactic acid glycolic acid.

ethanolic mixture (8:2) containing dissolved HPMCP (Shin-Etsu Chemical) was dispersed in distilled water at 65°C, resulting in a quasi O/W emulsion. By ethanol extraction and diffusion from the emulsion droplet, HPMCP nanospheres were obtained. The average diameter of HPMCP nanoparticles (pseudolatex) was 120 nm with a polydispersity index of 0.172. The enteric coating of riboflavin granules with the present system was successfully conducted using a fluidized bed coating technique. Riboflavin-layered nonpareil particles were coated with aqueous HPMCP nanospheres (10%) using a draft tube inserted into a fluidized bed coater (Wurster type fluidized bed) with 30% TEC and talc as plasticizer and lubricant, respectively. Scanning electron microphotographs of the cross-section of the coated granules are shown in Figure 6. With HPMCP nanoparticles, a smooth surface coating was obtained as compared with micronized HPMCP particles. Due to the dense internal structure of the film made from nanoparticles, the amount of coating required to obtain satisfactory acid resistance of the granules coated with nanospheres was found to be much less than with the commercially available micronized HPMCP, as shown in Figure 7. It was also found that the film thickness required to obtain enteric resistance was 10 μm or more, as seen in Figure 8 (25).

Fukumori et al. (26) have synthesized ethyl acrylate(EA)/methyl methacrylate (MMA)/2-hydroxyethyl methacrylate (HEMA) lattices by emulsion polymerization to coat fine particles using a Wurster type fluidized bed coater to produce controlled-release microcapsules with an average size smaller than 100 μm. By changing the composition ratio of the polymer, it was found that the physicochemical properties could be modified intentionally. The monomeric units of methacrylic derivatives contributed to the rigid, hard, and brittle nature of the resulting film, while those of the acrylic derivatives contributed to the softness and flexibility. The introduction of HEMA in the polymer enhanced water permeability of the film produced. Poly(EA/MMA/HEMA) with a molar ratio of 9:9:10 was found to be suitable for the preparation of short-term delayed release microcapsules by the Wurster coating process (26). These microcapsules can be applied to the formulation for masking unpleasant taste. The composition ratio of poly(EA/MMA/HEMA) = 9:9:4 was desirable for the preparation

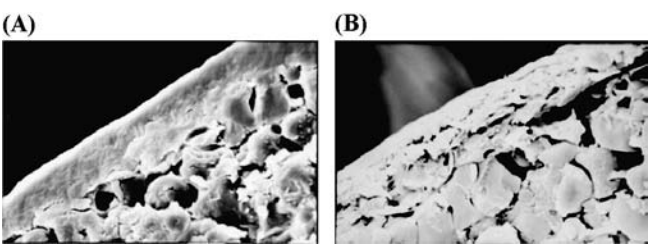



**Figure 6** Scanning electron microphotographs of the cross section of coated granules with (**A**) HPMCP nanoparticles and (**B**) HPMCP UF. *Abbreviation*: HPMCP, hydroxypropyl methylcellulose phthalate.

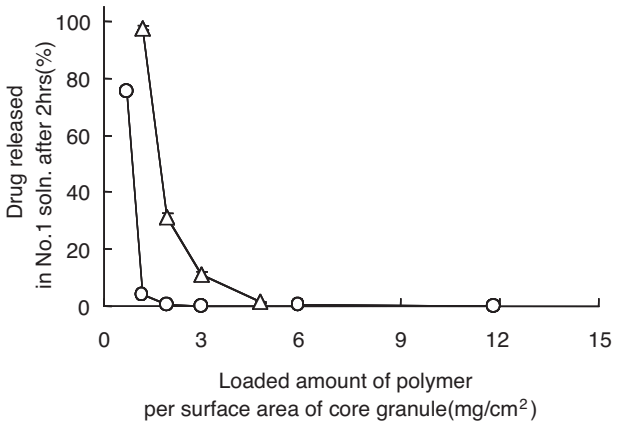



**Figure 7** Relationship between acid resistance in JP No. 1 solution and loaded amount of polymer: (○) HPMCP nanoparticles and (Δ) HPMCP UF. *Abbreviation*: HPMCP, hydroxypropyl methylcellulose phthalate.

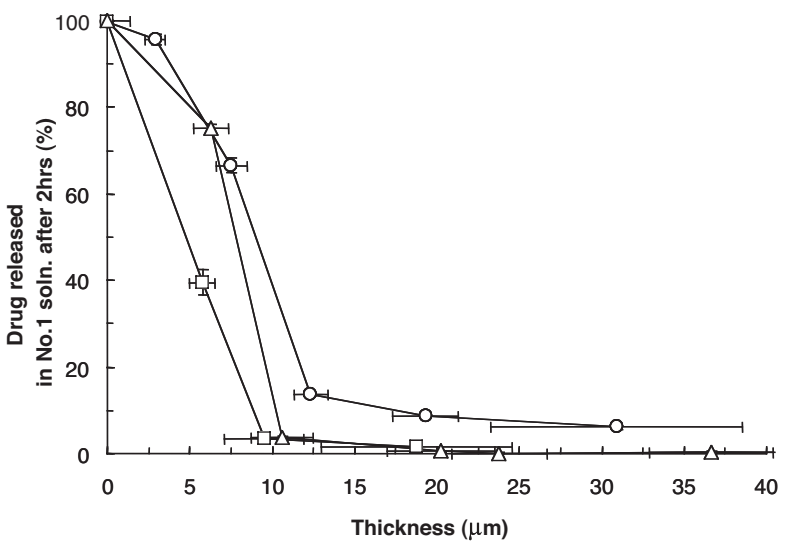



**Figure 8** Relationship between acid resistance in JP No. 1 solution and coating film thickness. Particle diameter of core particles are (○) 180–300 μm, (□) 355–500 μm, and (Δ) 840–1000 μm.

of drug released suppressed microcapsule with gadolinium for neutron-capture therapy by the Wurster process (27). Vaithiyalingam and Khan (28) developed novel controlled-release multiparticulate beads of verapamil HCl coated with a customized cellulose acetate butyrate dispersion using a fluidized bed coater. They optimized the dissolution profile by modeling three selected variables, i.e., coating weight gain, curing time, and plasticizer concentration with response surface methodology and artificial neural network.

## PREPARATION OF MICROPARTICLES WITH POLYMERS FOR CONTROLLED DRUG RELEASE BY THE SPRAY-DRYING TECHNIQUE

The spray-drying technique has been widely applied to prepare microparticles of drugs with polymers. There are two types of microparticles: microcapsules and microspheres. When a drug crystal suspension in a polymer solution is spray-dried, microcapsuled particles are prepared. Spray drying a drug solution and a dissolved polymer leads to the formation of drug microspheres, wherein the particle structure depends on the crystallizing properties of the drug. When the drug readily crystallizes out during the spray-drying process, the structure of the resultant spray-dried particles is similar to that of microcapsules. In other cases, the resultant particles form a microsphere structure, in which the drug molecules or drug crystals are dispersed. The particles tend to have a spherical shape and are freely flowing in spite of the final particle structure. These properties are preferable for pharmaceutical manufacturing processes such as tabletting and capsule filling.

The objectives of microencapsulation of drugs include controlled release, stabilizing the drug, and taste masking. However, the film coating formed by spray drying is usually thin and sometimes porous, and much attention should be paid to the selection of coating materials and operating conditions. Tabletting of spray-dried microcapsules is a useful application to design oral dosage forms (29–31).

Takada et al. (32) successfully applied the spray-drying technique to the preparation of injectable sustained-release microparticles of PLGApoly containing thyrotropin releasing hormone (TRH). To prepare the PLGA microspheres, an aqueous solution of TRH was dispersed in a PLGA solution of organic solvents such as dichloromethane, acetone, and acetonitrile. The resultant o/w emulsion with a mannitol solution was fed to a spray-dryer by using a double nozzle. The extent of the burst release of drug was a function of the type of the organic solvent as well as the drug content in the formulation. The particles prepared under optimal conditions showed a constant drug release rate profile for one month.

Wan et al. (33) prepared spray-dried microparticles of theophylline with a coating polymer in an aqueous system. Hydroxypropyl methylcellulose (HPMC) (1.25% w/v) and the drug (0.25% w/v) were dissolved in water and then spray-dried using a laboratory spray dryer (Pulvis Minispray GA32, Yamato, Japan) equipped with a two-fluid pressure nozzle. The spray-drying process was carried out with changing the operation conditions such as spray nozzle size, inlet drying temperature, drying air flow rate, spray rate of feed, and atomizing pressure to

confirm their effect on the drug release and micromeritic properties of the resultant spray-dried particles. A high inlet drying temperature and a faster drying air flow rate led to the production of coated theophylline particles with a slower drug dissolution rate and better flowability. These authors also pointed out that the addition of a suitable plasticizer influenced the drug release rate of the resultant spray-dried microcapsules (34,35).

Forni et al. (36) prepared microparticles of diltiazem hydrochloride with EC using a spray-drying technique. Diltiazem hydrochloride was either dispersed in a benzene solution of EC or dissolved in methanol solution of EC with 1:1 to 1:5 of drug:EC ratio, followed by spray drying. Microcapsule structure was obtained for the suspension system, while a microsphere structure, where the drug was in the amorphous state, was formed from the solution system. Complete coating of the drug crystals was observed when the drug:EC ratio was smaller than 1:2.5. The drug:EC ratio being equal, the release rate of drug from the microcapsules was faster than that from the microspheres. From these results, it was concluded that the release was not affected by the drug dissolution process.

Takeuchi et al. (37) demonstrated that polymeric theophylline microparticles prepared by the spray-drying technique was useful in preparing matrix tablets for sustained release of drug. Microcapsules of individual theophylline crystals were prepared by spray drying a theophylline suspension with Eudragit NE 30 D or RS 30 D. The drug release rate from the compressed microcapsules of theophylline with Eudragit NE 30 D or RS 30 D was found to be dependent on the polymer content in the particles as shown in Figure 9. The drug release patterns of tablets prepared with the microcapsules having a polymer content greater than 2% for NE 30 D microcapsules and 15% for RS 30 D microcapsules were described by the matrix type releasing model developed by Higuchi (38). The release pattern was changed to a zero-order-like release pattern when the polymer content was smaller than the critical values. The drug release was completely independent of the pH of the dissolution media, owing to the permeability properties of Eudragit

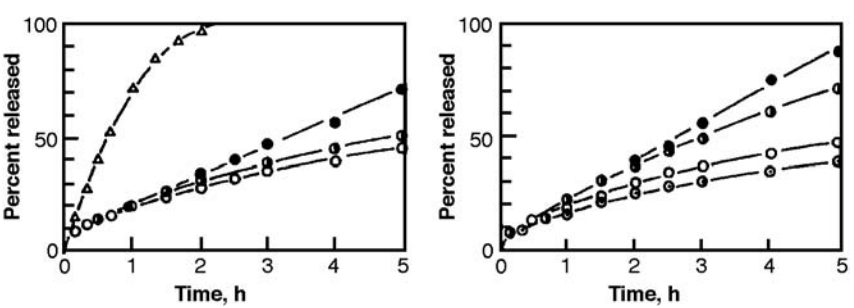



**Figure 9** Drug release profiles of tableted microcapsule of theophylline with Eudragit® NE 30 D (*left*) and RS 30 D (*right*). Drug/polymer: ◐, 3:1; ○, 20:3; ◑, 50:1; ●, 100:1; Δ, crystalline theophylline tablet.

NE 30 D and RS 30 D, and the release profile was similar to that of Theo-dur, which is a popular sustained released, commercially available tablet of theophylline, as shown in Figure 10. Prolonged drug release was not observed for tablets prepared from physically mixed powders of theophylline crystals and powdered Eudragit RS 30 PM, which has the same chemical structure as Eudragit RS 30 D, at the same drug to polymer ratio. This result implies that the uniformity of polymer distribution in matrix tablets is important in controlling the drug release. Tabletting microencapsulated individual drug crystals leads to the formation of a desirable polymer matrix for prolonging drug release.

Some hydrophilic polymers such as HPMC and hydroxypropylcellulose have been used as the basis for hydrophilic matrices for controlled-release oral delivery. The matrix systems can be prepared by directly compressing a mixture of drug and polymer powders. The preparation process of the matrix tablet is much simpler than that of other sustained-released systems such as polymer coated tablets. Thus, the matrix tablets are expected to be widely used as practical controlled drug release systems.

It has been reported that the drug release rate and pattern are affected by various factors with respect to the formulation such as the types of polymer and drug, the ratio of drug to polymer, and the particle size of the polymer and drug (8,39–42). There have been attempts to modify the drug release rate of matrix tablets by improving the formulation or additional modification of the system. Daly et al. (43) observed

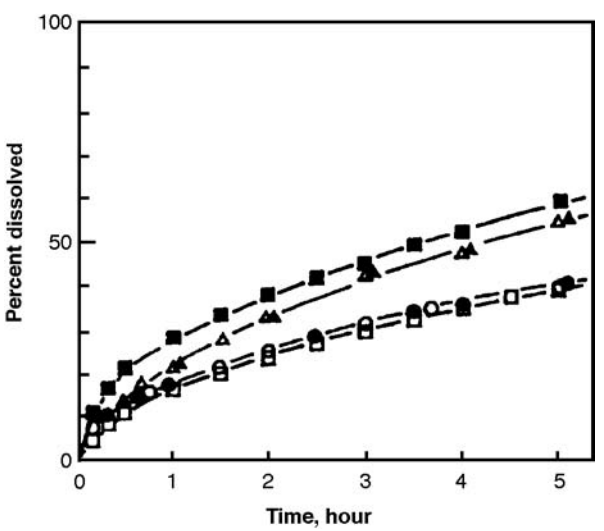



**Figure 10** Drug release patterns of tablet of spray-dried theophylline with Eudragit® NE 30 D and those of Theo-dur® (100 mg) in the disintegration test solutions specified in JP X (pH 1.2 and 6.8). ○, ●, Δ, ▲: NE 30 D tablet, theophylline NE 30 D = 20:15 (circle), 20:3 (triangle); □, ■: Theo-dur tablet. Open symbol, pH 1.2; closed symbol, pH 6.8.

that formulation of an anionic surfactant sodium dodecylsulphate into HPMC matrix tablets could retard the release of a cationic drug (chlorpheniramine maleate) from the matrix. Feely and Davis (44) suggested that the formation of ion complexes between drug and surfactant molecules is important in retardation of drug release. Colombo et al. (45) reported that impermeable coating of matrix tablets caused changes in the relaxation rate of the matrix, which led to a slowing of the drug release.

The drug release rate could also be controlled by modulating the erosion rate of the gel layer in the matrix tablets. Takeuchi et al. (Takeuchi H, Umeda M, Kawashima Y, unpublished data) demonstrated that the surface modification of HPMC particles with tannic acid (TA) or Eudragit RL 30 D was able to modulate the rate of erosion of the resultant matrix tablets. The dissolution rate of drugs from tablets prepared with the TA-treated HPMC or Eudragit RL 30 D coated HPMC particles and crystalline theophylline powders was more retarded than that of nontreated HPMC tablet as shown in Figure 11. When the matrix tablets were prepared from a physical mixture of crystalline theophylline and powdered Eudragit RSPM, which has the same chemical structure as that of Eudragit RS 30 D, the drug dissolution rate was not retarded. These results suggest that the polymer distribution in the matrix tablet is very important to control the erosion rate of the tablets, i.e., the drug dissolution rate, and the surface modification of HPMC particles with polymers by the spray-drying method is one of the most effective methods for distributing the polymer uniformly through the matrix.

When HPMC particles were coated with a pH dependent soluble polymer, Eudragit L 30 D, the resultant drug dissolution pattern from the coated HPMC tablets was found to be pH dependent. As shown in Figure 12, the dissolution

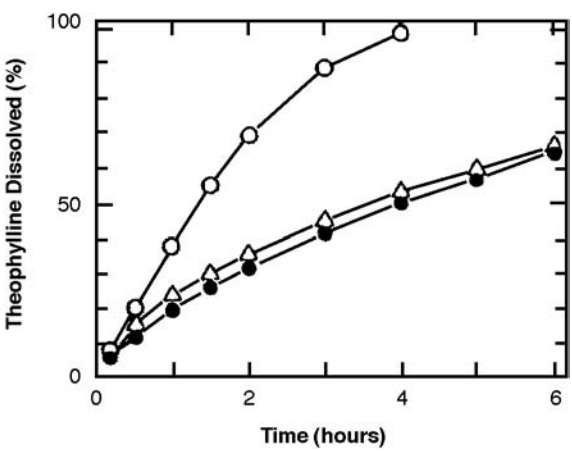



**Figure 11** Drug dissolution profiles of matrix tablets of HPMC spray-dried with tannic acid or Eudragit® RL 30 D. ○, untreated HPMC; ●, HPMC spray-dried with tannic acid; Δ, HPMC spray-dried with Eudragit RL 30D.

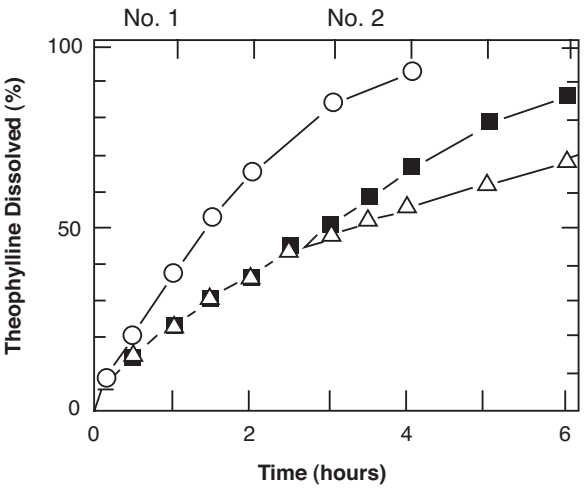



**Figure 12** Drug dissolution profiles of matrix tablet of HPMC spray-dried with Eudragit® L 30D. ■, Tablet of HPMC spray-dried with Eudragit L 30D; ○, tablet of untreated HPMC; Δ, tablet of HPMC spray-dried with Eudragit RL 30D.

rate in an acidic dissolution medium was the same as that of Eudragit RS 30 D modified HPMC tablet, while the drug dissolution rate was accelerated in the artificial intestine solution specified in JPXII because the gel layer became more erodible. One of the drawbacks of the hydrophilic swellable matrices is that the drug release rate declines continuously through the dissolution time in the GI tract. Zero-order release pattern is preferable in this point. Baveja et al. (46) obtained nearly a zero-order release pattern of hydrophilic matrix tablets of β-adrenergic blockers by the inclusion of the anionic sodium carboxymethylcellulose with HPMC in the matrix at an optimal ratio. The use of surface modified HPMC particles with a pH dependent polymer may be an alternative technique to solve the problem.

## COATING OF DRUG PARTICLES FOR TASTE MASKING IN RAPIDLY DISINTEGRATING TABLETS

Rapidly disintegrating tablets (RDTs), which are designed to disintegrate in the oral cavity, have received much attention as a new type of solid oral dosage form. These tablets can be taken with a small amount of water or without water. Children and elderly people who have difficulty in swallowing conventional tablets or capsules can take RDTs easily and comfortably. Several commercial tablets such as Gaster D and Takepron OD are available in Japan.

As RDTs disintegrate rapidly in the oral cavity, the unpleasant taste, bitterness, or odor of a drug becomes more serious problems than in the case of

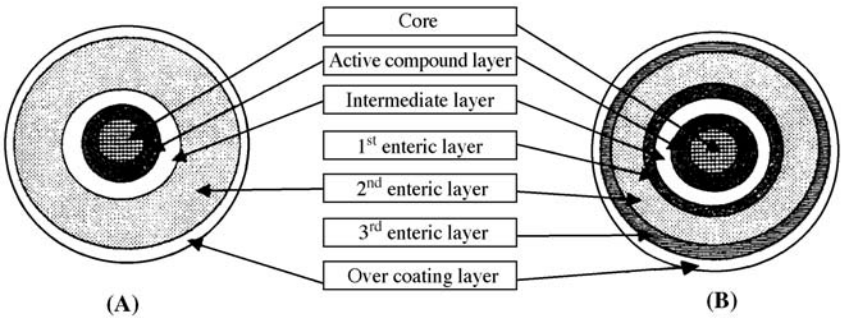



**Figure 13** Schematic presentation of cross section of enteric-coated microgranules: (**A**) enteric-coated microgranules comprising five layers and (**B**) enteric-coated microgranules comprising seven layers. *Source*: From Ref. 49.

conventional tablets. Coating with suitable polymers is one of the most popular methods to overcome these unfavorable characteristics. Ideally, the drug dissolution will be suppressed in the mouth, followed by rapid or controlled dissolution in the gastrointestinal tract. However, complete suppression at the initial stage of dissolution may lead to a retardation in the drug dissolution rate at a later stage.

Many efforts have been made to overcome these problems. It has been reported that famotidine crystals of the Gaster D tablets were coated for taste masking using a spray-drying technique. The particle size was around 100 μm to avoid an unpleasant feeling in the mouth (47). Lansoprazole is a proton pump inhibitor with a bitter taste. As the lansoprazole is unstable under acidic conditions, the rapidly disintegrating tablet, Takepron OD, was prepared by compressing the enteric microgranules of lansoprazole with suitable excipients (48–50). In preparing the enteric-coated microgranules, the drug layer formed on the surface of the core particle was coated with the enteric polymer, Eudragit L 30 D, in combination with Eudragit E. For acrylic polymer coating, a plasticizer must be added into the film formulation. Triethyl citrate is a good plasticizer for the acrylic polymers, especially in coating particles for tabletting, because the resultant film possesses a relatively higher tolerance to the compressing pressure. One of the problems

**Table 1** Formulation of Ethylcellulose Spray Dispersion

| | |
|---|---|
| CX-1 (g) | 121.5 |
| Mannitol (g) | 2.44 |
| Triacetin (g) | 9.12 |
| Water (g) | 106.94 |
| Total (g) | 240 |

**Table 2** Process Conditions of Ethylcellulose Layer

| | |
|---|---|
| Inlet air temperature (°C) | 75 |
| Inlet air volume ($m^3$/sec) | 0.35 |
| Atomizing air volume (Nl/min) | 17.5 |
| Spray rate (g/min) | 6.0–8.0 |

associated with this plasticizer is its bitter taste. On the other hand, macrogol 6000 does not have an unpleasant bitter taste and is more compatible than triethyl citrate. Thus, the resultant coated particle is composed of three layers of enteric polymers, as shown in Figure 13: the outer enteric layer was formed with macrogol 6000 for taste masking, the middle enteric layer was formed with triethyl citrate for reducing the damage during compression, and the inner enteric layer was formed with macrogol 6000 for better compatibility with the drug.

Harnal® D tablets (Yamanouchi Pharmaceutical Co. Ltd., Tokyo, Japan) containing tamsulosin were developed as an alternative dosage form to Harnal capsules. A sustained release formulation of tamusulosin was required to avoid side effects. In preparing tamusulosin RDT, the drug-containing particles as small as 200 μm were coated with a suitable polymer. A special coating system based on the fluidized bed coating equipment has been patented by the company (47).

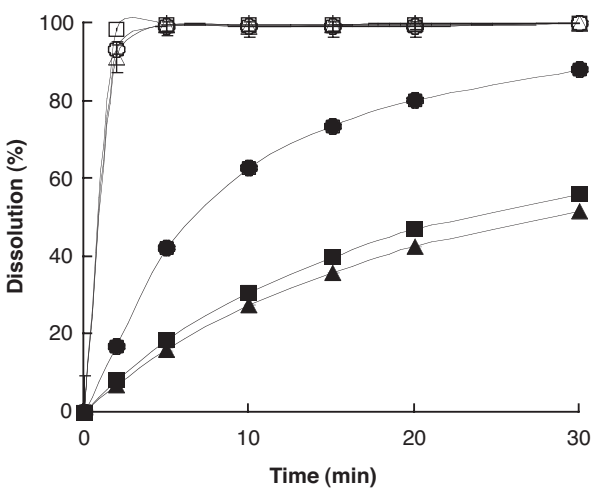



**Figure 14** Drug release patterns of original model drug and particles coated with ethylcellulose in water, pH 1.2 and 5.0 medium: (●) particles in pH 1.2 medium, (▲) particles in pH 5.0 medium, (■) particles in water, (○) original in pH 1.2, (□) original in pH 5.0 medium, and (□) original in water.

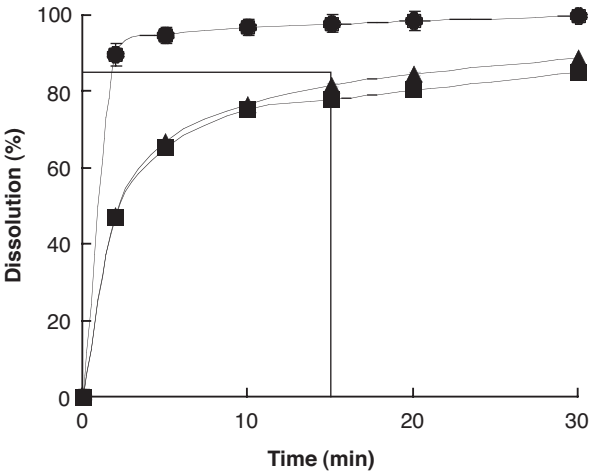



**Figure 15** Drug release patterns of tablets formulated model drug particles coated with ethylcellulose in water, pH 1.2 and 5.0 medium: (●) pH 1.2 medium, (▲) pH 5.0 medium, and (■) water.

Katayama et al. (Katayama N, Hoashi Y, Kai T, unpublished data) also studied the taste masking of a model drug which has an intense bitterness, by coating with an aqueous dispersion of EC (CX-1, Asahi Kasei Chemicals). EC has been frequently used in pharmaceutical formulations as a sustained release coating material. Triacetin was formulated in EC aqueous dispersion as a plasticizer to improve flexibility and elongation of the coating films. Mannitol was added in the dispersion to create small pores in the resultant EC films for introducing water into the particles, since EC is insoluble in water. Table 1 shows the coating formulation of the spray solution. The coating process was performed using a Wurster coater (MP-01, POWREX), which is a bottom spray fluidized bed coater and often used in the coating of small particles. Table 2 indicates the process conditions of the fluidized bed coater.

**Table 3** Formulation of Spray Dispersion of Citric Acid Layer

| | |
|---|---|
| TC-5 RW (g) | 5.3 |
| Citric acid anhydrous (g) | 0.96 |
| PEG-6000 (g) | 0.53 |
| Water (g) | 73.21 |
| Total (g) | 80 |

**Table 4** Process Conditions of Citric Acid Layer

| | |
|---|---|
| Inlet air temperature (°C) | 75 |
| Inlet air volume ($m^3$/sec) | 0.40 |
| Atomizing air volume (Nl/min) | 15.0–22.5 |
| Spray rate (g/min) | 4.5–7.8 |

Figure 14 shows the resultant dissolution patterns of model drug particles in the dissolution media (pH 1.2 and 5.0) and water. Dissolution rates from coated particles were reduced compared with uncoated DA in all dissolution media, especially pH 5.0. The results from human sensory tests for these particles confirmed that drug bitterness was reduced. RDTs containing particles were prepared, and dissolution tests were performed, as shown in Figure 15. Dissolution rates from the RDT were reduced in pH 5.0 media and water, because the model drug is a basic drug, whose solubility decreases with increasing pH of the dissolution media. In order to optimize the dissolution profile, multicoating particles were prepared. Crystals were coated with citric acid and HPMC under an EC coating layer in order to suppress rising pH in the particles (Tables 3 and 4). Figure 16 shows the dissolution patterns of the RDT containing particles coated with EC and citric acid. As a result, the dissolution rate became faster than that

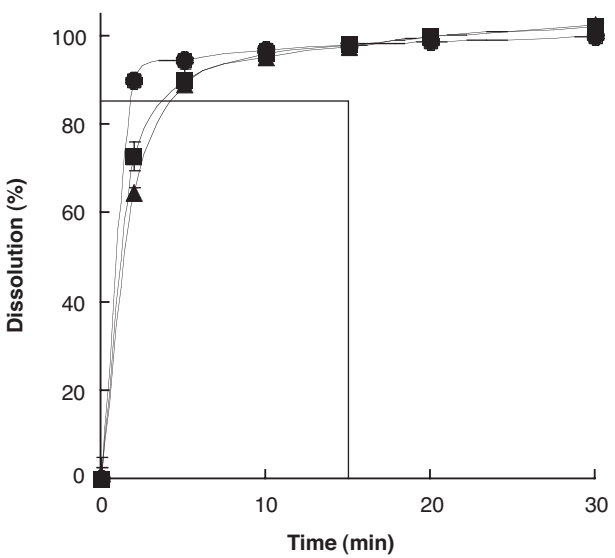



**Figure 16** Drug release patterns of tablets of formulated particles coated with ethylcellulose and citric acid in water, pH 1.2 and 5.0 medium: (●) pH 1.2 medium, (▲) pH 5.0 medium, and (■) water.

of the RDT-formulated particles coated with only EC. It was also confirmed that bitterness of the coated particles was sufficiently suppressed with the modification in the coating.

## ACKNOWLEDGMENT

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# 13

# Polymer Interactions with Drugs and Excipients

**L. Diane Bruce**
*Aptuit Inc.,*
*Kansas City, Missouri, U.S.A.*

**James W. McGinity**
*College of Pharmacy, The University of Texas at Austin,*
*Austin, Texas, U.S.A.*

## INTRODUCTION

Interactions between drugs and excipients with polymeric film-forming agents influence the properties, functionality, and permeability of the applied film. Interactions can take place in the solid state at the substrate and polymer film interface, during preparation of a coating solution, or during film formation and dissolution.

Solvent-based polymer film coatings were in general use until the 1970s, when a gradual transition occurred to aqueous-based systems (1). Aqueous-based polymeric coating systems are comprised of polymers that are readily soluble in water or aqueous colloidal dispersions of insoluble polymer particles. Although aqueous-based, the polymer solutions and polymeric colloidal dispersions differ in their film-forming mechanisms, each having advantages and disadvantages of use. Aqueous polymer solutions when prepared with high solids content can be highly viscous, leading to potential clogging of spray nozzles. Film formation in aqueous polymer solutions occurs as the polymer chains become entangled once sprayed droplets hit the substrate surface and water begins to evaporate. As drying occurs, a viscous, gelled, three-dimensional polymer network transforms into a continuous film. The strength and durability of the resultant film is a function of the polymer molecular weight and concentration of polymer solids in solution.

Alternatively, aqueous polymeric colloidal dispersions consist of water-insoluble polymer particles suspended in an aqueous medium. The solids content of the dispersion can be increased without a significant increase in viscosity, thus reducing the potential for spray nozzle clogging. A higher solids content limits water penetration into the substrate and requires less water to be removed during the coating and drying process. This reduces processing energy requirements and overall time required for coating. Film formation for aqueous polymeric colloidal dispersions is a complex mechanism where water evaporates from between spherical polymer particles after deposition onto the substrate. The polymer particles begin to coalesce as they are drawn closer together as a result of viscous flow and surface tension. Frenkel's equation describes this phenomenon through a relationship between the half angle of contact, $\theta$, as a function of surface tension, $\sigma$, time, $t$, polymer viscosity, $\eta$, and particle radius, $r$ (2). The degree of particle coalescence is characterized by the angle $\theta$ and improves as surface tension or interfacial tension increases, and as the viscosity of the polymer spheres decrease. Plasticizing agents added to the dispersion are necessary for softening and deformation of the polymer spheres by swelling the polymer particles and reducing the minimal film-forming temperature, thus enhancing polymer coalescence and entanglement, which lead to film formation. The balance of forces required to maintain a stable disperse system make colloidal dispersions particularly sensitive to shear forces, additives, and temperature, requiring special care during preparation and processing.

Some drug–polymer and excipient–polymer interactions are important in the polymeric film-formation processes described and are even required in some instances for a strong and durable film to form. However, other drug–polymer or excipient–polymer interactions have deleterious effects on the functionality of the film. The physicochemical properties of the polymer, excipients, and substrate must be considered in order to avoid unwanted interactions.

## NONCOVALENT INTERACTIONS

Many of the interactions that occur between drugs, excipients, and polymers can be categorized as noncovalent. Noncovalent interactions include van der Waals attractions (or dispersion forces), hydrogen bonding, and electrostatic interactions (also called ionic bonding). All of these interactions involve an electrical charge due to temporary dipoles or ion formation. Dipoles occur when electrons are not shared equally between two atoms having different electronegativities. The atom with the greater electronegativity draws the shared electron pair closer to it, resulting in partial positively charged and negatively charged ends of the molecule.

Electrostatic interactions and hydrogen bonding are the strongest noncovalent type interactions. A hydrogen bond is the result of very strong dipole–dipole attraction between hydrogen atoms bonded to small, strongly electronegative atoms that have at least one unshared pair of electrons (typically nitrogen, oxygen, and fluorine). Electrostatic interactions or ionic bonding occurs commonly in

inorganic molecules and salts of organic molecules due to the attraction between negatively and positively charged atoms.

The interactions between drugs, excipients, and polymers can involve a single interaction or a combination of these noncovalent interactions. The results of these interactions can produce a wide variety of outcomes such as poor dissolution and bioavailability, film failure or enhancement as a result of excipient–polymer interactions, or even a novel sustained-release dosage form due to drug–polymer interaction. Several studies have been conducted to determine how drug and excipient interactions with polymers affect the polymer system.

## DRUG INTERACTIONS WITH EUDRAGIT® POLYMERS

Eudragit® acrylic polymer dispersions and resins have a variety of pharmaceutical applications, and interactions have been characterized for these polymers with several drug substances (3–14). The functional groups on the Eudragit polymer backbones (and in some cases, the charges associated with the Eudragit polymers) make them readily reactive with drug substances.

Eudragit polymers used in the referenced studies were divided into anionic (Eudragit L and Eudragit S), cationic (Eudragit E), and zwitterionic (Eudragit RS and Eudragit RL) categories. In most of the case studies, complexes or coprecipitates were prepared between different drug substances and Eudragit polymer dispersions using a technique where the dispersions were diluted and neutralized prior to introduction of an aqueous solution of a drug. Solid dispersions were also prepared by dissolving the Eudragit polymers and a drug in a solvent mixture and evaporating the solvent to collect the dried precipitate. The techniques used to study the interactions included carbon nuclear magnetic resonance (c-NMR) or proton nuclear magnetic resonance (h-NMR) spectroscopy, Fourier transform–infrared (FT-IR) spectroscopy, and differential scanning calorimetry (DSC) analysis of physical mixtures and formed complexes of the drugs and polymers, as well as dissolution studies. In all of the investigations, when an interaction between the drug substances and the Eudragit polymer was indicated, the interaction was found to be due to either a saline bond formation (ionic) or hydrogen bonding between the drug and the polymer.

In one study, a complex was formed between carteolol HCl and Eudragit L. Analyses of the complex using NMR spectroscopy demonstrated that the drug carteolol HCl was in the ammonium salt form. During preparation of the complex, the Eudragit polymer was neutralized with NaOH to form (R-COONa) subunits. Carteolol HCl, when added to the neutralized polymer, interacted to form an ionic bond with the carboxylate anions on the polymer. The carteolol ammonium salt interaction with the polymer carboxylate ion groups is illustrated in Figure 1 (3). A similar salt (ionic bonding) was also reported between propranolol HCl and Eudragit L in another study. The complex between propranolol HCl and Eudragit L polymer was prepared similarly by neutralizing the polymer with NaOH prior to addition of the drug. The authors of this study confirmed the presence of a salt

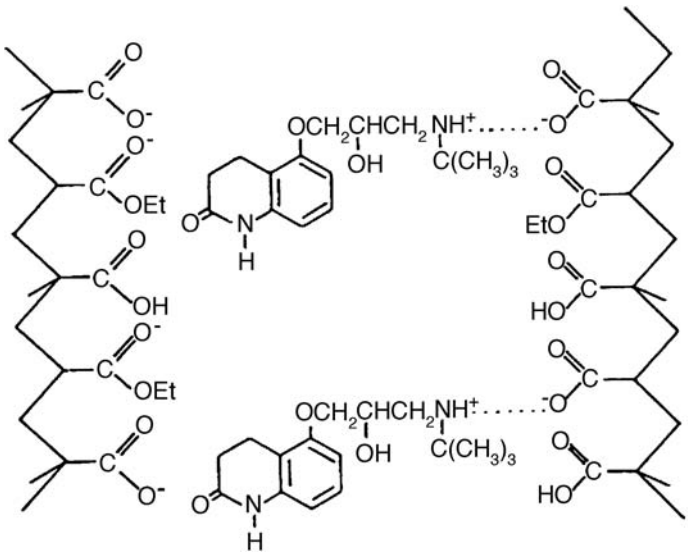

**Figure 1** Types of bonds between drugs and Eudragit® L: saline bond corresponding to carteolol. *Source*: From Ref. 3.

or ionic bond between propranolol and Eudragit L by FT-IR analysis of the complexes (4). Additional findings of ionic bonding between the ammonium salts of drug substances and the anionic group of the Eudragit L polymers are reported in the literature (9,14).

Free-base drug substances have also been reported to interact with Eudragit polymers. When morphine HCl was added to neutralized Eudragit L polymer to form a complex, analysis using NMR spectroscopy indicated the drug was in its free-base form. Morphine free–base was shown to interact with Eudragit L by hydrogen bonding with the polar groups of the polymer (5,6). Two possibilities of hydrogen bonding are shown in Figure 2 between morphine free–base hydroxy and amine nitrogen groups with the polymer carboxylic functional groups. Similar hydrogen bonding between the nitrogen groups of dipyridamole free–base and Eudragit S, and naltrexone free–base and Eudragit L have also been observed (7,8).

Differences in structures between drugs directly affect the type of interaction and strength of the bond that will form with Eudragit polymers. In the two preceding examples with carteolol HCl and morphine HCl, the differences in structures of these two drug molecules resulted in different types of interactions with the Eudragit polymer. The secondary amine functional group in the carteolol is more reactive and less stable than the tertiary amine in morphine, resulting in an ionic bonding between the drug and polymer instead of hydrogen bonding. The coprecipitates prepared in the interaction between morphine HCl and Eudragit L were high in drug content. The high yield and efficiency of the process was at-

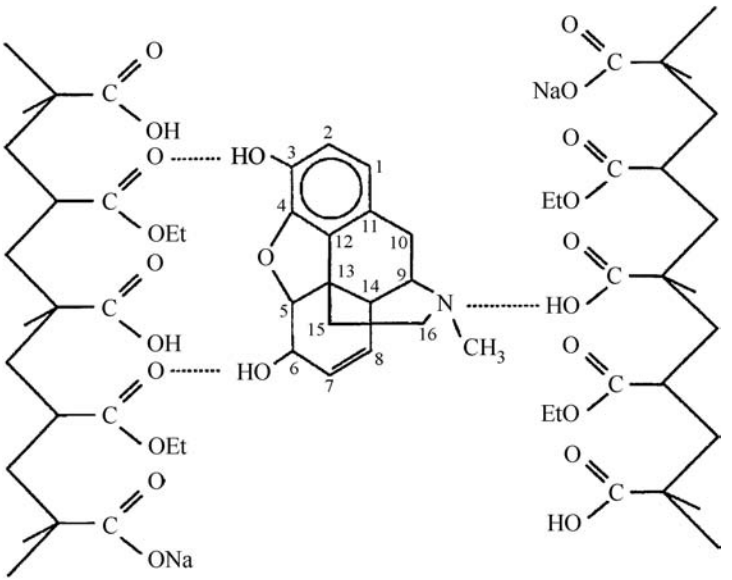

**Figure 2** Hydrogen bonds between morphine and Eudragit® L. *Source*: From Ref. 6.

tributed to the ability of the morphine to react with the polymer at multiple sites via hydrogen bonding.

In some cases, drug substances show signs of interaction with one category of Eudragit polymers but no interaction with others. Such an example occurred in coprecipitates prepared from ibuprofen and anionic (Eudragit S 100) or zwitterionic (Eudragit RL/RS) polymers. No interaction was found between the drug and these polymers using FT-IR, X-ray diffraction, or DSC analysis of the coprecipitates (10). However, when the drug was coprecipitated with a blend of Eudragit E 100 and Eudragit S 100, a significant interaction was demonstrated due to the addition of the cationic polymer (Eudragit E). Dissolution studies of coprecipitates of ibuprofen and Eudragit RS and RL showed a delayed release of the drug; however, this was explained to be due to the swelling of the zwitterionic polymers rather than due to an interaction with ibuprofen. The release rate of the drug continued to decrease with increased polymer concentration as a result of increased thickness of the diffusion layer surrounding the drug.

Several studies were conducted by Lin et al. using a variety of drug substances including indomethacin, warfarin, and piroxicam combined with one or all categories of the previously described Eudragit polymers, primarily Eudragit E, RL, and S (11–13). The drug substances were found to interact with the Eudragit E polymer, but not with the other Eudragits. Indomethacin and warfarin were observed to increase in solubility when a saturated amount of the drug was combined with Eudragit E in acetone. The solubility of the drug substances was also

shown to increase when the drugs were combined in solution with Eudragit S and RL, but not to the extent observed with Eudragit E. The enhanced solubility was attributed to an interaction or binding between the drug substance and the polymer, thereby increasing the drug solubility in the medium. With each of the three drug substances, there was a shift in FT-IR spectra when dissolved in acetone with Eudragit E, but no shift was observed when the drug substances were combined with Eudragit RL or S. The shift in spectra was substantial evidence of a drug–polymer interaction due predominately to hydrogen bonding between the drug substances and the Eudragit polymer. The release of warfarin and indomethacin from compacts of physical mixtures, ground mixtures, and films of Eudragit polymers containing drug supported this conclusion. As shown in Figure 3, the release of warfarin in pH 7.4 phosphate buffer from tablets prepared from warfarin–Eudragit cast film or ground mixture is significantly delayed due to the molecular interaction between warfarin and Eudragit E (13). Similar results were demonstrated for indomethacin. A delayed-release profile between these drug substances and Eudragit RL was also observed due to the insolubility of the polymers in pH 7.4 phosphate buffer rather than due to an interaction as observed by other authors. No indication of an interaction was found using FT-IR or DSC analysis of physical mixtures, ground mixtures, cast films, and preheated samples of drug substance and Eudragit RL combinations.

Drug–polymer interactions can also occur during the dissolution process as observed in prepared films of Eudragit RS and Eudragit RL containing salicylic

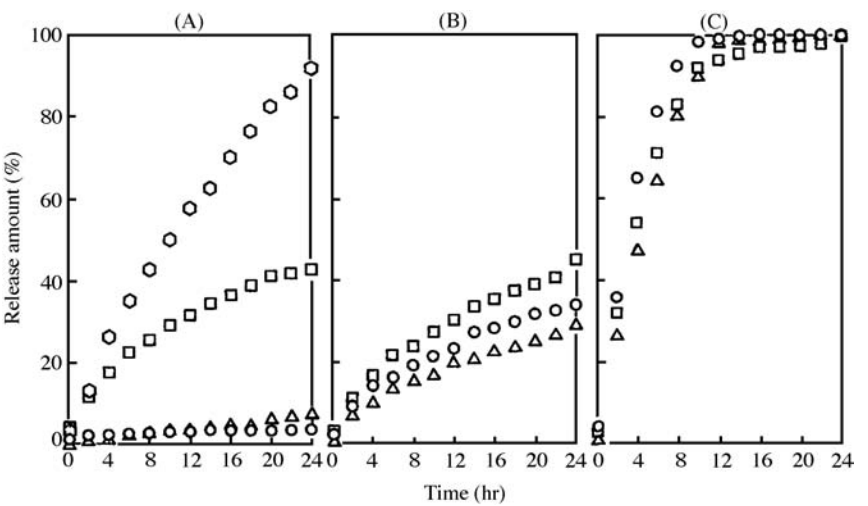


**Figure 3** Release behavior of warfarin from tablets prepared by warfarin–Eudragit® resins: (**A**) Eudragit E; (**B**) Eudragit RL; (**C**) Eudragit S. (⬡) tablets prepared from warfarin/spray-dried lactose; (□) tablets prepared from physical mixture; (△) tablets prepared from the cast film; (○) tablets prepared from 24 hr ground mixture. *Source*: From Ref. 13.

acid (15,16). Jenquin et al. (15) found the rate of drug release from Eudragit films to be related to the properties of the drug and the type of polymer in the film. Both salicylic acid and chlorpheniramine maleate (CPM) were incorporated into Eudragit RS and RL films with increasing drug concentrations. For CPM, the release of drug from the film increased with increasing drug loading. However, when salicylic acid was incorporated into Eudragit RL film, a trend (at 2%, 5%, and 10% drug concentration in the film) of a peak in the concentration of the salicylic acid released into the media followed by a sharp decline in concentration occurred (Fig. 4) (15). This decline in drug concentration in the dissolution media was later shown using Langmuir adsorption isotherms to be due to adsorption of salicylic acid onto the Eudragit polymers. It was theorized that the salicylic acid after diffusing through the film, ionized (became negatively charged) in the neutral pH of the dissolution media and interacted with the positively charged quaternary ammonium groups on the polymer via electrostatic binding. This adsorption was greater for Eudragit RL than for Eudragit RS due to the greater ratio of quaternary ammonium groups in the Eudragit RL available to bind with the salicylic acid. The adsorption isotherms clearly showed adsorption of salicylic acid to RL and RS polymers and no adsorption occurring for CPM (Fig. 5). Furthermore, salicylic acid release decreased with increasing ionic strength of the dissolution media. This effect was due to a decrease in adsorption of the drug to the polymer by inhibition of electrostatic binding in

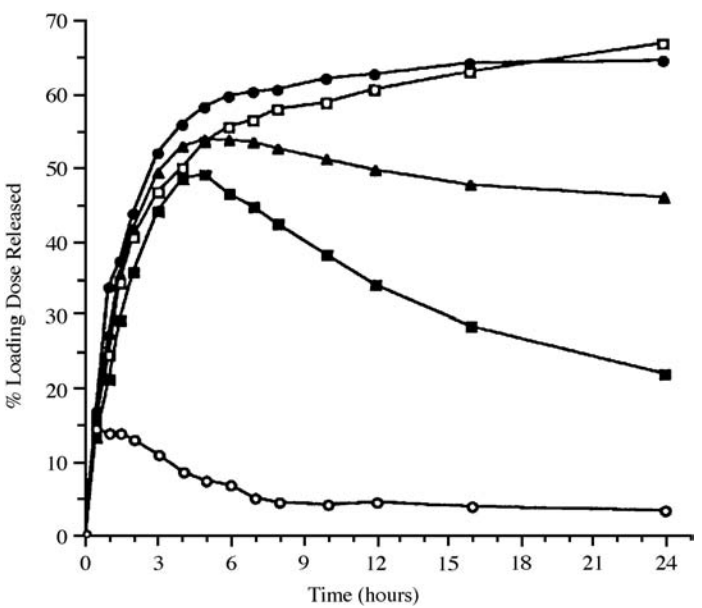


**Figure 4** Effect of drug concentration on the release of salicylic acid from Eudragit® RL PM films. (□) 20% drug; (●) 15% drug; (▲) 10% drug; (■) 5% drug; (○) 2% drug. *Source*: From Ref. 15.

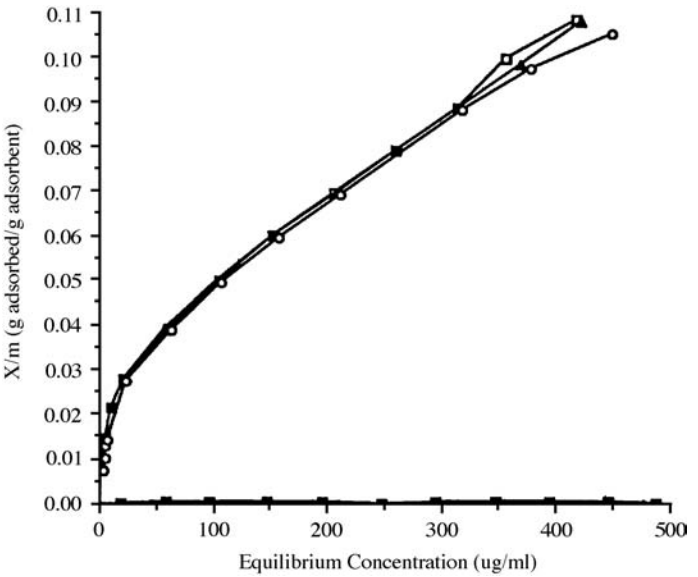


**Figure 5** Isotherms for the adsorption of SA and CM to Eudragit® RL 100 particles of varying sizes. (□) SA, polymer size 106 to 125 μm; (▲) SA, polymer size 180 to 250 μm; (○) SA, polymer size 420 to 600 μm; (■) CM, polymer size 420 to 600 μm. *Abbreviations*: SA, salicylic acid; CM, chlorpheniramine maleate. *Source*: From Ref. 15.

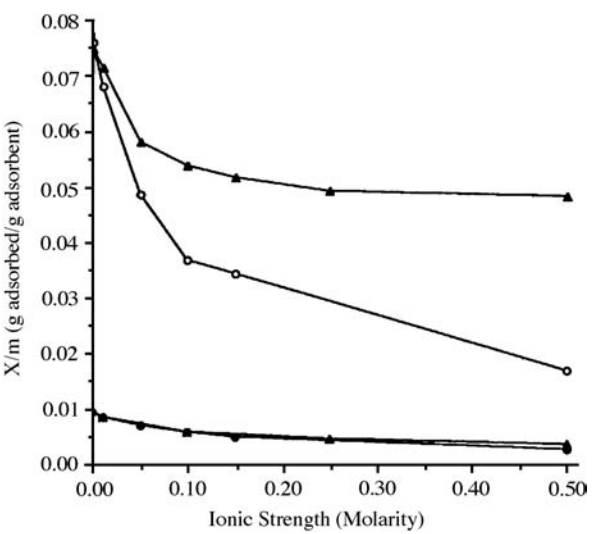


**Figure 6** Effect of ionic strength on the adsorption of SA to Eudragit® RL 100. Two initial drug concentrations and two ionic strength systems were evaluated: (△) 0.1 mg/mL SA in NaCl; (▲) 1.0 mg/mL SA in NaCl; (●) 0.1 mg/mL SA in Tris–HCl; (○) 1.0 mg/mL SA in Tris–HCl. *Abbreviation*: SA, salicylic acid. *Source*: From Ref. 15.

the presence of Cl ions in the Tris buffers (Fig. 6). The chloride ions in the media interacted with the quaternary ammonium groups on the polymer and buffered the electrostatic charge so that the negatively charged groups of the salicylic acid were unable to bind. Some adsorption was maintained even with the increase in ionic strength of the media, which may have been due to hydrogen bonding and van der Waals forces of attraction, referred to by the authors as non-electrostatic interactions. When CPM was incorporated into the Eudragit RS/RL film, the same dissolution phenomenon did not occur. CPM remained ionized (positively charged) in the dissolution media. The positively charged CPM and the positively charged quaternary ammonium groups on the Eudragit polymers were not electrostatically attracted, resulting in constant concentration of CPM in the dissolution medium.

## INTERACTIONS WITH COLLOIDAL DISPERSIONS

An interaction between a drug or excipient and a polymer can be the result of a disturbance in the electrostatic balance of the polymeric dispersion medium. When fine particles are dispersed in a liquid medium, collisions occur between particles due to Brownian movement. When particles collide, they will either remain in permanent contact or rebound to remain freely suspended. The status of the particles is dependent upon the attractive and repulsive forces of interaction between the particles. There are five possible types of forces that influence particle stability: electrostatic forces of repulsion, van der Waals forces or electromagnetic forces of attraction, Born forces or short-range repulsive forces, steric forces dependent on the geometry and conformation of molecules at the particle interfaces, and solvation forces due to changes in quantities of adsorbed solvent on approach of neighboring particles (17). According to the DLVO (Derjaguin, Landau, Verwey, Overbeek) theory, electrostatic charge stabilization of dispersed particles is a result of the balance between electrostatic repulsive and van der Waals attractive forces between particles (18). An electrostatic repulsive charge around each dispersed polymer particle prevents aggregation or flocculation. A double layer of charge exists at the surface of the particle: one that is tightly bound to the particle surface and another that is more diffuse. Ions on the particle surface attract counter-ions from the media and form the tightly bound layer. As distance increases from the particle surface, the counter-ion concentration becomes more diffuse until eventually the concentrations of anions and cations result in electric neutrality. The zeta potential is the difference in the charge potential between the surface of the tightly bound layer and the neutral region in a solution (18). If the zeta potential of a colloidal dispersion is reduced below a certain value (which is different for every system), the attractive van der Waals forces will exceed the repulsive forces, and the particles will flocculate. This effect is a disadvantage of polymeric colloidal dispersions that results in a sensitivity to additives such as electrolytes, changes in pH, temperature, and shear forces. All of these factors can lead to changes in the thickness of the diffuse double layer between adjacent suspended polymer particles, leading to coagulation or flocculation. Numerous drug–polymer or excipient–polymer interactions may result from the disturbance

of polymer colloidal particle electrostatic balance and compression of the electric double layer between polymer particles.

## Interactions with Colloidal Dispersions Due to Changes in the Diffuse Double Layer

Goodman and Banker were familiar with polymeric colloidal dispersion flocculation in the presence of drug substances, and used this phenomenon as a novel approach to formulate a sustained-release dosage form. The acid salts of cationic nitrogen–containing drugs that were found to flocculate acrylic anionic copolymer emulsions are listed in Table 1 (19). These drugs readily caused flocculation of the dispersions with flocculation values of 10 to 20. The flocculation value is the concentration of drug in mmoles/L required to cause complete flocculation within two hours. The flocculation or drug entrapment procedure called for slowly adding the acrylic copolymer emulsion to a constantly mixed solution of drug (methapyrilene hydrochloride) in distilled water. This resulted in immediate flocculation and precipitation of the system. The mixture was vacuum filtered, collected and dried for four hours at 50°C, and then comminuted and screened. The interaction between the drug and polymer was studied by plotting the relationship between drug concentration and acrylic copolymer drug entrapment ratio, determining flocculation values at various polymeric emulsion pH levels, and determining in vitro release rates of precipitates and tablet preparations. A linear relationship was observed between the initial amount of drug in solution and the amount of drug entrapped in the solid product. Additionally, the pH of the anionic polymeric copolymer emulsion affected the amount of drug entrapped.

**Table 1** Flocculation of an Acrylic Copolymer Emulsion System by Acid Salts of Various Cationic Nitrogen-Containing Medicinals

| Compound | Molecular weight | Type of amine | Flocculation value |
|---|---|---|---|
| d-Amphetamine sulfate | 368.5 | Primary | 10 |
| Chlorpromazine HCl | 355.3 | Tertiary | 10 |
| Atropine sulfate | 694.9 | Tertiary | 10 |
| Homatropine methyl bromide | 370.3 | Quaternary ammonium | 20 |
| Ephedrine HCl | 201.7 | Secondary | 20–25 |
| Phenylephrine HCl | 203.7 | Tertiary | 40–50 |
| Morphine sulfate | 758.9 | Tertiary | 10–15 |
| Dihydrocodeinone bitartrate | 494.5 | Tertiary | 20 |
| Methapyrilene HCl | 297.9 | Tertiary | 10 |
| Pyrilamine maleate | 401.5 | Tertiary | 10 |
| Chlorpheniramine maleate | 390.9 | Tertiary | 10 |

*Source*: From Ref. 19.

Raising the pH of the polymer emulsion improved the stability of the polymer against electrolyte-induced flocculation by increasing the hydrophilicity and thus the solvation of the polymer. Decreasing the pH of the polymer emulsion had the opposite effect, increasing the hydrophobicity of the polymer particles and making them more prone to flocculating in the presence of methapyrilene HCl. Goodman and Banker (19) theorized the cause of flocculation to be due to the added electrolyte (methapyrilene HCl) decreasing the thickness of the diffuse ionic layer between polymer particles in the latex emulsion. Analyses of the drug–polymer precipitate indicated that the drug was still in its chloride salt form. The authors concluded that the drug did not chemically interact with the polymer by forming an ionic bond, and that the interaction was therefore due to the ability of the polymeric particles to enclose or spatially surround the drug molecules. This interaction phenomenon resulted in the formation of precipitates that, when pressed into tablets, yielded suitable sustained-release properties and reduced toxicity when tested in animal models. In another study, Rhodes et al. demonstrated that entrapment and flocculation of an acrylic copolymer dispersion can also be influenced by drug salt type (20). In this study, carboxylic acid anion salts were found to facilitate and enhance the amount of drug (chlorpheniramine) bound or entrapped by the polymer for sustained-release action.

Bruce et al. observed chlorpheniramine maleate to flocculate Eudragit L 30 D-55 dispersions (21). This interaction was theorized to be responsible for poor film formation and premature drug release from the enteric-coated CPM pellets in acidic media. Additional weight gain of the enteric polymer on the CPM pellets was required to delay drug release in acidic media. Adsorption isotherms were used to study the drug–polymer interaction by plotting the log of the amount of drug adsorbed per unit mass adsorbent as a function of log CPM concentration remaining in solution. A linear relationship was observed that best correlated with the Freundlich model, indicating that adsorption of CPM to Eudragit L 30 D-55 takes place in multiple layers rather than by a specific chemical interaction between the drug and the polymer. FT-IR scans of the drug and polymer precipitate and physical mixture were identical, verification that no specific chemical bonding occurred between the drug and polymer system. The interaction between drug and polymer was attributed to the change in the thickness of the diffuse ionic layer around the polymer particles by CPM and resultant entrapment of CPM in the polymer floccules.

The incompatibilities between the drug substances and the colloidal dispersions observed by these authors could affect the film-formation process and explain premature drug leakage and dose dumping from modified or sustained-release film-coated dosage forms. A flocculation interaction at the substrate polymer film interface can also occur during film application. A film may not form properly if the drug and polymer interact, as demonstrated by Bodemeier and Paeratakul (22). They were unable to prepare films from ethylcellulose pseudolatex (Aquacoat® and Surelease®) and Eudragit NE 30 D dispersions incorporating the drugs propanol HCl and CPM due to flocculation of the colloidal dispersions.

The authors postulated the flocculation was due to interaction of the cationic drug salts with the anionic surfactants (sodium lauryl sulfate or ammonium oleate) used to stabilize the polymer emulsion systems. This type of electrostatic interaction with the surfactant changed the thickness of the double layer stabilizing the dispersed polymer particles. To prove that the cationic drug salts interacted with the anionic surfactant, the authors prepared a plasticized ethylcellulose pseudolatex by replacing the anionic surfactants with the nonionic surfactant Pluronic P103. The same cationic drug salts were added to the newly processed polymeric dispersions (Pluronic P103 stabilizing the disperse system) and flocculation did not occur. As a result, films were successfully prepared.

## Interactions with Colloidal Dispersions Due to Bridging or Depletion Flocculation

Hydrophilic, water-soluble polymers such as hydroxypropyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC), and polyethylene glycol (PEG) are commonly used to increase or accelerate drug release from coatings or films prepared from water-insoluble polymers (23–26). During dissolution, the incorporated water-soluble polymer dissolves, allowing pores to form that can increase film permeability. Addition of these pore-forming polymers to polymeric colloidal dispersions must be done with caution and at appropriate concentrations to avoid flocculation. The added polymers can adsorb onto the surface of the polymer colloidal particles, and the chains of the adsorbed polymer extend into the aqueous media. This leads to two possible occurrences. First, the colloidal particles may

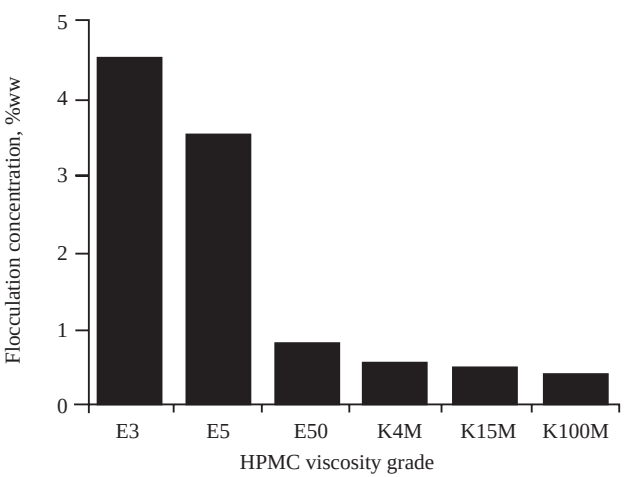


**Figure 7** Flocculation concentration (based on solids content of Aquacoat®) of different HPMC viscosity grades (Aquacoat, 15% w/w solids content). *Abbreviation*: HPMC, hydroxypropyl methyl cellulose. *Source*: From Ref. 28.

collide, and the interpenetrating polymer chains create a zone of osmotic pressure differential and diffusion of the medium into itself, driving particles apart. Second, polymer adsorption onto the colloidal particles may cause destabilization of the colloidal system by means of bridging flocculation. Bridging flocculation occurs when the adsorbed polymer chain extends to another particle and forms a bridge, typically occurring at low polymer concentrations. At higher polymer concentrations, the particles may become coated with the adsorbed polymer and repel one another, potentially restabilizing the polymeric colloidal dispersion (27). Flocculation may also occur with nonadsorbing polymers. Free nonadsorbing polymers added to the dispersion can reach a critical flocculation concentration and cause a phase separation through a sudden increase in the viscosity of the dispersion. This phenomenon is known as depletion flocculation.

Depletion flocculation was observed when HPMC was added as a film pore-forming agent to an ethylcellulose dispersion (Aquacoat) (28). The extent of flocculation was determined by measuring the sedimentation volume *F* of the flocculated dispersion. *F* is defined as the ratio of flocculated sediment to original dispersion volume. The addition of HPMC to the ethylcellulose dispersion flocculated the colloidal polymer particles above a critical HPMC concentration. The minimum HPMC concentration and viscosity grade necessary to cause flocculation are shown in Figure 7. Flocculation was observed to occur at ranges of 3% to 10% HPMC concentration (based on polymer content). The higher-molecular-weight grades of HPMC were more efficient flocculants. The solids content of the ethylcellulose dispersion influenced flocculation, and the HPMC concentration necessary to cause flocculation decreased with increasing solids content of the

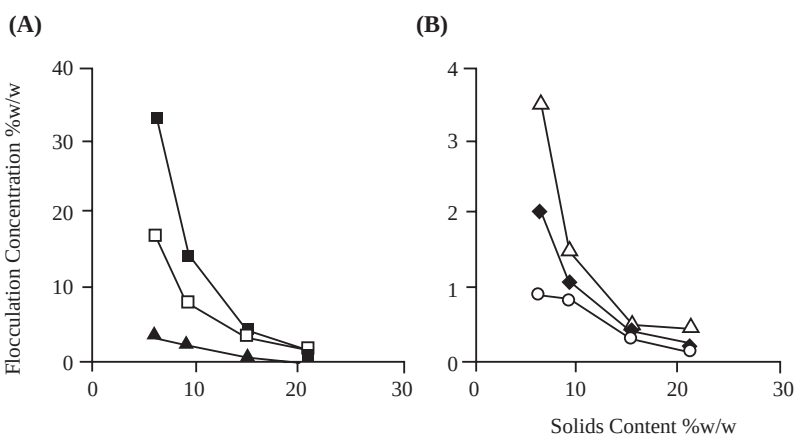


**Figure 8** Flocculation concentration (based on solids content of Aquacoat®) as a function of pseudolatex solids content with different HPMC viscosity grades: (**A**) (■) E3; open squares, E5; (▲) E50; (**B**) (△) K4M; (♦) K15M; (►) K100M. *Abbreviation*: HPMC, hydroxypropyl methyl cellulose. *Source*: From Ref. 28.

dispersion (Fig. 8). According to this study, low-molecular-weight pore-forming agents should be added to the colloidal dispersion and prepared at low solids concentration to prevent flocculation and interaction.

## PLASTICIZATION OF POLYMERIC FILMS BY DRUGS AND EXCIPIENTS

### Interactions Between Polymers and Plasticizers

Film-forming polymers typically require the addition of excipients or adjuvants in order to enhance the film-forming process and properties of the film. Plasticizers are added to impart flexibility and distensibility, increase toughness, improve strength, and reduce brittleness of the polymer. The plasticizer is usually a small compound with low-molecular-weight and functional groups that interact with the polymer to decrease the intermolecular cohesive forces between polymer chains, thereby increasing polymer segmental mobility and free volume. To be an effective plasticizer, the compound must be compatible and miscible with the polymer. The size, shape, and the nature of the functional groups will determine the functionality of the plasticizer. The degree of interaction between plasticizer and polymer will affect film mechanical properties, glass transition temperature ($T_g$), drug release, and permeability of the film. In general, the lower the molecular weight of the compound, the greater the plasticizing action it will exhibit on the polymer. Plasticizers commonly used in film coating applications can be divided into three groups: polyols consisting of propylene and polyethylene glycols, organic esters including the phthalate and citrate esters, and vegetable oils and glycerides such as acetylated monoglycerides.

Several methods may be employed to determine the compatibility or degree of interaction between a plasticizer and polymer material and include determination of the change in $T_g$ of the plasticized polymer, comparison of the plasticizer–polymer solubility parameters, measurement of the intrinsic viscosity of the polymer dissolved in the plasticizer, examination of a plasticized polymer film [either visually or by scanning electron microscopy (SEM) for transparency], and mechanical testing of the plasticized polymer film. These are typical methods employed to determine plasticizer–polymer compatibility; other methods can be found in the literature (29).

#### Glass Transition Temperature

The plasticizing effect of a compound on a polymer will result in a change in the polymer's $T_g$. This is the temperature where the polymer changes from a hard glassy material to a softer, rubbery state. A differential scanning calorimeter or modulated differential scanning calorimeter is employed to measure the $T_g$ of the polymer–plasticizer combination. A polymer will exhibit a lowering of $T_g$ when combined with a compatible plasticizer if sufficient interaction occurs to result in plasticization. A plasticizer with a high degree of interaction will cause a greater lowering in the glass transition temperature of the polymer than an equivalent

concentration of one having a poor interaction. If the $T_g$ of the polymer increases rather than decreases, the compound has an antiplasticizing effect on the polymer, due to immobilization of the polymer chains by hydrogen bonding, van der Waals attractions, and steric hindrance between the polymer and plasticizer, thereby increasing the stiffness of the polymer chains (30). Jackson and Caldwell explained the occurrence of antiplasticization as a result of a reduction in the free volume of the polymer, interaction between the polar groups of the polymer and the antiplasticizer, and a physical stiffening action due to the presence of rigid antiplasticizer molecules adjacent to the polar groups of the polymer (31).

### Solubility Parameter

The solubility parameter is calculated from the heat of mixing of two components and predicts component interaction and compatibility as demonstrated by Okhamafe and York from the relationship defined by Hildebrand and Scott (29) in Equation 1:

$$\Delta H = V_m [(\Delta E^1/V^1)^{1/2} - (\Delta E^2/V^2)^{1/2}]^2 \varphi_1 \cdot \varphi_2 \quad (1)$$

where $V_m$ is the total volume of the mixture, $\Delta E$ is the energy of vaporization, $V$ is the molar volume, and $\varphi$ is the volume fraction of the components. $\Delta E/V$ is generally referred to as the cohesive energy density and its square root as the solubility parameter $\delta$. Thus, the above equation can take the following form (Eq. 2):

$$\Delta H = V_m(\delta_1 - \delta_2)^2 \varphi_1 \cdot \varphi_2 \quad (2)$$

If $\delta_1$ and $\delta_2$ are equivalent, the heat of mixing is zero, indicating maximum interaction, solubility, and compatibility. Therefore, equivalency of polymer and plasticizer calculated solubility parameters dictates the compatibility and miscibility of the two compounds. Wang et al. calculated the solubility parameters for Eudragit RS 30 D and plasticizer combinations including acetyl tributyl citrate (ATBC), acetyl triethyl citrate (ATEC), diethyl phthalate (DEP), triacetin, and triethyl citrate (TEC), and found all these plasticizers to differ from the polymer by less than 6.3 $(J/cm^3)^{1/2}$, indicating miscibility and compatibility with Eudragit RS 30 D (32). Solubility parameters were used by Wu and McGinity to predict the compatibility and effectiveness of CPM, ibuprofen, and methylparaben and theophylline as plasticizers for the polymer Eudragit RS 30 D (33). Compounds whose solubility parameters differed from the polymer by 9.4 $(J/cm^3)^{1/2}$ demonstrated no plasticization effect on Eudragit RS 30 D.

### Intrinsic Viscosity

Polymer–plasticizer interactions can be studied by determining the intrinsic viscosity of the polymer dissolved in the plasticizer solution using the following relationship (Eq. 3):

$$\eta_{sp}/c = [\eta] + k'[\eta]^2 c \quad (3)$$

where $\eta_{sp}/c$ is reduced viscosity, $[\eta]$ is intrinsic viscosity, defined as the limit of the reduced viscosity ($\eta_{sp}/c$) as the concentration approaches zero, $c$ is the concentration of the solution, and $k'$ is an interaction constant, also called the Huggins constant (34).

A high intrinsic viscosity value indicates a greater degree of polymer–plasticizer interaction, reflecting the tendency of the polymer to uncoil and associate with the plasticizer solvent. Shah and Zatz measured intrinsic viscosity to assess the plasticizer–polymer interaction between cellulose ester polymers and dimethyl phthalate, diethyl phthalate, dibutyl phthalate, and glyceryl triacetate (35). The authors found that intrinsic viscosity dropped as the phthalate hydrocarbon chain length increased, but the results did not directly correspond with mechanical testing observations. Assessing polymer–plasticizer interactions by the intrinsic viscosity method has limitations, since not all polymers can be dissolved in a plasticizer. This method also assumes that the concentration of polymer in the system is low, and thus cannot accurately reflect the levels of polymer–polymer interaction in the system. Hutchings et al. found that differences for $\eta$ (intrinsic viscosity) and $k'$ (interaction constant) for various plasticizers evaluated did not reflect differences between the plasticizers with respect to their interactions with ethylcellulose. Determination of solubility parameters indicated a rank order with methanol > PEG > citrate esters and triacetin > diesters > oleic acid/oleyl alcohol, but no differences in intrinsic viscosity or interaction constant could be identified. This was attributed to the rigidity of the ethylcellulose molecules, where influences of the solvent molecules (plasticizer) on the polymer chains are less significant, and changes in intrinsic viscosity from one solvent system (plasticizer) to another are more subtle. Due to this, the authors suggested that evaluation of polymer–plasticizer interactions via intrinsic viscosity and interaction constant is not an ideal method for determining plasticizer suitability for film-coating additives (36).

## Mechanical Properties

Interactions between plasticizer molecules and polymer molecules have an effect on the mechanical properties of the polymer film. An ideal film should be hard and tough without being brittle. Mechanically, this translates into having a high tensile strength and large elongation or strain before breaking. These properties can be quantified through tensile testing and plotting the resulting stress ($\sigma$) versus strain ($\varepsilon$) curve. The tensile strength, also referred to as ultimate tensile strength, is the maximum tensile stress sustained by a test specimen during a tensile test. The area under the stress–strain curve is a measure of the material's toughness (37).

Hutchings et al. illustrated the relationship between plasticizer functional groups and molecular structure and free film mechanical properties (38). The authors prepared free films with 10 different plasticizers from the following classifications: branched esters, di-acid esters, and fatty acids/alcohols. Stress, strain, and elastic modulus were plotted as a function of plasticizer type or class and concentration. A rank order for influence on mechanical properties can be seen

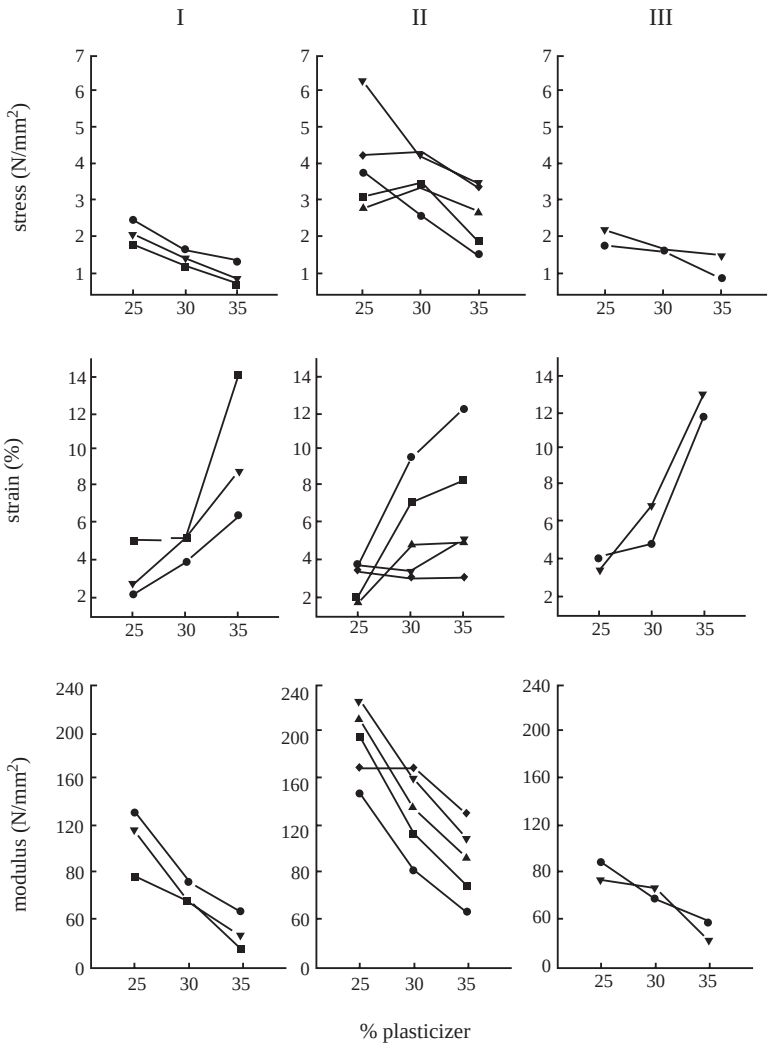


**Figure 9** Effect of plasticizer type and amount on free film stress (N/mm$^2$), strain (%), and modulus (N/mm$^2$). (**I**) Di-acid esters: (●) DBS; (▼) DBA; (■) DMS; (**II**) Branched esters: (●) TEC; (▼) ATEC; (■) TBC; (▲) ATBC; (◆) TRI; (**III**) fatty acid/alcohols: (●) OALC; (▼) OLAC. *Abbreviations*: TEC, triethyl citrate; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; DEP, diethyl phthalate; DBS, dibutyl sebacate; DBA, dibutyl adipate; DMS, dimethyl sebacate; TRI, triacetin; OALC, oleyl alcohol; OLAC, acid oleic. *Source*: From Ref. 38.

within each class (Fig. 9). In general, increasing the amount of plasticizer in the films lead to a reduction of free film modulus and stress values while strain at rupture values increased. Values obtained for stress for the di-acid esters, and the fatty acid/alcohol were generally lower than those obtained for citrate esters and triacetin. The authors attributed this to the long-chain molecular structure of the di-acid esters and fatty acid/alcohols. In the branched ester class, the plasticizers with hydroxyl groups, TEC and tributyl citrate (TBC), demonstrated the lowest modulus values as a result of hydrogen bonding interactions with the polymer. The esterified compounds ATEC, ATBC, and triacetin are unable to interact with the polymer as effectively.

Gutiérrez-Rocca and McGinity were also able to explain differences in mechanical properties of polymeric films by considering the chemical structure

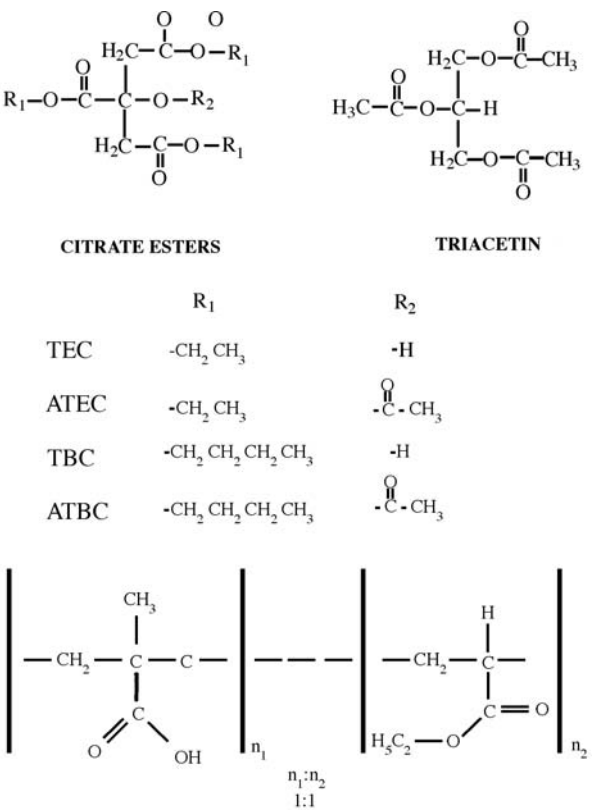


**Figure 10** Molecular structure of triacetin and the citrate ester plasticizers and structural characteristics of poly(methacrylic acid ethyl acrylate), commercially available as Eudragit® L 30 D and L 100–55. *Abbreviations*: TEC, triethyl citrate; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate. *Source*: From Ref. 39.

of the plasticizer (39). The plasticizers used in this study were TEC, ATEC, TBC, and ATBC incorporated in Eudragit L 100–55. All plasticizers lowered the glass transition temperature of the polymer with increasing concentrations except for TBC and ATBC, which plateaued at 10% w/w (based on dry polymer weight). TBC and ATBC are water-insoluble plasticizers that are poorly miscible with the polymer. All plasticizers added to the film resulted in a reduction of tensile strength. The water-soluble plasticizers resulted in a significant increase in percent elongation of the film. The elastic modulus (Young's modulus) continually decreased with increasing concentration of water-soluble plasticizers. There were no statistically significant changes in elastic modulus when greater than 10% concentration of the water-insoluble plasticizers were incorporated into the film. These results correlated with the findings for glass transition temperature. Eudragit L 100–55 contains carboxylic functional groups capable of interacting with the plasticizer molecules by hydrogen bonding, electrostatic interactions, and dispersion forces. The results of the mechanical and thermal testing can be explained by examining the chemical structures and functional groups of both the polymer and the plasticizers (Fig. 10). The smaller plasticizers triacetin and TEC have the greatest ability to interact with the polymer. In triacetin, the carbonyl oxygens are readily available to interact through hydrogen bonding with the carboxyl hydrogens of the copolymer. This is also true for TEC, but the presence of the ethyl group may reduce the accessibility of the carbonyl oxygen for hydrogen bonding. Side chains on the other compounds hinder the availability of the functional groups for bonding. The results of the study indicate that smaller water-soluble plasticizers have a higher affinity to diffuse into, and interact with, the polymer, increasing the molecular mobility of the polymer chains. These results are in agreement with the findings of Bodemeier and Paeratakul, who also examined the differences that water-soluble and water-insoluble plasticizers have on the mechanical properties of both dry and wet films (40). Dry Eudragit RS 30 D films plasticized with the water-soluble plasticizers TEC and triacetin had higher elongation and lower puncture strength, corresponding to a lower elastic modulus compared to the water-insoluble plasticizers. This indicated that the water-soluble plasticizers were more efficient plasticizers. Corresponding wet films were significantly more flexible than the dry films plasticized with the water-soluble plasticizers. However, a disadvantage in using water-soluble plasticizers is the tendency for the compounds to leach from the films (as determined amount of plasticizer remaining shown in Table 2), impacting the film's mechanical properties.

A compatible and efficient plasticizer will function to make a softer, tougher polymer, and will reduce brittleness. Using an indentation test, Alton and Abdul-Razzak observed that HPMC films plasticized with PEG 600, 1500, 4000, and 6000 became softer and more viscoelastic with increasing plasticizer content (41). Mechanical testing of the same films showed a reduction in tensile strength, an increase in elongation, and lowering of elastic modulus as the molecular weight of the PEG decreased (Fig. 11). The lower-molecular-weight PEG proved to be

**Table 2** Mechanical Properties of Dry and Wet Eudragit® RS 30 D Films Plasticized with Water-Soluble and Water-Insoluble Plasticizers (20% w/w) (Standard Deviation in Parentheses)

| Plasticizer (film thickness μm) | Puncture strength (MPa) | | Elongation (%) | | Plasticizer remaining (%) |
|---|---|---|---|---|---|
| | Dry | Wet | Dry | Wet | |
| TEC (309) | 1.99 (0.22) | 0.93 (0.05) | 142.8 (1.3) | 38.4 (4.6) | 56.29 (1.79) |
| Triacetin (302) | 1.82 (0.38) | 0.61 (0.07) | 120.9 (6.0) | 6.8 (0.6) | 35.92 (1.06) |
| ATBC (314) | 4.30 (0.09) | 1.11 (0.13) | 77.8 (7.6) | 85.2 (3.6) | 101.84 (1.67) |
| ATEC (323) | 4.01 (0.18) | 1.01 (0.02) | 86.9 (5.5) | 64.3 (8.5) | 90.38 (0.05) |
| DBP (327) | 3.18 (0.47) | 0.88 (0.19) | 93.2 (12.6) | 106.9 (9.2) | 99.95 (1.88) |
| DBS (324) | 2.37 (0.09) | 0.79 (0.04) | 91.8 (2.0) | 59.7 (3.6) | 88.34 (0.66) |
| DEP (324) | 2.47 (0.40) | 0.91 (0.03) | 91.1 (3.2) | 51.0 (3.8) | 95.27 (1.53) |
| TBC (319) | 2.37 (0.40) | 0.86 (0.03) | 113.5 (1.8) | 86.6 (3.4) | 97.79 (2.06) |

*Abbreviations*: TEC, triethyl citrate; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; DEP, diethyl phthalate; DBS, dibutyl sebacate; DBP, dibutyl phthalate.
*Source*: From Ref. 40.

the most efficient plasticizer and produced the best films. The authors used the gel theory to explain the interaction between plasticizer and polymers as a competition between a plasticizer, the polymer, and solvent (water) molecules for polymer active sites. According to this theory, there will be more of the lower molecular weight PEG molecules to compete for and interact with polymer active sites. The

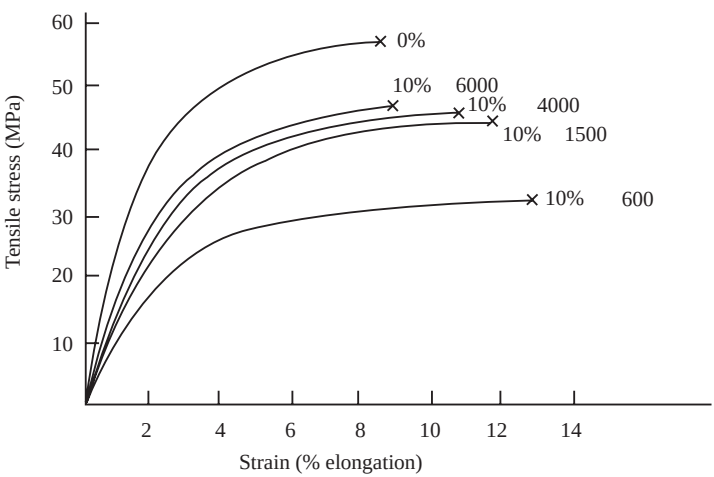


**Figure 11** Stress–strain curves for HPMC films containing 10% of different grades of polyethylene glycol. *Abbreviation*: HPMC, hydroxypropyl methyl cellulose. *Source*: From Ref. 41.

plasticizer thus reduces the number of active sites available for polymer-polymer contact and thereby reduces the rigidity of the polymer.

## Film Permeability/Dissolution

Addition of a plasticizer not only changes the mechanical properties of a film, but also changes the permeability, adhesive, and drug-release characteristics. Plasticization of films has been shown to increase permeability as well as the rate at which compounds are released. Typically, plasticizing agents added to aqueous colloidal polymeric dispersions lower the rate of drug release from the resultant film due to enhanced coalescence of colloidal polymer particles, decreased brittleness, and an increase in flexibility, toughness, and strength. These effects contribute to improved film performance (1).

Plasticizing agents can also have the opposite effect, however; they can increase the rate of drug release due to increased polymer segmental mobility during processing. After processing, the polymer chains remain in a loosened state upon cooling and are thus more permeable. Additionally, an excess of plasticizing agent incorporated into a film can migrate to the film surface, accelerating the rate of drug release due to picking and sticking or attraction of moisture (42,43). Drug-release rate can also be influenced by the solubility of the plasticizing agent (44). TEC, a water-soluble plasticizer, was incorporated into Eudragit RS films containing the drug propanolol HCl. Release rates of propanolol HCl were plotted versus TEC concentration in the films. The release rate constant was high at low

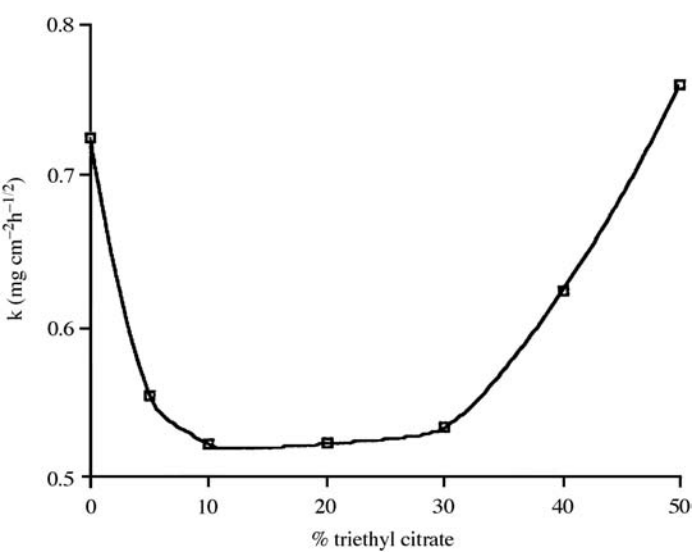


**Figure 12** Effect of triethyl citrate concentration on release rate constant of propranolol HCl (50 mg)—Eudragit® RS films. *Source*: From Ref. 44.

plasticizer content, dropped to a minimum plateau, and then increased again with higher plasticizer concentrations (Fig. 12). The observed increase in release rate with higher TEC concentrations was explained as leaching of the water-soluble plasticizer from the film. The high release rate constant at lower plasticizer levels was attributed to incomplete film formation and polymer coalescence due to insufficient plasticizer content. In contrast, the release rate of Eudragit L 30 D-55 was delayed in pH 5.5 media by the incorporation of high-molecular-weight PEG, a water-soluble plasticizer (45). The drug-release rate from the films decreased with the addition of PEG, as the molecular weight of the PEG increased. Films containing PEG 8000 had the slowest rate of release in pH 5.5 due to the formation of a film that was not permeable or soluble at a pH where Eudragit L 30 D-55 normally dissolves.

## NONTRADITIONAL PLASTICIZERS

Compounds other than those commonly recognized as plasticizers can produce plasticization effects in film coatings. In certain applications, excipients and drug compounds have the potential to act as nontraditional plasticizers. Drug compounds have been reported in the literature to function as polymer-plasticizing agents (33,46,47). This is important to keep in mind during the formulation development of a film-coated system. Drug compounds and excipients can migrate during the application of an aqueous film coating, depositing in the film and influencing the mechanical and drug-release properties. Lidocaine HCl, as an example, was found to function as a plasticizer in Eudragit E 100 for both extruded and solvent-cast films (46). The polymer $T_g$ was lowered and the elongation at failure was increased with the addition of lidocaine HCl either alone or in combination with the plasticizing agent TEC. Lidocaine was a more effective plasticizer in solution-cast films than extruded films due to better intermolecular mixing in solution than in the melt.

Other compounds that have been shown to act as film-coating plasticizers include citric acid and urea. Okhamafe and York incorporated citric acid and urea in HPMC and polyvinyl alcohol (PVA) films, and then used thermomechanical analysis (TMA) and DSC analysis to measure plasticizer effectiveness (48). The authors found the two compounds to be effective plasticizers for both polymers based on a significant lowering of the polymer $T_g$. Urea and citric acid were shown to be better plasticizers than PEG 1000 when the $T_g$ data were compared, indicating that additives with many hydrogen bonding groups strongly interact with the polymers to enhance segmental mobility.

Citric acid was also found to plasticize Eudragit L 30 D-55 films in another study by Bruce et al. (49). Citric acid reduced polymer $T_g$ by 26°C when incorporated at 10% w/w based on polymer dry weight. The $T_g$ of the films was reduced by an additional 15°C when 15% w/w (based on polymer dry weight) TEC was also incorporated into the film along with the citric acid (Table 3). This data helped explain an observed reduction in drug release from sodium valproate enteric-coated

**Table 3** Average Glass Transition Temperature Values of Eudragit® L 30 D-55–Cast Films Containing Varying Levels of Citric Acid ($n = 3$)

| Citric acid (% based on dry polymer) | Film $T_g$ (°C) | |
|---|---|---|
| | Without triethyl citrate | With 15% triethyl citrate |
| 0 | 110 ± 4.2 | 84 ± 1.0 |
| 5 | 112 ± 2.0 | 76 ± 2.2 |
| 10 | 84 ± 2.5 | 69 ± 1.8 |
| 20 | 88 ± 4.0 | 62 ± 2.8 |
| 40 | 80 ± 2.3 | 65 ± 1.3 |

*Source*: From Ref. 49.

pellets when citric acid was included in the pellet matrix. The citric acid not only lowered pellet microenvironmental pH to prevent premature ionization of the polymer and reduced pellet solubility by conversion of the sodium valproate to valproic acid, but also plasticized the film and lowered the film elastic modulus.

Methyl paraben, ibuprofen, chlorpheniramine maleate, and theophylline were investigated as nontraditional plasticizers for Eudragit RS 30 D by Wu and McGinity (33). All the compounds except theophylline resulted in a decrease in the polymer $T_g$ when incorporated into the film. Methyl paraben, CPM, and ibuprofen were also shown to decrease the Young's modulus of Eudragit RS 30 D when compression testing of coated beads was conducted using a Chatillon digital force gauge. A decrease in Young's modulus was also observed for films containing increasing concentrations of methyl paraben. These compounds are able to interact with the ammonium and ester groups of the polymer by hydrogen bonding and electrostatic forces, which weaken the interchain bonding within the polymer. This explanation was supported by X-ray diffraction analysis, which demonstrated that the Eudragit RS 30 D dispersion changed from a crystalline to an amorphous pattern when methylparaben, CPM, and ibuprofen were included in the film.

## ANTIPLASTICIZATION

Functional groups on a plasticizer that strongly interact with a polymer can result in an increase in the polymer $T_g$ or produce an antiplasticization effect (50). When a compound antiplasticizes a polymer, there is an opposite effect to plasticization on thermal and mechanical properties; $T_g$ and Young's modulus can both increase rather than decrease, and elongation decreases. This was the case when streptomycin sulfate was incorporated and cast into Eudragit E 30 D and Scopacryl D340 films. Streptomycin sulfate made the films brittle with decreased elongation at the failure (51). In the same study, Dittgen (51) also found that when plasticizers (such as glycol monoethyl ether, propylene glycol, glycerol, and ethylene glycol) were

added to films, the molecular weight of the plasticizers as well as the hydroxyl groups and position of hydroxyl groups available to interact with the polymers affected the plasticization of the films and the elongation at break. In general, the glycol with the lower-molecular-weight had the greatest plasticizing action. The monoethyl ether of glycol was the most effective plasticizer, demonstrating the greatest percent elongation on the films, which was attributed to the ability of the functional groups to interact with the polymer and reduce internal polymer–polymer interactions, thus increasing polymer molecular mobility. Alternatively, antiplasticization can occur from interactions between the plasticizer and polymer, resulting in a decrease in polymer mobility. Jackson and Caldwell concluded that antiplasticization is the result of a combination of factors that include the reduction of polymer free volume, interaction between the polar groups of the polymer and antiplasticizer, and physical stiffening resulting from the presence of the rigid antiplasticizer molecules adjacent to the polar groups of the polymer (31). Antiplasticization yields an increase in both tensile strength and Young's modulus. Guo found that antiplasticization occurred at low levels of plasticizer concentration (for triacetin and PEG) in cellulose acetate films (52). However, when the plasticizer content was increased above 5% w/w, plasticization occurred, resulting in a concurrent increase in film creep compliance with increas-

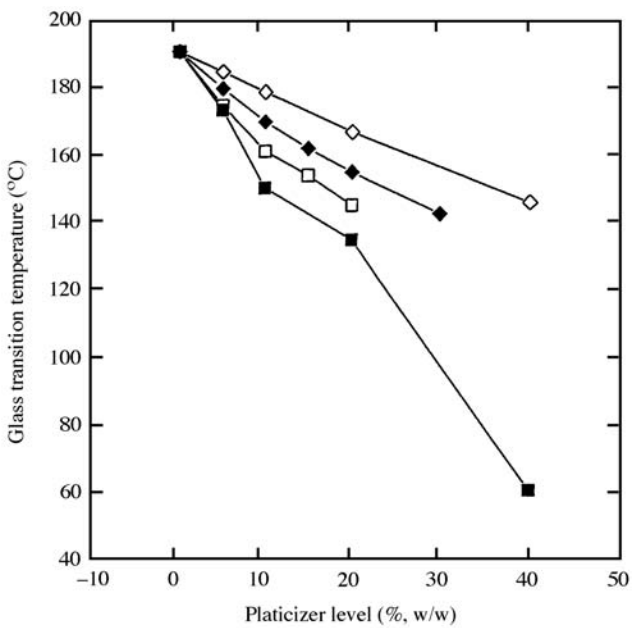


**Figure 13** The effects of plasticizers on the glass transition temperature of cellulose acetate–free films. (◇) PEG 8000; (◆) PEG 4000; (□) PEG 600; (■) triacetin. *Source*: From Ref. 52.

ing plasticizer concentration. A plasticizing effect was demonstrated when the $T_g$ of cellulose acetate films decreased with increasing PEG and triacetin content in the films (Fig. 13). Although a decrease in film $T_g$ at a 5% w/w concentration of plasticizer was observed, an associated drop in creep compliance at 37°C was also noted, which is indicative of antiplasticization. The lower-molecular-weight plasticizers demonstrated the greatest effect on reduction of $T_g$, similar to the findings of Dittgen for glycols. The relationship between the molecular weight and $T_g$ between a polymer and a second component (e.g., plasticizer) can be explained in terms of the Couchman and Karasz equation (Eq. 4) (53):

$$T_g = (T_{g1} \cdot M_1) + (T_{g2} \cdot M_2) \tag{4}$$

where $T_g$ is the glass transition temperature of the plasticized polymer, $T_{g1}$ and $T_{g2}$ are the glass transition temperatures of the respective pure components, and $M_1$ and $M_2$ are the mass fractions. According to this relationship, films that are plasticized with a higher-molecular-weight plasticizer should have a higher $T_g$ than films plasticized with a lower-molecular-weight compound.

Wang et al. observed a significant increase in the tensile strength of pellet formulations containing Eudragit RS 30 D plasticized with low levels of TEC, ATBC, ATEC, DEP, and triacetin (32). In this study, a plasticization threshold

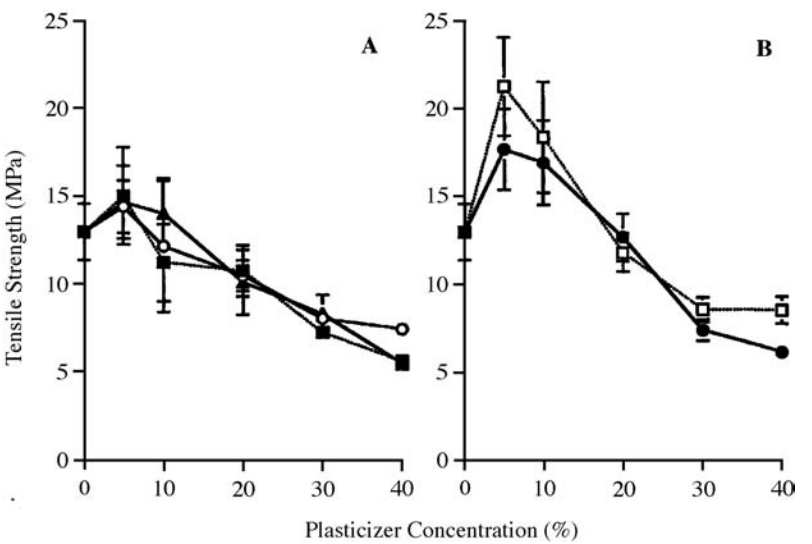


**Figure 14** Tensile strength of pellets as a function of plasticizer content: (**A**) (■) ATEC; (○) TEC; (▲) ATBC; (**B**) (●) DEP; (□) triacetin. Concentrations of plasticizers are based on the dry weight of Eudragit® RS polymer. *Abbreviations*: TEC, triethyl citrate; ATEC, acetyl triethyl citrate; ATBC, acetyl tributyl citrate; DEP, diethyl phthalate. *Source*: From Ref. 32.

was evident once a critical plasticizer concentration was reached, similar to the findings by Guo. At higher concentrations, a plasticization effect occurred, as demonstrated by plotting tensile strength and Young's modulus as a function of plasticizer concentration (Fig. 14). The glass transition temperature of the plasticized polymer demonstrated a continual decrease with plasticizer concentration.

## EFFECT OF INSOLUBLE EXCIPIENTS ON POLYMER PROPERTIES

### Insoluble Additives in Film Coatings

Insoluble additives included in aqueous film coatings can provide both color and photolytic protection, enhance appearance, and act as processing aids. Additives of this type commonly used in film coatings include pigments, surfactants, and antitack agents. The size, shape, concentration, and surface chemistry of insoluble additives can significantly influence polymer properties. The quality and surface chemistry of each insoluble additive must be considered for possible interactions.

Pigments used in film coatings include aluminum lakes of water-soluble dyes and opacifying agents such as titanium dioxide and iron oxides. These additives typically result in an increase in Young's modulus, with a corresponding decrease in tensile strength, leading to detrimental effects on the mechanical properties of the film (54–58). Interactions have been associated with the resulting size, shape, volume concentration, orientation, and chemical and physical bonding of the additive with the polymer. Moreover, insoluble additives may also influence water vapor permeability, crushing force, and dissolution of films (42,59).

Interactions between insoluble additives and polymer coating solutions can result in coagulation or agglomeration. In the case of polymethacrylate latexes, this may be due to polymer sensitivity to electrolytes and pH change, described previously in this chapter. The quality of the additive can influence the stability of the polymer, as in the case of low-quality colored lakes associated with small amounts of water-soluble dyes containing strong electrolytes. This phenomenon was observed when the adjuvant Sicopharm rot 30, a red iron oxide pigment, was added to Eudragit L 30 D-55 dispersion (59). The resulting Eudragit dispersion coagulated during the preparation of a coating suspension containing high pigment concentration. This interaction was caused by the high conductivity of the pigment due to adhering electrolytes (Table 4). To stabilize the dispersion, Sicopharm rot 30 was solvent extracted to remove adhering electrolytes, and sodium carboxymethylcellulose (NaCMC) was added to sterically stabilize the pigment particles. Compression of the electrical double layer between the polymer particles by the pigment disturbed the electrostatic balance of the polymer particles in the colloidal dispersion leading to polymer coagulation. Coagulation may also occur due to binding of fine pigment particles with a polymer-stabilizing emulsifier, or if surface charges associated with the pigment are opposite to those on the surface of a latex polymer. To avoid these interactions, electrolytes, acids, and bases are often added as solutions after first

**Table 4** Characterization of Pigments

| Pigment | Particle size (μm) | Morphology | Chemical composition | Density ($g/cm^3$) | Surface area ($m^2/cm^3$) | pH of suspension | Supernatant conductivity (μS) |
|---|---|---|---|---|---|---|---|
| Titanium dioxide Kronos A | <15 | Spherical | Titanium dioxide | 4.02 | 36.98 | 8.29 | 380 |
| Iriodin 110 | <15 | Platelets | Titanium dioxide—coated mica | 2.85 | 34.20 | 9.57 | 75.4 |
| Iriodin 100 | 10–60 | Platelets | Titanium dioxide—coated mica | 3.01 | 22.73 | 9.97 | 87.6 |
| Mica M | <15 | Platelets | Mica | 2.49 | 16.48 | 8.29 | 32.2 |
| Talkum IT extra | <15 | Platelets | Talc | 2.76 | 22.35 | 9.66 | 77.5 |
| Sicopharm rot 30 | <15 | Platelets | Hematite (red iron oxide) | 5.08 | 49.28 | 5.31 | 34.6[a] |
| EM 140662 | <15 | Platelets | Hematite-coated mica | 3.90 | 30.58 | 4.30 | 343 |
| Iriodin 502 | 10–60 | Platelets | Hematite-coated mica | 3.49 | 17.80 | 5.06 | 204 |

Density determined in a gas comparison pycnometer, surface area determined by Brunauer, Emmet and Teller (BET) method, pH of suspension measured with a pH-meter, and conductivity of the suspensions' supernatant determined using a conductometer.

[a]Soxhlet-extracted.

*Source*: From Ref. 59.

being diluted as much as possible. Good compatibility of latexes is generally found with talc, titanium dioxide, aluminum oxide, calcium phosphate, aluminum silicate, and ferrous oxides.

The degree of a polymer–filler interaction influences the internal stress of a polymer system. Additives lead to discontinuities in the polymer matrix network when adjacent polymer hydrogen bonds are broken. The bonding interaction occurring between the pigment and polymer, being a weaker interaction (usually dipole–dipole), constitutes an overall weakening in the structure and can result in a stress concentration. As filler concentration rises, internal stresses of the resultant films can also increase, leading to a fall in tensile strength, as explained by Okhamafe and York (56). Polymer–filler interactions such as adsorption of polymer onto the surface of solid particles decrease polymer chain mobility, often resulting in a rise in $T_g$, a decrease in the deformation capacity of the film, and a corresponding decrease in polymer elongation. The polymer–filler interaction can influence the permeability of films, since voids become more extensive as the degree of interaction increases (60,61). As the amount of filler increases, the critical pigment volume concentration (CPVC) will eventually be exceeded. CPVC is the concentration at which the amount of polymer is not sufficient to bind the additive particles (60). This concentration must be determined experimentally for each additive and polymer system. Furthermore, localized thermal stresses can develop due to the differences between the thermal expansion coefficients of the polymer and added solids, resulting in film cracking.

Porter studied the effect of titanium dioxide and lake additives on both free films and films applied to tablets by evaluating stress–strain relationships, diametrical crushing strength, and water vapor permeability (58). The tensile properties of HPMC films were found to decrease with increasing concentration of titanium dioxide and FD&C yellow no. 5 aluminum lake, or a combination of both. Similar values were obtained for films prepared with either additive or in combination. The author also performed diametrical crushing tests on film-coated tablets containing the same additives. The crushing strength of film-coated tablets decreased as pigment volume concentration increased. The reduction in tensile strength was explained by the interaction of pigment with the polymer particles. This yielded discontinuities in the polymer matrix and internal polymer stress concentrations. Internal stress tends to increase as hydrogen bonds between adjacent polymer particles are broken and the pigments interact with polymer molecules. An increase in pigment concentration in the HPMC films resulted in a significant net decrease in water vapor permeability, particularly when titanium dioxide was added. The pigments served as a barrier to moisture diffusing through the film. However, when the concentration of titanium dioxide was raised above 10%, the permeability of the film increased. At higher concentrations (CPVC), the polymer cannot bind the pigment particles together, allowing pores to form in the film.

Pigments may differ significantly in their shapes and sizes depending on the manufacturer. Particle morphology can have a greater influence than surface chemistry on film properties. Morphology influences particle packing, orientation,

and interaction with a polymer, as well as moisture and media penetration through a film. Maul and Schmidt compared the effect of pigment morphologies (platelets, spheres, and needles) on the drug-release properties of Eudragit L 30 D films (59). The authors found that platelet-shaped pigments reduced drug release from enteric-coated pellets regardless of the surface activity or chemical constitution of the additives. For example, titanium dioxide platelets demonstrated more of a sustained release effect than titanium dioxide spheres or iron oxide needles when incorporated into film coatings applied to pellets. Although a difference in surface polarity of the compared pigments existed, the shape of the pigments played the most influential role on drug release properties of the films. The titanium dioxide spheres and the iron oxide needles were observed to form aggregates less than 1 μ in size within the films, and acted to wick-in the dissolution medium leading to faster drug release. When drug release was compared from film coated pellets containing various pigments of comparable shape and size having chemically different constitution, in all cases the platelet-shaped pigments reduced drug release. In a study by Gibson et al., particle shape was responsible for a greater increase in the internal stress and Young's modulus of HPMC films (62). This was also observed by Okhamafe and York (56) supporting the theory that particle shape rather than chemistry has a greater influence on drug release rate and film permeability. Additional discussions of the influence of insoluble excipients on the properties of film coatings can be found in the literature (63).

## SUBSTRATE EFFECTS ON POLYMER FILM FUNCTIONALITY

During aqueous film coating, highly water-soluble drug substances can dissolve or migrate in the aqueous dispersion and deposit in the coating layer. Changes in film permeability brought on by an interaction between the drug and polymer may result, producing a poorly formed film. Excessive plasticization of the film can also occur, leading to premature dissolution of the drug through the polymer film due to formation of channels or pores, or premature ionization of an enteric polymer. Migration and deposition of the drug substance in the film coating could occur due to the affinity of the drug to the polymer or drug solubility in the polymer. In one example, Bodemeier and Paeratukul exposed CPM and ibuprofen beads coated with ethylcellulose to thermal treatment. The treatment led to a retardation of drug release for the highly water-soluble CPM, as compared to an increase in release of the ibuprofen compound (64). Typically, the compound with the greater water solubility migrates into the film. In this case, release was enhanced due to migration of the poorly water-soluble drug substance (ibuprofen) into the film. This study showed that ibuprofen had a greater affinity for and solubility in the ethylcellulose polymer than CPM. Crystals of ibuprofen were observed in the film surface, confirming that drug migration had occurred. In another study by the same authors, crystals of propranolol HCl were observed in propranolol HCl–Eudragit NE films. Drug release from the film increased with increasing drug loading due to release of propranolol HCl through fluid-filled pores in the

film. Permeability was enhanced due to pores or voids created by dissolution of drug crystals that migrated and dispersed throughout the film (65).

Drug substances in a substrate can interact with polymer or ionic surfactants that stabilize a coating, resulting in agglomeration of polymer particles as the coating is deposited on the substrate surface. As discussed earlier in this chapter, anionic surfactants used to stabilize colloidal dispersions (e.g., Aquacoat, an ethylcellulose dispersion) can react with ionic salts of drug substances. If the substrate is a strong electrolyte or ionic salt, and is also very water soluble or hydrophilic, the substrate can wick away water needed to power the film coalescence. This will result in a discontinuous film and require greater amounts of polymer coating application to prevent film failure during dissolution. In addition, highly water-soluble substrates deposited in films during application, prematurely release drug through water-filled channels in the coating and can increase the internal osmotic pressure of the film (66). This can result in undesirable osmotic pumping of drug through the membrane.

## SUBSTRATE PH EFFECTS ON ENTERIC POLYMER FUNCTIONALITY

Alkaline substrates can prematurely ionize enteric polymer coatings as water and media penetrate into the substrate core. Several studies have documented the effect of acidic and alkaline substrates and the associated microenvironmental pH on release properties of enteric film coatings (21,67–71). Dangel et al. conducted a series of studies to determine the effect of drug acidity or alkalinity on the enteric polymer dispersion Kollicoat MAE 30 DP (67,68). To study this effect, the authors determined differences in the weight increase of tablets and pellets containing acetyl salicylic acid, indomethacin, and diclofenac sodium exposed to 0.1N HCl for two hours. The drug-release profiles of tablets and pellets in phosphate-buffered media were examined. Acid resistance was improved when an acidic drug such as acetyl salicylic acid or indomethacin comprised the tablet or pellet core. The improvement in acid resistance is in contrast to earlier work by the same authors where a more neutral compound, caffeine, was shown to have poorer acid resistance. When the release of indomethacin and diclofenac sodium pellets and tablets was compared in simulated intestinal fluid, release from the substrates containing diclofenac sodium occurred much more rapidly. The authors attributed the higher release and the lower acid resistance of the pellets and tablet cores to the deprotonation of the film former by the alkaline drug. Increasing the thickness of the enteric film coating from 3 to 4 mg/cm$^2$ improved the acid resistance of both the pellets and the tablets containing diclofenac sodium. The weight increase observed during the acid resistance test as a result of gastric fluid (0.1N HCl) absorption or ingress was greater for pellets containing diclofenac sodium than for the tablets. This was attributed to the greater surface area of the pellets. Upon analysis, the amount of diclofenac sodium released into the acidic media was found to be relatively low, a finding attributed to the low solubility of this drug in acid.

Ozturk et al. modeled the release kinetics from enteric-coated dosage forms in buffered media (70). This model predicted that tablet core pH would influ-

ence the pH profile in the coating layer, thereby affecting the dissolution rate of the polymer. The authors explained that dissolution for enteric-coated dosage forms may be modified by interaction of the polymer with drug and excipients in the core. The model was tested with three sample groups of polyvinyl acetate phthalate (PVAP) enteric-coated tablets to investigate the effect of the core pH on the enteric coating dissolution time. The enteric-coated tablets contained aspirin to obtain an acid core, citrate salts to maintain a core pH of 6.5, and a placebo control. According to this model, the presence of an acidic drug in the core formulation was predicted to lower the pH in the coating layer relative to that of the bulk dissolution media. Near the tablet surface (tablet/polymer interface), the $H^+$ concentration should be higher, suppressing the ionization of the polymer. At the polymer/boundary layer (polymer/dissolution media layer) interface, $H^+$ concentration decreases and ionization of the polymer proceeds, leading to an eventual increase in dissolution of the drug. A high surface pH would ionize the enteric polymer, leading to even faster dissolution rates of the tablet and drug. Tablets containing placebo and citrate salts had faster disintegration rates, consistent with model predictions. These data also explain the findings of Dressman and Amidon,

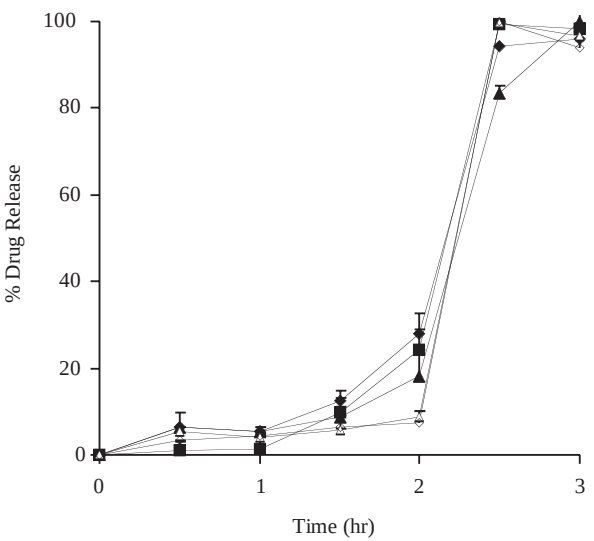


**Figure 15** Influence of pellet composition on drug-release properties of pellets comprised of 10% w/w CPM and varying levels of Avicel®, Emcompress®, or citric acid and coated with 10% weight gain Eudragit® L 30 D-55: (◆) formulation C, 55% Emcompress; (■) formulation A, 47% Avicel and 40% lactose; (▲) formulation B, 87% Avicel; (△) formulation D, 20% citric acid; (◇) formulation E, 40% citric acid. Dissolution media consisting of 0.1N HCl, pH 1.2 from zero to two hours, and 0.05M phosphate buffer from two to three hours, 37°C, 100 rpm ($n = 3$). *Abbreviation*: CPM, chlorpheniramine maleate. *Source*: From Ref. 21.

who reported a significant effect on the disintegration times of enteric-coated tablets administered to dogs when tablet core pH was varied (71). In their studies, mean disintegration times were greater for tablets with a core pH of 5 than for tablets with a core pH of 3 or 4. These data suggest that lower tablet microenvironmental pH delayed the dissolution of the enteric polymer.

Delayed dissolution in buffered media resulting from incorporation of an acid into a tablet core was also reported by Crotts et al., evidence that acidic tablet or pellet cores suppress ionization of enteric polymer functional groups (69). Doherty and York theorized that the pH of the diffusion layer at the surface of a dosage form resembles that of a saturated solution of drug and excipients in the dissolution media and represents the microenvironmental pH of the system (72). Doherty and York were able to actually measure the microenvironmental pH and surface pH using a micro-pH probe. In this study, they found an excellent correlation between the saturated solution pH and the measured surface pH during dissolution for a pure frusemide compact, further supporting the theory that acidic or basic drugs can influence the ionization and release of enteric polymers.

Pellet core pH was also shown to correlate with the release rate for CPM enteric-coated pellets in studies performed by Bruce et al. (21). Pellets comprised of 10% w/w CPM and 55% w/w Emcompress® released 27% w/w CPM in acidic media after two hours, whereas formulations comprised of the same level of CPM

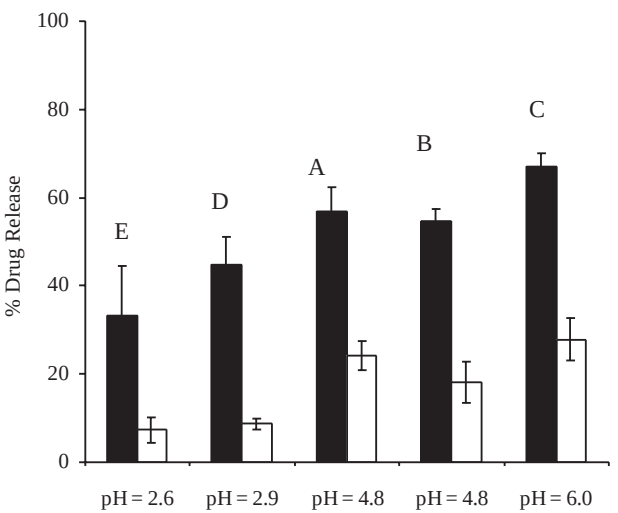


**Figure 16** Comparison of drug-release properties of enteric-coated pellet formulations (A to E) after two hours in 0.1N HCl, pH 1.2, as a function of uncoated pellet core pH: (■) pellets coated with 7% weight gain Eudragit® L 30 D-55; (□) pellets coated with 10% weight gain Eudragit L 30 D-55. Dissolution conditions: 2 hr, 750 mL 0.1N HCl, 37°C, 100 rpm ($n = 3$). *Source*: From Ref. 21.

and 20% w/w or 40% w/w citric acid passed the enteric test with less than 10% w/w CPM release under the same conditions (Fig. 15). The pellets were coated with a 10% weight gain of Eudragit L 30 D-55. Pellet pH was measured by grinding a sample of pellets, combining them with water, and measuring the pH of the resultant slurry. A trend of increasing drug release with increasing pellet pH was observed (Fig. 16). This finding supports the theory that an increase in pellet substrate microenvironmental pH (in this case, using 55% w/w Emcompress, dibasic calcium phosphate) can potentially lead to the ionization of an enteric polymer coating, resulting in premature drug release.

## PREVENTING DRUG–POLYMER EXCIPIENT–POLYMER INTERACTIONS

### Subcoating to Prevent Interactions

The most widely used method to prevent drug–polymer interactions is by the application of a seal coat or subcoat between the film-forming polymer and the substrate. The subcoat is typically a 2% to 3% weight gain of HPMC or some other nonfunctional or soluble polymer. A subcoat seals off the substrate from the functional polymer coating to prevent commingling. A subcoat may also be applied to prevent migration of a drug substance through the film of a functional polymer coating.

Yang and Ghebre-Sellassie used X-ray microprobe analysis of the cross-section of a diphenhydramine pellet core coated with Aquacoat to visually see the migration of drug into the film coating layer (73). Chlorine atoms of the incorporated HCl salt were used as a probe to monitor drug distribution into the film. Samples were bombarded with an electron beam, producing X-ray emissions specific to chlorine. The resulting emissions were detected by an X-ray spectrometer. At lower coating bed temperatures, migration of drug into the film coating was enhanced. Applying a HPC subcoat prior to coating the pellets with Aquacoat limited drug migration into the film layer. This effect can be seen in Figure 17B SEM photomicrograph and X-ray dot maps as a sharply defined boundary layer between the pellet core and the film layer. The release-rate constants calculated for pellets coated with Aquacoat at various coating temperatures were lowest when a subcoat was applied (Tables 5 and 6).

Subcoats can also act as a barrier between the substrate and functional polymer. A well-known use of subcoating as a barrier is described in patent 4,786,505, or the "505" patent by Astra for the product Prilosec (74). This patent claimed an oral pharmaceutical preparation comprising: (*i*) a core region of omeprazole plus an alkaline-reacting compound, alkaline omeprazole salt, and/or combinations thereof; (*ii*) an inert rapidly soluble subcoat; and (*iii*) an outer layer deposited onto the subcoat comprising an enteric coating. The subcoat was necessary to prevent the acid labile omeprazole from contacting acidic functional groups of the enteric polymer, thereby preventing a detrimental interaction.

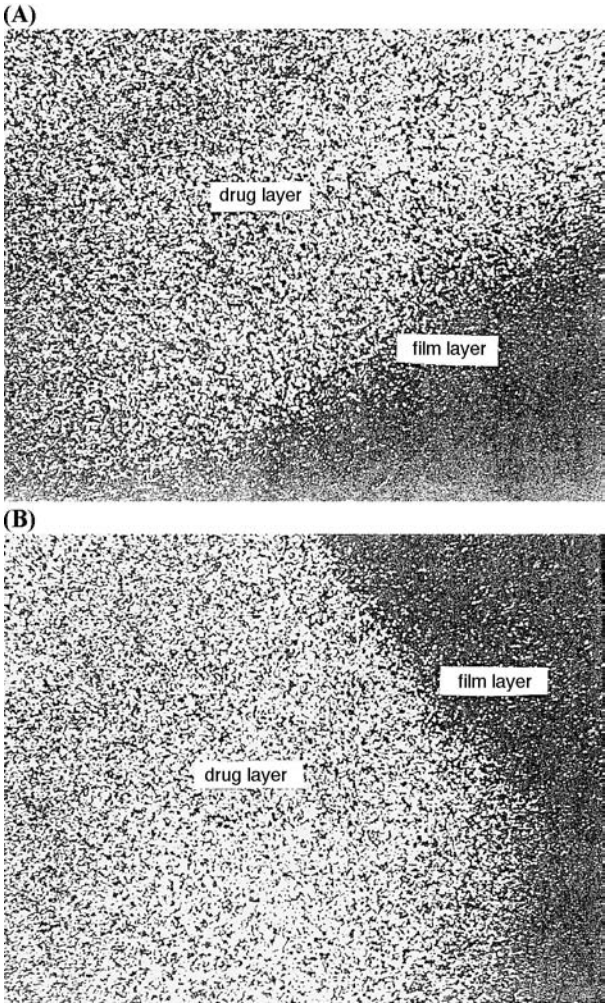


**Figure 17** (**A**) SEM photomicrograph of a cross section of a pellet coated with Aquacoat® at 22°C and the corresponding dot map. (**B**) SEM photomicrograph of a cross section of a pellet subcoated with HPC and subsequently coated with Aquacoat at 22°C and the corresponding dot map. *Abbreviations*: SEM, scanning electron microscope; HPC, hydroxy propyl cellulose. *Source*: From Ref. 73.

In addition to acting as a barrier, subcoats may also increase the diffusional path length that drug substances must travel for dissolution to occur. Less of the functional polymeric coating may therefore be required, providing a cost savings in manufacturing. Several authors have reported improved acid resistance and the need for less enteric polymer to pass either the enteric dissolution or disintegra-

**Table 5** Release Rate Constant for Pellets Coated with Aquacoat® at Different Bed Temperatures

| Bed temperatures (°C) | $k_1$ ($hr^{-1}$)[a] | $k_2$ ($hr^{-1}$)[b] |
|---|---|---|
| 22 | 1.045 | |
| 25 | 0.402 | 0.201 |
| 30 | 0.300 | 0.109 |
| 35 | 0.262 | 0.101 |
| 40 | 0.312 | 0.123 |
| 45 | 0.335 | 0.264 |
| 50 | 0.450 | 0.381 |

[a]First-order rate constant for the initial phase of dissolution (up to 2 hr).
[b]First-order rate constant for the final phase of dissolution (after 2 hr).
*Source*: From Ref. 73.

tion test when a subcoat was applied to a tablet or pellet core (21,48,69,75–77). The subcoat in these cases acted as a barrier to prevent an interaction between the substrate and enteric polymer, or increased the diffusional path length of the drug.

When selecting a suitable subcoat, the solubility of the substrate or core, properties of the polymeric subcoat, and required coating weight gain must all be considered in order to select the appropriate subcoat polymer to apply for the appropriate release kinetics. The effect of core solubility on drug release from enteric-coated pellets was demonstrated in studies performed by Bruce et al. (21). A weight gain of only 7% w/w Eudragit L 30 D-55 was required for pellets containing 30% w/w theophylline (a poorly water-soluble compound) to pass the enteric test. In contrast, pellets containing 10% w/w CPM (a highly water-soluble compound) required greater than 10% w/w weight gain of the same enteric polymer. The

**Table 6** Release Rate Constants for Subcoated Pellets Subsequently Coated with Aquacoat®

| Bed temperatures (°C) | $k_1$ ($hr^{-1}$)[a] | $k_2$ ($hr^{-1}$)[b] |
|---|---|---|
| 22 | 0.536 | – |
| 25 | 0.308 | 0.185 |
| 30 | 0.295 | 0.104 |
| 35 | 0.261 | 0.136 |
| 40 | 0.267 | 0.103 |
| 45 | 0.290 | 0.217 |
| 50 | 0.418 | 0.301 |

[a]First-order rate constant for the initial phase of dissolution (up to 2 hr).
[b]First-order rate constant for the final phase of dissolution (after 2 hr).
*Source*: From Ref. 73.

authors experimented with three polymeric subcoats: Eudragit RD 100, an immediate release coating; Eudragit RS 30 D, a sustained-release polymer; and Opadry AMB, a moisture barrier consisting of an immediate release polymer. All subcoats were applied to pellets at a 3% w/w polymer weight gain followed by a 7% w/w polymer weight gain of Eudragit L 30 D-55. None of the subcoated pellets passed the enteric test at this low level of enteric coating; however, drug-release rates were found to correlate with both the wettability or contact angle and the water vapor transmission rate of the subcoat material. Subcoat materials with higher contact angle values and lower water vapor transmission rates (Eudragit RS 30 D and Opadry AMB) were more effective in delaying drug release in acid. Since CPM interacted with the Eudragit L 30 D-55 polymer, subcoating the pellet also prevented contact between drug and polymer, allowing a functional enteric film to form.

## SUMMARY

Interactions between drugs, excipients, and polymeric coatings may be favorable or unfavorable, as the examples and literature references given in this chapter have shown. Whether trying to avoid detrimental interactions or accomplish favorable interactions, it is necessary to consider the chemical make-up of a drug substance and any excipients used in the preparation of a substrate or film former. Considerations that should be made during formulation development include: overall solubility of a drug in water or dissolution media; drug solubility in the polymeric film former; functional and ionizable groups available in the drug and excipients that could interact with the polymer; acidity or alkalinity of the drug substance; and plasticizing effects that both drugs and excipients can have on a polymer. The application of a barrier subcoat has proven effective in preventing most unwanted interactions between drugs or excipients in a substrate and an overlying functional polymeric film.

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# 14

# Properties of Aqueous Pseudolatex Dispersions of Biodegradable Polymers

**Steven E. Frisbee**
*Biovail Technologies, Chantilly, Virginia, U.S.A.*
**Mark D. Coffin**
*GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
**James W. McGinity**
*College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*

## INTRODUCTION

The coating of dosage forms can be traced to ancient times; it evolved to large-scale pan coating using sugar and, finally, to the use of polymers for film coating (1). The application of polymeric films onto solid oral dosage forms was a major advance in drug delivery, because the coatings could modulate drug release as well as protect the drug from a surrounding environment. Traditionally, most polymer-based film coating has been done using solvated solutions of polymers. The acceptability of using organic solvents for pharmaceutical coating processes has been decreasing due to a variety of factors, including stricter emission limits, worker safety, and health issues.

The development and commercialization of aqueous dispersions of pharmaceutically acceptable polymers opened the way for the use of aqueous-based film coating for controlled-release drug products. However, the list of commercially available, pharmaceutically acceptable, pH-independent, hydrophobic polymers in an aqueously dispersed or redispersible powder form is surprisingly short. More importantly, none of these available aqueous-based products are biodegradable. As the delivery of new therapeutic entities becomes ever more challenging, novel

fabrication methodologies using aqueous-based biodegradable polymers will hold significant promise.

Currently, fabrication technologies using biodegradable polymers typically entail the use of organic solvents, heat, and pressure (2,3). Aqueous-based pharmaceutical processing using a biodegradable polymer would have application for macromolecules that require the maintenance of their aqueous conformational state, heat-sensitive drugs, or any drug requiring a degradable polymeric release mechanism. Conventional aqueous-based coating and granulating processes can thus be exploited to develop a wide variety of specialized products. These may include matrix or coated implants, tablets, and multiparticulates for human, veterinary, or agricultural use.

This chapter is a review of the properties of aqueous-based polymeric dispersions of biodegradable polymers for pharmaceutical applications. Although no commercial dispersions are currently available, it is hoped that pharmaceutical scientists may someday have such materials at their disposal for the development of the dosage forms of the future.

## AQUEOUS COATING TECHNOLOGIES

The process of film coating encompasses a variety of technologies. The most prevalent for the coating of pharmaceutical dosage forms is that of perforated pan coating, used primarily for the coating of compressed tablets. For aqueous-based coating processes in particular, high-volume air flow in the coating pan is required to provide sufficient evaporative capacity. Air suspension processing is another technology commonly used in this area. Coating, granulating, and drying operations can all be done in one air suspension unit. Coating of multiparticulates such as beads, granules, and powders is a particularly desirable capability of the air suspension technique. Advances in Wurster-based coating now allow the more rapid application of polymer from aqueous dispersions onto discrete particles below 100 μm, sometimes below 50 μm.

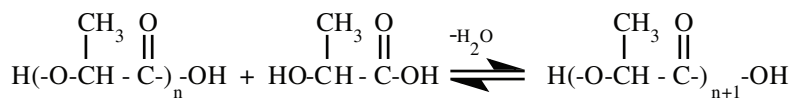
Granulation processes are most often used to improve flow and compression properties of powders for further processing into dosage forms. They can also be used for controlled-release drug development. By using hydrophobic polymers that retard drug release to bind the granule, compression forms a matrix that impedes drug release. A popular use of aqueous dispersions has been as binders for such granulations. While the methacrylic copolymers such as Eudragit® NE 30 D are the most commonly used aqueous dispersions, specialty polymers in pseudolatex form have also been investigated. Omelczuk and McGinity, for example, used a poly(DL-lactic acid) pseudolatex as a granulating binder in their investigations of matrix tablets containing polylactic acid (PLA) (4,5). As the delivery of new therapeutic entities becomes more challenging, novel fabrication methodologies using aqueous-based polymers will hold significant promise. The ability to use a biodegradable polymer such as poly(DL-lactide) from an aqueous-

based dispersion in conventional coating equipment may lead to the production of innovative dosage forms produced on a large scale for global distribution.

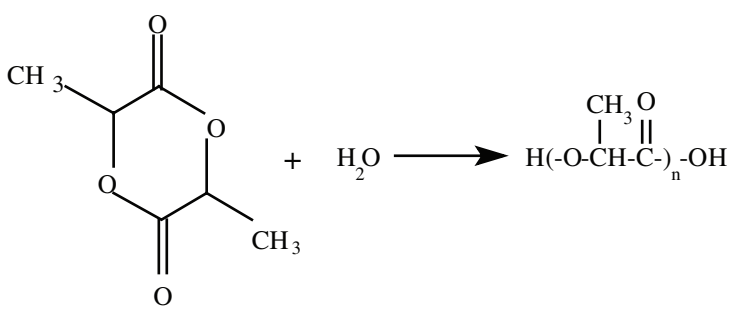
## BIODEGRADABLE POLYMERS USED IN AQUEOUS DISPERSIONS

The bioresorbable polyesters used in drug delivery applications are primarily derived from lactic or glycolic acids. PLA is a member of the group that can be generally named poly(α-hydroxy)acids. The PLAs are one of the most common degradable polymer types used in pharmaceutical drug delivery research and development. Lactic acid is a chiral compound and has two optically active isomers, dextro- and levo-rotatory enantiomers. All of the poly(α-hydroxy) acids use these forms of lactic acid as base monomers for polymerization. The racemic mixture of the isomers can be widely found in nature. Lactic acid is present widely in humans, principally as a by-product of carbohydrate metabolism under anaerobic conditions (6).

Polymers of lactic acid are generally produced using two different type of reactions: condensation and addition. Low-molecular-weight polyesters are produced by a condensation reaction. As a step-type reaction proceeds, the polymer shows a steady rise in molecular weight. The monomer disappears quickly as dimers, trimers, and then oligomers are formed. This method is characterized by a broad molecular weight distribution of the product at the end of the reaction. Limitations on what molecular weights can be achieved are controlled by the difficulty in maintaining dehydration, the requirement of exact starting stoichiometry (functional groups must be present in exactly equal amounts), and the purity of the starting materials (7). Maintaining the degree of dehydration necessary becomes the effective limitation to achieving molecular weights higher than 10,000 in weight average molecular weight (8).



High-molecular-weight polymers of PLA are best produced using addition polymerization. Cyclic dimers of lactic acid are used in the desired conformation (8). The reaction for polymerization from the cyclic diester is as follows:



Poly(DL-lactide) is hydrophobic and water insoluble. By virtue of its racemic form, it is amorphous, has no melting point, and has a glass transition temperature of around 57°C. The pure L form by contrast is crystalline, has a melting point, and is even more hydrophobic than the DL form. Due to its degradable nature, poly(lactic acid) and its copolymers have been considered as materials of the future that will replace the commonly used polymers of today, such as poly vinyl chloride and polystyrene (9).

## FABRICATION METHODS FOR BIODEGRADABLE PSEUDOLATEXES

The most common technique for fabrication of degradable pseudolatexes is based on solvating the polymer in a suitable solvent and forming an oil-in-water emulsion with the polymer solution as the internal phase. Through an evaporative process, the solvent is lost from the internal phase with agitation, and discrete nanospheres are precipitated out into the aqueous phase. Central to this method is the use of an emulsifying agent to stabilize the polymer solution droplets. The final dispersion will thus contain this emulsifier. An agent should be selected that will provide stabilization of the nanosphere after precipitation.

Some of the first investigations of pseudolatexes using poly(DL-lactic acid) were by Gurny et al., who studied controlled release of potent drugs from injectable latexes (10). They produced testosterone-loaded latexes using different surfactants and tested their tissue compatibility in rats, as well as the chemical stability of the dispersions.

A novel alternative method for the production of poly(DL-lactic acid) nanospheres was developed by Alléman et al. using a salting-out procedure (11). First a water-soluble polymer and a saturated electrolyte solution were used to form a gel (to become the external phase). PLA and drug dissolved in acetone were added and emulsified as the internal phase. The acetone was salted-out by the electrolyte, and thus the two-phase system was maintained. Once emulsified, water was added to allow diffusion of the acetone into the external phase, thus causing precipitation of the PLA and any drug as well.

## CHARACTERIZATION OF BIODEGRADABLE PSEUDOLATEXES

In the manufacture of a pseudolatex, the properties of nanosphere size and molecular weight distribution are the most important to characterize. The size of the polymeric nanosphere will determine the effectiveness of surfactants in stabilizing the particle, as well as for analysis of the influence of emulsification variables and processes in the manufacture of the pseudolatex. The molecular weight distribution is important from the standpoint of evaluating stability of the degradable polymer and surfactant system. Degradation of the polymeric components of a pseudolatex can be from chemical reaction, mechanical degradation, or a combination of the two. An accurate representation of changes in molecular weight can be performed by a combination of molecular weight average determination and analysis of the distribution itself.

## STABILIZATION OF POLY(DL-LACTIDE) PSEUDOLATEX DISPERSIONS

Nonionic surfactants have certain inherent advantages over ionic surfactants. Principally, while the presence of electrolytes in the emulsion can effect the nonionic types, mainly through cloud point changes and micellar properties, these effects are minor in comparison to the ionic types. In addition, and most importantly from a formulation standpoint, systemic variations in the polarity of the surfactant can be made by simply changing the length of the polyoxyethylene chain. Ionic emulsifiers are limited in this respect because variations in chain length are controlled by the solubility of the agent, and ionic head group changes cannot be performed systematically.

Poly(DL-lactide) pseudolatexes have been successfully stabilized using nonionic surfactants in research investigations. This is based on work published by Coffin and McGinity, who studied the influence of different classes and combinations of surfactants on the physical and chemical stability of poly(DL-lactide) pseudolatexes (12). Their results determined that the nonionic surfactant systems used in their investigation conferred very good physical and chemical stability on refrigerated dispersions of poly(DL-lactide) pseudolatex.

The weight average molecular weights ($M_w$) of PLA in unbuffered pseudolatexes as a function of time, storage temperature, and surfactant system are shown in Figure 1. It is apparent from the data that at 37°C, there was extensive degradation of PLA in all three formulations. At this temperature, the anionic

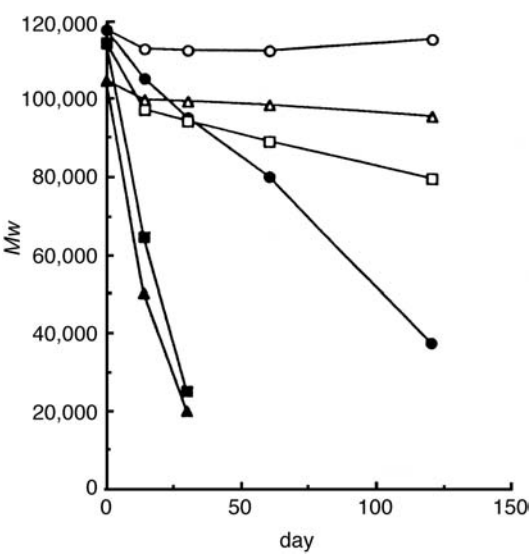



**Figure 1** Effect of the pseudolatex surfactant system and temperature on the degradation of PLA in unbuffered pseudolatexes: (○) nonionic, 5°C; (●) nonionic, 37°C; (△) potassium oleate, 5°C; (▲) potassium oleate, 37°C; (□) sodium dodecyl sulfate, 5°C; (■) sodium dodecyl sulfate, 37°C. *Abbreviation*: PLA, polylactic acid. *Source*: From Ref. 12.

surfactants facilitated the degradation of PLA, as evidenced by the $M_w$ of PLA decreasing to less than 30,000 after 28 days at 37°C in the potassium oleate and sodium dodecyl sulfate (SDS) formulations. In the nonionic formulation, the $M_w$ of PLA was nearly 100,000 after 28 days at 37°C. At 5°C, the rate of decrease in the $M_w$ of PLA was much slower in each dispersion. The nonionic formulation showed no appreciable drop in $M_w$ after four months at 5°C, indicating that PLA in the colloidal dispersion was chemically stable during this period of time. In the formulations containing the anionic surfactants, the $M_w$ of PLA dropped to less than 100,000 after four months at 5°C and suggested that hydrolysis of the PLA was occurring (12).

Representative chromatograms of PLA in the SDS formulation, from which some of the $M_w$ values in Figure 1 were calculated, are shown in Figure 2. These samples were taken from the initial dispersions, one-month samples at 37°C, and four-month samples at 5°C. These gel permeation chromatography (GPC) traces indicate that very substantial degradation had occurred in the 37°C sample and to a much lesser extent at 5°C. For comparison, it should be pointed out that the GPC traces of the 5°C, four-month samples for the nonionic formulations were virtually perfect layovers of their initials, which confirms the greater chemical stability of these dispersions. The chromatograms in Figure 2 also suggest that hydrolysis of the polymer chains occurs through a two-stage process. First, the formation of the shoulder and tail in the 5°C sample shows that the intermediate and low-molecular-weight chains are hydrolyzed first. The position of the shoulder correlates well with a previous report (13) that an $M_w$ of 60,000 represents a stable

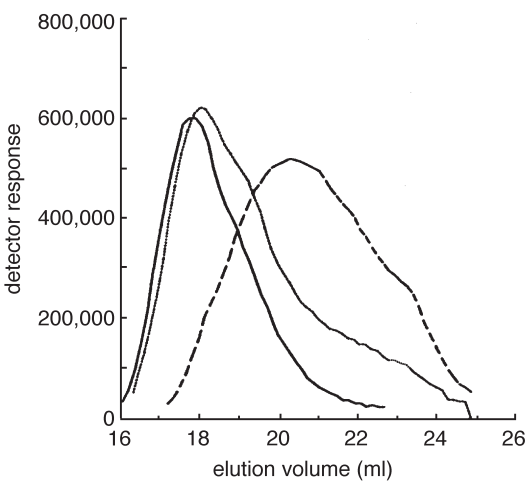



**Figure 2** GPC chromatograms of PLA in pseudolatexes prepared with sodium dodecyl sulfate: (—) initial; (·····) four months at 5°C; (- - -) one month at 37°C. *Abbreviations*: GPC, gel permeation chromatography; PLA, polylactic acid. *Source*: From Ref. 12.

fraction in PLA. This enhanced stability is due to some structural order in this portion of the polymer. The appearance of shoulders and tails in the chromatograms was followed by overall shifting of the traces, which resulted from the hydrolysis of the high-molecular-weight chains (12).

The results in Figure 3 reveal that the pH data for the PLA pseudolatex were in good agreement with the $M_w$ results obtained from GPC. The pH of the pseudolatex decreased rapidly at 37°C from pH 6.0 to pH 3.3 after 115 days. At 5°C, the pH of the PLA pseudolatex was essentially unchanged and confirmed the $M_w$ data, which showed that PLA was stable in a pseudolatex at these temperatures. At 25°C, the pH of the pseudolatex was unchanged for a period up to 115 days. It then began to drop and reached pH 4.0 after 250 days. This decrease in pH at 25°C can be ascribed to the generation of the low-molecular-weight polymer chains that do not appreciably influence the $M_w$ of the PLA. The drop in pH was a precursor to degradation that was detected by GPC analysis at the 350-day time point. The hydrolysis of PLA has been described as autocatalytic (13). The mechanism of autocatalysis may be due either to a decrease in the pH of the polymer's microenvironment or to plasticization of the bulk polymer by the low-molecular-weight chains produced by hydrolysis (14). In general, the pH of the PLA pseudolatex was a good measure of PLA stability, since as the polymer degraded, more carboxyl groups were created. For every hydrolysis reaction that occurred, an additional carboxyl group was produced (12).

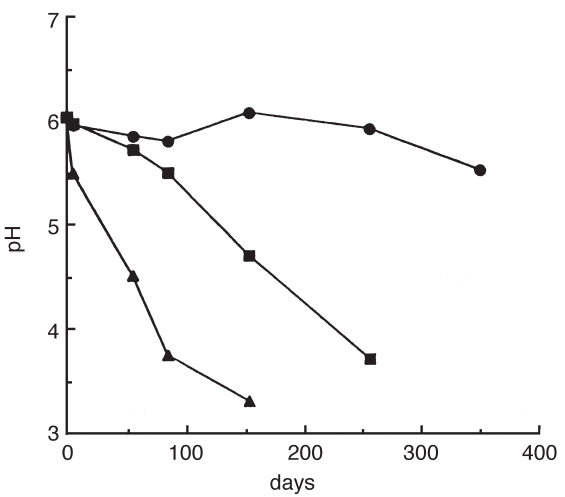



**Figure 3** Effect of temperature on the pH of unbuffered PLA pseudolatexes formulated with the nonionic surfactant system: (●) 5°C; (■) 25°C; (▲) 37°C. *Abbreviation*: PLA, polylactic acid. *Source*: From Ref. 12.

## MECHANOCHEMISTRY IN PSEUDOLATEX PRODUCTION

Polymers can undergo degradation in many different ways, by numerous different processes, including thermal, mechanical, ultrasonic, hydrolytic, chemical, biological, and radiological. In the investigation of the manufacture of poly(DL-lactide) pseudolatexes, degradative processes as a result of emulsification of the poly(DL-lactide) were of particular interest.

Mechanochemistry is a polymer field that studies reactions induced by stress. The major processes involving the effects of mechanochemistry of commercial polymers include comminution, mixing, and extrusion. Most of the research contributions in this field have been generated in the engineering arena, related to polymer processing. The increasing research and development of polymer-based specialized drug delivery devices in the pharmaceutical field requires that pharmaceutical scientists begin to consider the mechanochemistry that may be involved in their fabrication processes. Changes of polymer systems during fabrication may alter or even control many of the properties of that system. The emulsification of such polymers into nanodroplets for nanosphere precipitation is an integral part of their manufacture. The field of mechanochemistry specific to that of polymers in a solution or emulsified state is therefore of considerable interest for further investigation.

In the study of mechanisms influencing the mechanical degradation of polymers in a process such as the emulsification of pseudolatexes, a complicating factor arises from the conditions and equipment used in the process. The different techniques used may involve multiple effects of hydrodynamic shear, turbulence, solvent vaporization, and intense local adiabatic heating effects (15). In addition, for a pseudolatex emulsion, the polymer solution is the internal phase of an aqueous system. The interface between the phases has adsorbed onto it a polymeric surfactant or mixture of surfactants that is also potentially subject to degradation, which may compromise its surface activity.

The investigation and characterization of mechanical degradation of polymers in pharmaceutical processes is not common. The use of highly characterized, high-molecular-weight polymers in specialized drug delivery systems is a relatively recent area of research. More fundamental research into the influence of processing technologies on polymers used in drug delivery is needed. Some examples of investigations of mechanical degradation of polymers during pharmaceutical processing are given below.

Polymeric surfactants are often used in the preparation of biodegradable pseudolatexes. The effects of microfluidization on model A-B-A block copolymers were studied by Silvestri et al. They found that the surfactants underwent mechanical degradation when processed over four passes thermostated at 23°C. Increasing the length of the terminal A blocks increased the overall percentage decrease (16). Biodegradable polymers used in pseudolatex formation are often of relatively high-molecular-weight. Polymers of very high-molecular-weight are particularly susceptible to mechanical degradation. Gum tragacanth of average

molecular weight (840,000 g/mol) was subjected to four passes through a Microfluidizer® (Microfluidics Corp., Newton, Massachusetts) at three different processing pressures. Degradation was dependent on exposure time and interaction chamber pressure. Two distinct rate constants were required to describe degradation kinetics at each pressure studied. The initial processing rate constant was lower than the latter constant, suggesting either a change in mechanics of degradation or an approach to the latter first-order process (17).

## FILM FORMATION

The formation of films from aqueous dispersions of biodegradable polymers is a result of coalescence. Many different approaches are being taken to provide an understanding of the processes of ordering, deformation, and fusion that take place when discrete latex particles transform into a continuous film (18–20). Eckersley and Rudin reviewed many models proposed for latex film formation and advanced a physical model to fully describe the process of film formation (21). The model proposed that interfacial tension forces act along with capillary forces to cause film coalescence. Chevalier et al. (22) viewed this process as a succession of four steps: ordering, contact deformation, coalescence, and interparticle flow. In a pseudolatex system such as the poly(DL-lactide) pseudolatex, the steps will be quite similar. The surfactant molecules used to form and stabilize the nanospheres act to provide repulsive forces that allow ordering of the particles. When contact and deformation begins, the adsorbed surfactant will still cover the surface and serve to maintain separation. When coalescence does occur, the surfactant will orient together to form hydrophilic microregions as the dispersion inverts and the hydrophilic area becomes the internal phase. Excess surfactant of the aqueous phase will form larger domains or be exuded to the surface of the film with migrating water. Finally, the polymer cores themselves flow to form a continuous film. The surfactant at this stage may play a role as plasticizer, being distributed throughout the film during the polymer interdiffusion.

## ROLE OF SURFACTANTS IN BIODEGRADABLE PSEUDOLATEXES

The incorporation of agents such as surfactants is necessary for stabilization of the oil-in-water polymeric emulsion and for the consequent stabilization of the colloidal system. However, for consideration in film-forming drug delivery applications, poly(DL-lactide) pseudolatexes must not only be physically and chemically stable but must also be sufficiently hydrophobic and impermeable. Pseudolatexes formed from such formulations that contained high levels of surfactants were found not to control drug release or maintain film integrity in the hydrated state.

Surfactant selection criteria for a pseudolatex must importantly consider the effect of that surfactant on the important physical properties of the resultant nanosphere, including mean particle diameter, physical and chemical stability, and its

film properties. It has been established that the length of emulsion-processing time can influence the mean diameter of various solvent-evaporated dispersions, including ethylcellulose nanosuspensions (23) and poly(DL-lactide) pseudolatexes (24).

Manufacturing processes used for pharmaceutical emulsification apply varying degrees of shear, cavitative, and turbulent forces to the emulsion during processing. The degree of degradation will be a function of the polymer, solvent system, processing environment, and technique used. Nonionic surfactants used to stabilize the pseudolatex emulsion are polymeric in nature and will be subject to the forces of emulsification along with the poly(DL-lactide). The time that polymers spend under the influence of such forces is an important variable in the degradation process. Silvestri et al. (25) studied the effect of different processing times on degradation rates of three nonionic block copolymers in solution during microfluidization. They found a relationship between the length of the terminal blocks of a polymeric surfactant and the rate of degradation.

The hydrolytic stability of poly(DL-lactide) aqueous dispersions stabilized by different types of surfactants was extensively studied by Coffin and McGinity (12). Chemical and physical stability for the poly(DL-lactide) was achieved using refrigerated dispersions containing three levels of a three-component nonionic surfactant system. A triangular contour plot of the particle size regression equation, shown in Figure 4, demonstrates the effect of altering the percentages of the three surfactants in the blend. Pluronic® F68 and Myrj® 52-S were nearly equivalent, with the Pluronic F68 reducing the particle size slightly more at higher concentrations (26). Tween® 60 provided little contribution to the blend. Although a

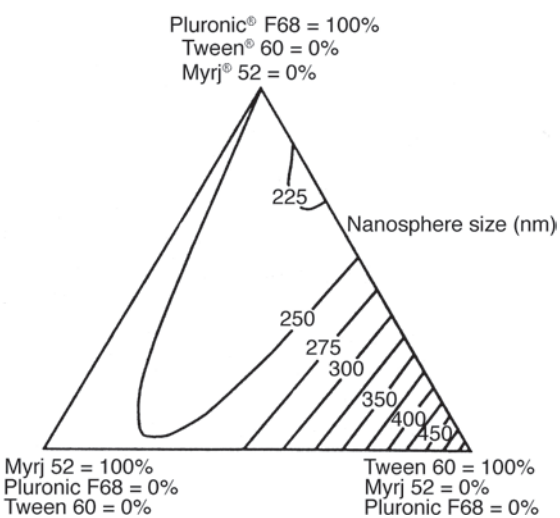



**Figure 4** Triangular contour diagram representing the effect of surfactant blending on the predicted mean diameter of poly(DL-lactide) nanospheres. *Source*: From Ref. 26.

small minimum was generated between the Pluronic F68 and Tween 60, no large synergistic effects resulted from the blending of these agents.

A combination of mechanisms was responsible for the comparative influences of these surfactants on nanosphere size. The process of pseudolatex formation involved stabilization of the interface, followed by dispersed phase evaporation to precipitate the polymer. The surfactant's chemical structure will determine not only its role in the stabilization of the emulsion interface but also its ability to adsorb to the surface of the polymer after precipitation occurs. In the case of a hydrophobic polymer such as poly(DL-lactide), polymer surfactant solubility will play a role. In addition, during the initial phase of emulsion stabilization, a partial solubilization of the surfactants in the dispersed phase will be required, and this will help determine its distribution at the phase interface (27). A correlation between a surfactant's solubility in blends of organic solvents and the particle size of resultant poly(DL-lactide) pseudolatexes has been established by Coffin (24).

The inclusion of surfactants in a polymeric drug delivery system will influence or even control the system's properties. There are numerous examples of such systems in the literature. One specific example that relates directly to this investigation is that of Park et al. (28), who prepared a series of degradable polymeric matrices by blending poly(L-lactic acid) with Pluronics. The selection of Pluronics with appropriate hydrophobicities was found to create miscibility with the amorphous regions of the poly(L-lactic acid). Films formed from these blends were found to have intact surface morphologies.

## EFFECT OF SURFACTANT/STABILIZER BLENDS ON PSEUDOLATEX NANOSPHERE SIZE

Poly vinyl alcohol (PVA) is an emulsifying agent that has been used successfully in the stabilization of biodegradable nanospheres (29). It has also been shown to increase the hydrophilicity of PLA nanoparticles for adsorption of poloxamer (Pluronic) polymers and poloxamine (30). It is believed that the OH functional groups on the PVA can interact with the ether oxygens in the polyethylene oxide segments of surfactants, leading to compatibility enhancement (31). The use of PVA in preparations intended for intravenous administration has been questioned, however (32). It has been generally employed as a pharmaceutical excipient for oral routes, including the polymeric component of erodible matrices (33). PVA was also found to be nearly as effective as the polymeric surfactant Pluronic F68 in reducing the size of the poly(DL-lactide) nanospheres produced by emulsification/solvent evaporation.

## INFLUENCE OF NONIONIC SURFACTANTS ON THE PHYSICAL AND THERMAL PROPERTIES OF POLY(DL-LACTIDE) PSEUDOLATEX FILMS

Three surfactants investigated by Frisbee and McGinity (26) for stabilizing poly(DL-lactide) nanospheres also acted to plasticize cast films by lowering the

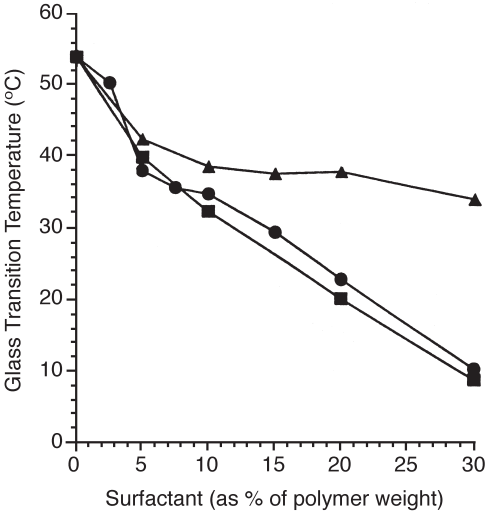



**Figure 5** Effect of three nonionic surfactants on the glass transition temperature of films cast from poly(DL-lactide) pseudolatexes: (●) Pluronic F68; (■) Myrj 52-S; (▲) Tween 60. *Source*: From Ref. 34.

$T_g$ of the polymer. The profiles in Figure 5 demonstrate the effect of increasing concentrations of Pluronic F68, Myrj 52-S, and Tween 60 on the glass transition temperature of the poly(DL-lactide) pseudolatex films. Pluronic F68 and Myrj 52-S had the most significant effect on the films. In addition to the $T_g$ determination, the traces from the differential scanning calorimeter showed a single transition for the polymer with both these surfactants, indicating surfactant miscibility in the poly(DL-lactide). Representative differential scanning colorimetry traces of poly(DL-lactide) pseudolatex films containing increasing concentrations of Pluronic F68 are superimposed on the same axis in Figure 6. Increasing the Pluronic level causes shifts of one uniform glass transitional region. Studies of poly(L-lactic acid) and Pluronic blends by Park et al. also showed that Pluronics with appropriate hydrophobicities create miscibility with the amorphous regions of the poly(L-lactic acid) (35). It has been shown that polymers containing carboxylic acid groups are readily miscible with polyethers through hydrogen bonding (36). This miscibility is confirmed by the effects seen in these studies. The ability of a plasticizer to lower the glass transition temperature of a polymer in an aqueous dispersion is a combination of its hydrophilicity (and resultant avoidance of segregation) and its level of interaction with the polymer itself. This is especially true in a pseudolatex system, where the surfactant is partially solubilized with the polymer in solution prior to nanosphere precipitation as well as adsorbed to the polymer surface afterward. The ability to optimally adsorb onto the polymer surface plays a role in both the stabilization and coalescence

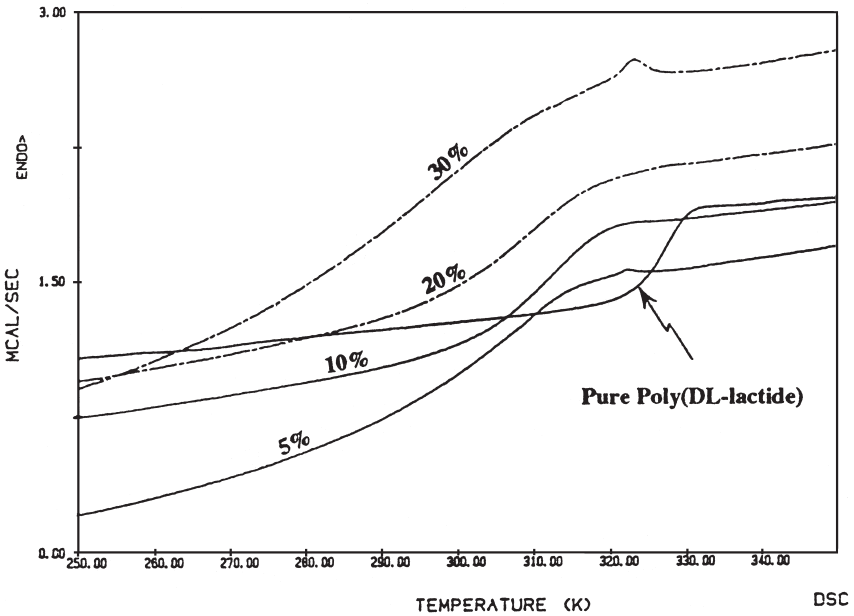



**Figure 6** Differential scanning calorimetry traces illustrating the effect of Pluronic F68 concentration (as percent of polymer weight) on the glass transition temperature of poly(DL-lactide). *Source*: From Ref. 34.

processes. Using the surfactant molecule in the optimal amount will then act to maintain repulsive forces that allow ordered packing of the nanospheres prior to coalescence. This effect of ordered packing was well characterized in studies with surfactant postadded to a latex dispersion and examined using atomic force microscopy (37).

## INVESTIGATION OF EMULSIFICATION VARIABLES ON THE FORMATION OF POLY(DL-LACTIDE) PSEUDOLATEXES

Factorial designs have been successfully applied to the study of many different pharmaceutical formulations and processes, such as slow-release tablets (38), hot-melt fluid bed coating (39), and preparation of biodegradable nanoparticles (40). The emulsion variables of polymer concentration and internal phase percentage were studied because they were the major formulation variables influencing the size of the nanospheres produced.

Emulsification variables are often studied in the context of optimizing some dependent variable, such as droplet or nanosphere size. In the case of a biodegradable pseudolatex dispersion, the investigation of these variables must also

consider the properties of the resultant film produced from the dispersion. The mechanical, thermal, and permeability properties of a polymer film may all be affected by changes in composition that resulted from optimizing the particle size of the pseudolatex. The results in Table 1 and Figure 7 demonstrate the effect that the added surfactants had on the $T_g$ of the poly(DL-lactide). Emulsification optimization experiments were designed by Frisbee and McGinity (26) to link the polymer and surfactant concentrations in a fixed ratio, thereby producing final films of identical composition across the experimental space. A central composite experimental design was selected to study the effect of the polymer/surfactant concentration and the internal phase percentage on the resultant nanosphere mean diameter. Regions of interest were narrowed to 20% to 40% (−1 to +1 in design)

**Table 1** Surfactant Mixture Experiments for Glass Transition Temperature of Poly(DL-Lactide) Pseudolatex Film: Summary of Controlled Factors, Observed and Predicted Values, and Regression Coefficients

| | Controlled factors | | | Glass transition temperature (°C) | | |
|---|---|---|---|---|---|---|
| Run no. | Pluronic F68 | Myrj 52-S | Tween 60 | Observed | Predicted | Residuals |
| 1 | 1.000 | 0.000 | 0.000 | 18.90 | 18.50 | 0.404 |
| 2 | 0.000 | 1.000 | 0.000 | 15.20 | 13.88 | 1.321 |
| 3 | 0.000 | 0.000 | 1.000 | 35.00 | 36.06 | -1.062 |
| 4 | 0.500 | 0.500 | 0.000 | 16.10 | 16.19 | -0.088 |
| 5 | 0.500 | 0.000 | 0.500 | 18.90 | 18.48 | 0.423 |
| 6 | 0.000 | 0.500 | 0.500 | 31.20 | 29.86 | 1.343 |
| 7 | 0.333 | 0.333 | 0.333 | 19.30 | 21.07 | -1.772 |
| 8 | 0.666 | 0.167 | 0.167 | 18.20 | 17.29 | 0.912 |
| 9 | 0.167 | 0.666 | 0.167 | 17.70 | 19.55 | -1.847 |
| 10 | 0.167 | 0.167 | 0.666 | 30.10 | 27.68 | 2.418 |
| 11 | 0.333 | 0.333 | 0.333 | 19.00 | 21.05 | -2.053 |

Regression coefficients for glass transition temperature

| Coefficient | Term | Standard error | *T* value | Confidence coefficient ≠ 0 |
|---|---|---|---|---|
| 18.50 | Pluronic F68 | 1.662 | 11.13 | 99.9% |
| 13.88 | Myrj 52-S | 1.662 | 8.349 | 99.8% |
| 36.06 | Tween 60 | 1.857 | 19.42 | 99.9% |
| -35.21 | (Pluronic F68)* (Tween 60) | 8.420 | 4.181 | 99.1% |
| 19.55 | (Myrj 52-S)* (Tween 60) | 8.420 | 2.321 | 94.0% |

*Source*: From Ref. 26.

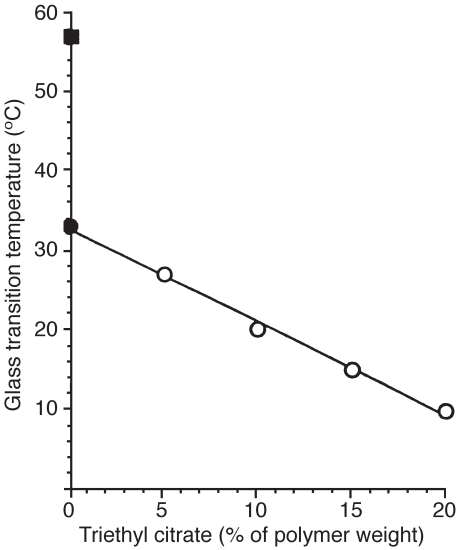



**Figure 7** Effect of surfactant and plasticizer on the glass transition temperature of poly(DL-lactide): (■) poly(DL-lactide); (●) pseudolatex with Pluronic F68; (○) pseudolatex with increasing concentrations of triethyl citrate. *Source*: From Ref. 26.

for the internal phase percentage, and 2.0:0.3 to 4.0:0.6% (−1 to +1 in design) for polymer/surfactant percentage. Pluronic F68 was the surfactant selected for the study. Thirteen pseudolatexes were produced to fulfill the design. Table 2 shows the observed and predicted values, residuals, and coefficients obtained from a quadratic fit to the experimental data. An ANOVA analysis comparing experimental error (from center replicates) to design error showed a high probability that any error in the results was due to the model's lack of fit and not experimental error.

A contour surface representing predicted nanosphere size as a function of the two independent variables was generated (Fig. 8). This surface established that the variable of internal phase percentage provided a minimum nanosphere size of between 20% and 30% of the total emulsion. Increasing the polymer/surfactant concentration variable increased the size of the nanospheres. The polymer in the internal phase had the predominant effect of increasing the size of the nanospheres as its concentration was increased. The mechanism responsible is a higher viscous resistance to the shear forces of emulsification. This occurred despite a concurrent increase in surfactant concentration that if taken alone would decrease the size of the nanospheres. Reducing the viscosity of the internal phase was found to predominate the increased surfactant effects in this fixed ratio study. The optimal region for minimizing the size of the nanospheres was found where the polymer and surfactant were at their lowest concentration (26).

**Table 2** Summary of Experiments that Define Predicted Nanosphere Size of Poly(DL-lactide) Pseudolatexes as a Function of Polymer/Surfactant and Internal Phase Percentage: Controlled Factors, Observed and Predicted Values, and Regression Coefficients

| | Controlled factors | | Nanosphere size (nm) | | |
|---|---|---|---|---|---|
| Run no. | Polymer/surfactant (%) | Internal phase (%) | Observed | Predicted | Residuals |
| 1 | 0.000 | 0.000 | 319.0 | 310.5 | 8.48 |
| 2 | 1.414 | 0.000 | 362.0 | 368.3 | -6.26 |
| 3 | -1.000 | 1.000 | 324.0 | 313.8 | 10.2 |
| 4 | 0.000 | 0.000 | 314.0 | 310.5 | 3.48 |
| 5 | 1.000 | 1.000 | 386.0 | 375.4 | 10.6 |
| 6 | 0.000 | 1.414 | 355.0 | 370.2 | -15.2 |
| 7 | 1.000 | -1.000 | 354.0 | 366.6 | -12.6 |
| 8 | 0.000 | 0.000 | 312.0 | 310.5 | 1.48 |
| 9 | 0.00 | -1.414 | 347.0 | 329.3 | 17.6 |
| 10 | -1.000 | -1.000 | 252.0 | 264.9 | -12.9 |
| 11 | 0.000 | 0.000 | 313.0 | 310.5 | -1.52 |
| 12 | 0.000 | 0.000 | 309.0 | 310.5 | -1.52 |
| 13 | -1.414 | 0.000 | 247.0 | 252.8 | -5.78 |

Regression coefficients

| Coefficient | Term | Standard error | T value | Confidence coefficient ≠ 0 |
|---|---|---|---|---|
| 310.5 | 1.00 | 4.514 | 68.80 | 99.9% |
| 4º0.83 | Polymer/surfactant concentration | 4.419 | 9.241 | 99.9% |
| 14.41 | Internal phase % | 4.419 | 3.262 | 98.8% |
| -10.00 | (Polymer/surfactant concentration)* (internal phase %) | 6.249 | 1.600 | 85.0% |
| 19.65 | (Internal phase %)2 | 4.698 | 4.183 | 99.6% |

*Source*: From Ref. 26.

## PHYSICAL AND CHEMICAL STABILITY OF POLY(DL-LACTIDE) PSEUDOLATEX DISPERSION

Gurny et al. (10) formulated drug-loaded poly(DL-lactide) nanoparticles for use as an injectable controlled-release delivery system. They produced testosterone-loaded latexes using different surfactants and tested their tissue compatibility in rats, as well as the chemical stability of the dispersions. Three surfactants were

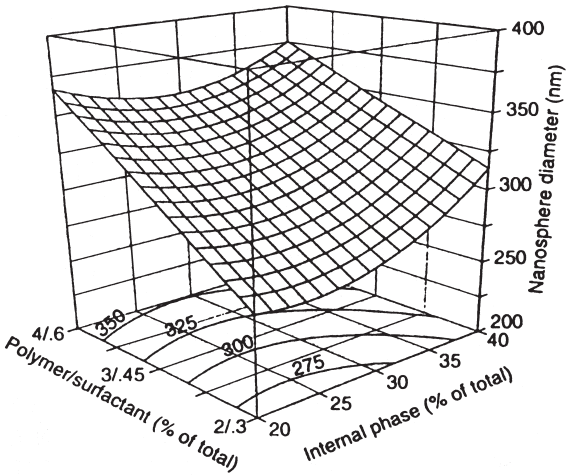



**Figure 8** Contour plot and three-dimensional graph representing the effect of polymer/surfactant and internal phase percentages on predicted mean diameter of poly(DL-lactide) nanospheres. *Source*: From Ref. 26.

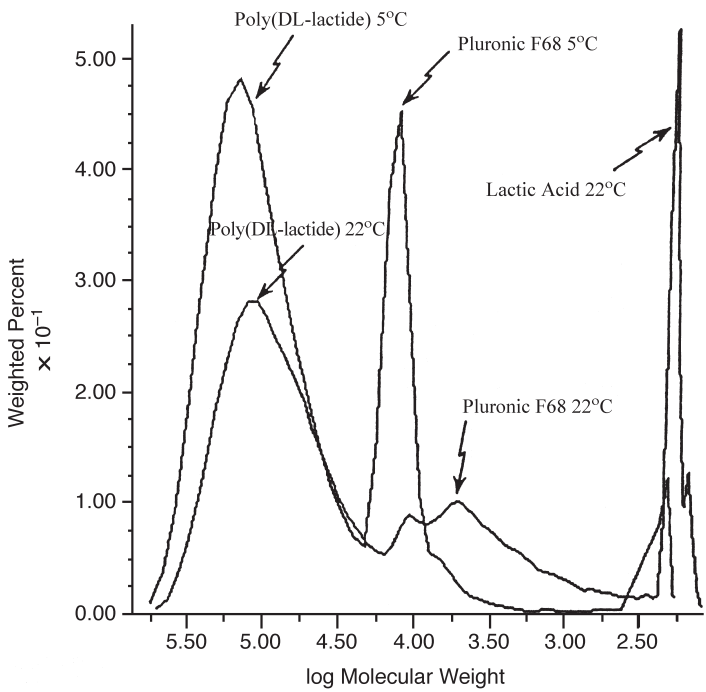



**Figure 9** Molecular weight distribution plots of poly(DL-lactide) pseudolatex dispersions stabilized with Pluronic F68, after storage for two years at 5°C and 22°C. *Source*: From Ref. 34.

used as single agents: Pluronic F68, Tween 80, and sodium lauryl sulfate. The chemical stability was studied at 25°C for four months and showed little change in average molecular weight. In terms of tissue compatibility, the Pluronic F68 and Tween 80 were well tolerated.

Stability studies published by Coffin and McGinity (12) determined that acceptable shelf life could be achieved for poly(DL-lactide) pseudolatexes using nonionic surfactant systems and refrigeration of the dispersion. No nonionic surfactants were investigated as single-agent stabilizers in their studies. An investigation of the physical and chemical stability of a poly(DL-lactide) pseudolatex dispersion containing only Pluronic F68 was performed by Frisbee (34). Pluronic F68 has a well-established safety record in a variety of drug formulation applications (41,42). The poly(DL-lactide) pseudolatex was fabricated using Pluronic F68 at ratio of 0.15:1.0 relative to poly(DL-lactide). The dispersion was stored at 5°C and 22°C for 25 months, with samples withdrawn at 6, 12, and 25 months for physical and chemical stability determinations.

The chemical stability of poly(DL-lactide) pseudolatexes containing Pluronic F68 was investigated by Frisbee (34) using GPC. The dispersions were stored at 5°C and 22°C. The results of molecular weight average calculations showed little change in the molecular weight distribution of the refrigerated pseudolatex. The room temperature sample showed a much more rapid change in molecular weight distribution. Molecular weight distribution plots of the 5°C and 22°C samples after two years are superimposed in Figure 9. The refrigerated dispersion showed a remarkable lack of change in its degradation pattern. In particular, the lack of any significant height in the lactic acid peak was the most prominent feature in the chromatogram of the refrigerated dispersion. The A-B-A triblock configuration of the Pluronic F68 copolymer allowed the hydrophobic B block to form protective ''trains'' along the polymer sphere surface, while the hydrophilic A blocks configured as ''trains'' into the aqueous surroundings. Of particular importance was the length of the hydrophilic portion of the A blocks. Maintaining the stabilization of the system depends on the mixing effects of these hydrophilic tails. The protrusion length of the A blocks for this surfactant was the most important factor in determining these effects. As the hydrophilic portions of the surfactants overlap, a local increase in osmotic pressure will occur, causing repulsion. Larger particles or surfactants with short hydrophilic chains will result in a deeper minimum and lower stability. In this case, the Pluronic F68 was protected from oxidation by its hydrophilic self-association at the polymer surface. This protected both the polymer and the Pluronic F68 during the two-year storage of the refrigerated dispersion.

Figure 9 also illustrates the significant shifts in molecular weight distribution seen in both poly(DL-lactide) and Pluronic F68 at 22°C. The hydrolysis of poly(DL-lactide) created the large peak of lactic acid monomer seen in the figure. Almost complete degradation of the original Pluronic F68 occurred over the two-year period. The distribution plot shows the formation of a large shoulder on the triblock polymer. Polyethers such as the polyoxyethylene chains on the Pluronic F68 are subject to oxidative attack (43). The polypropylene oxide portion, not

being water soluble, retained the triblock structure as the polyoxyethylene chains were slowly depolymerized to ethylene oxide volatiles by the oxidative process. Stabilization of polyoxyethylene has been achieved by the addition of 2% to 5% isopropyl alcohols to its aqueous solution (44). Addition of an alcohol could prove beneficial to the stability of poly(DL-lactide) pseudolatexes, by both eliminating mold growth and preventing oxidation of the Pluronic F68.

## EFFECT OF EMULSIFICATION PROCESSING TIME ON THE PSEUDOLATEX PARTICLE SIZE USING DIFFERENT PROCESSING EQUIPMENT

The effects of emulsification processing on the mean diameter of poly(DL-lactide) pseudolatexes has been investigated (26,40). During emulsification, force is imparted to form the interface, usually a combination of shear, cavitation, and turbulence. In the investigation, five different emulsification processes were studied. A Polytron mixer represented rotor/stator technology, which imparts energy to the system solely through shear forces. Ultrasonic emulsification was studied using two methods: standard probe sonication and an ultrasonic continuous flow cell. High-pressure homogenization was investigated using a Microfluidizer Ml10-T and a Gaulin homogenizer. All processing equipment were configured to maintain isothermal conditions for the bulk phase. A time-dependent reduction in nanosphere size was seen with all methods to varying degrees.

Pseudolatex processing, as well as a number of other types of pharmaceutical processing, is often performed by high-pressure emulsification techniques. Two quite common techniques used are high-pressure homogenization and microfluidization. High-pressure homogenizers, such as the APV Gaulin® (Invensys APV, London, U.K.) use a valve assembly and pressure effect to cause cavitation. A Microfluidizer uses one or more patented ceramic interaction chambers in series and high pressurization to force cavitation and impingement of the emulsion. Both units in these studies were fitted with product stream cooling coils to maintain the bulk emulsions near 22°C. The results by Frisbee (34) demonstrated that these units were very comparable in both their rate and their extent of emulsification. A plateau in nanosphere size was achieved by both pieces of equipment within five minutes of processing, or five passes through the machines. These high-pressure methods proved superior in their ability to reduce the droplet size of the pseudolatex emulsion quickly to a minimal level. The pressure of 6000 psi was considered nominal for both methods.

## INFLUENCE OF EMULSIFICATION PROCESSING TIME ON THE MOLECULAR WEIGHT DISTRIBUTION OF POLY(DL-LACTIDE) PSEUDOLATEXES USING DIFFERENT PROCESSING EQUIPMENT

The application of different emulsion-processing equipment to the production of the poly(DL-lactide) pseudolatex dispersion has an impact on its physical properties.

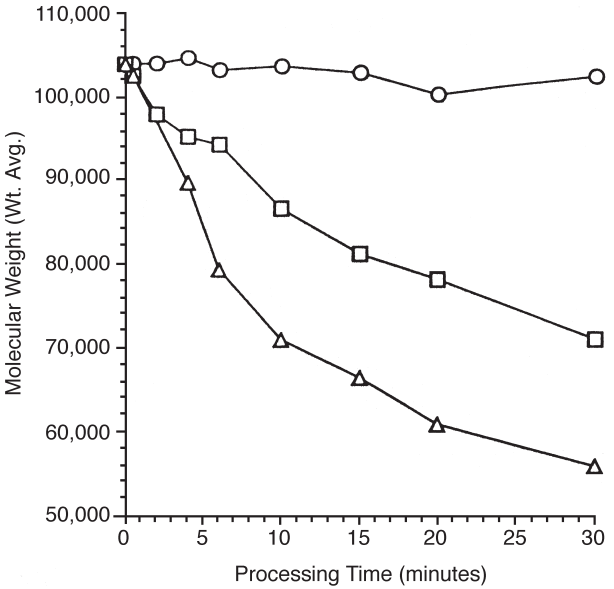



**Figure 10** Effect of rotor/stator and ultrasonic processing on the molecular weight of poly(DL-lactide) pseudolatex nanospheres: (○) rotor/stator; (□) probe ultrasonification; (△) flow cell ultrasonification. *Source*: From Ref. 34.

High-pressure homogenization, ultrasonification, and microfluidization techniques all provided the shear, cavitative, and turbulent forces necessary to minimize the mean particle diameter of poly(DL-lactide) pseudolatexes. Each process uses a unique combination of mechanisms to impart energy into the emulsion. It was therefore hypothesized that the mechanochemical effects on the poly(DL-lactide) and Pluronic F68 during each process would be different. Specifically, mechanical degradation will occur as a result of the unique mechanics of each process, and the mechanisms involved will alter or control the properties of films produced from the pseudolatex. Little research in the area of pharmaceutical technology has focused on the effects of such processes on the properties of pharmaceutical products. In the case of the poly(DL-lactide) pseudolatex, if changes in molecular weight distribution of the polymer and/or the surfactant occur during processing, this will impact the physical and chemical properties of the system. This will in turn affect or even control the performance of the pseudolatex film in drug delivery applications.

Poly(DL-lactide) pseudolatexes were produced using the five emulsification technologies outlined in the previous section. Samples of the emulsions were withdrawn during processing and concentrated into dispersion form by evaporation of the ethyl acetate and a portion of the aqueous phase. The dispersions were then dried and subjected to molecular weight distribution analysis by GPC. The results were plotted as a function of processing time for each emulsion technique. Results from the Polytron (rotor/stator design) and two ultrasonic methods

are shown in Figure 10. The rotor/stator mixer caused no change in molecular weight distribution of the poly(DL-lactide) pseudolatex, even with 30 minutes of isothermal processing. Similar mechanical shear techniques have been shown to degrade other polymers in solution (45). In those studies with a Gifford–Wood minimill, it was found that the annular spacing of the mill was of no consequence, with all degradation apparently resulting from the blade, running at maximum speed. The Polytron in these studies was also run at its highest speed. The lack of mechanical degradation seen with the poly(DL-lactide) emulsion was due to the fact that mechanical shear on the droplets of the internal phase provided insufficient shear force to impact the polymer residing in that phase. Once the droplet was reduced to the minimum size obtainable by virtue of the annular spacing, no further reductions in droplet size resulted. The droplets simply circulated through the mixer space and the polymer was protected by its existence in the minimized droplet. By contrast, studies with the polymer in solution showed the polymer to be constantly subjected to mechanical shear throughout the process. Therefore, simple shear degradation using a rotor/stator mechanism of action was unable to cause degradation of the emulsified polymer, due to an internal phase protective mechanism during processing.

The processing of the poly(DL-lactide) pseudolatex using two ultrasonic techniques is also given in Figure 10. A substantial reduction in pseudolatex mo-

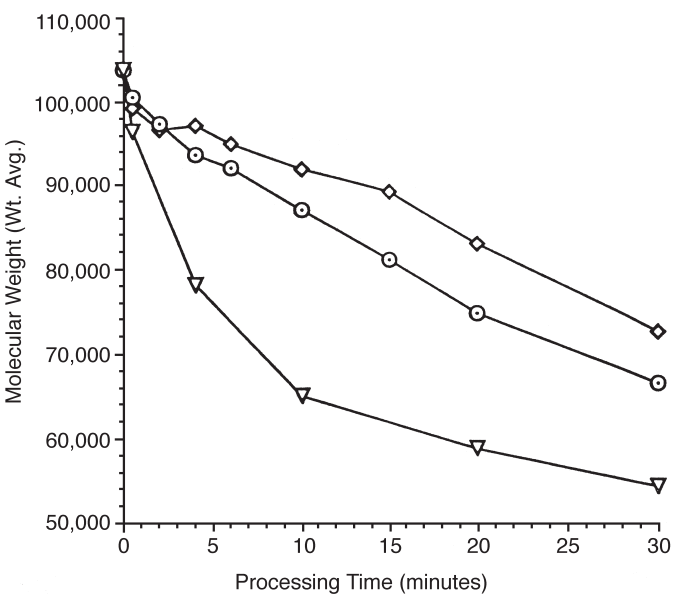



**Figure 11** Effect of high-pressure homogenization and microfluidization processing on the molecular weight of poly(DL-lactide) pseudolatex nanospheres: (◊) high-pressure homogenization 6000 psi; (·) microfluidization 6000 psi; (▽) microfluidization 12,000 psi. *Source*: From Ref. 34.

lecular weight resulted from both probe and flow cell ultrasonification. The flow cell processing was particularly damaging to the pseudolatex, reducing weight average molecular weight from over 105,000 to less than 80,000 in the first five minutes of processing. The analysis of the molecular weight distributions in the following section will offer an explanation to elucidate the mechanisms involved in the degradation.

High-pressure homogenization techniques are the standard emulsification processing technology used in larger batch production of emulsions. The two high-pressure techniques studied in the previous section were also examined in terms of molecular weight changes during bulk isothermal processing. Figure 11 illustrates the effects of these processes. The Gaulin was used at a process pressure of 6000 psi, whereas the Microfluidizer was used at pressures of 6000 and 12,000 psi. The Microfluidizer used had pressure capabilities up to 17,000 psi, and newer technology units can now process to 40,000 psi. The current unit could maintain only 12,000 psi with the available house air supply. The Gaulin and Microfluidizer at 6000 psi had comparable degradation rates on the pseudolatex, with the Microfluidizer showing a higher initial rate. At 12,000 psi, the Microfluidizer showed a dramatic change in its degradation curve. As with the ultrasonic flow cell degradation, molecular weight distribution was reduced from 105,000 to less than 80,000 in a matter of minutes. This indicated that a different or ad-

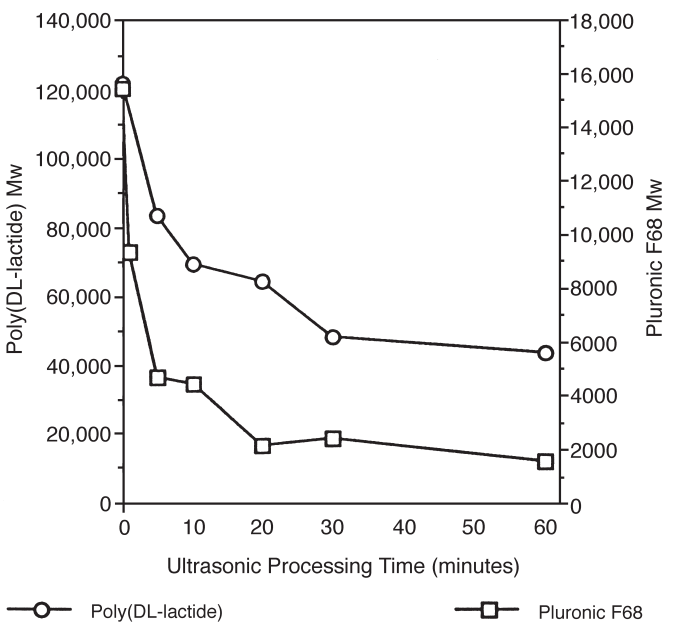



**Figure 12** Separate ultrasonic flow cell processing of poly(DL-lactide) and Pluronic® F68, each in a 30%-to-70% ethyl acetate-to-water emulsion: (○) poly(DL-lactide); (□) Pluronic F68. *Source*: From Ref. 34.

ditional mechanism for degradation of the polymer had occurred at the higher pressure.

Since the poly(DL-lactide) pseudolatex was composed of two polymers, the poly(DL-lactide) and the polymeric surfactant Pluronic F68, it was important to study the degradation of each polymer individually in the emulsion system. When combined in the poly(DL-lactide) pseudolatex emulsion, the effect on each polymer can be studied through an analysis of the peak shifts of each polymer on the GPC chromatograms, as was done in one of the previous investigations. In this study, however, each polymer in its pseudolatex concentration was processed in the emulsion individually by flow cell ultrasonification. The results in Figure 12 show that both polymers were degraded significantly by the processing. It can also be seen from this figure that the rates of degradation were similar and that each polymer approached a unique degradation plateau as the processing proceeded. The approach to a limiting molecular weight while undergoing mechanical degradation has been reported by other researchers, using materials as diverse as polystyrene (45) and DNA (46). For the poly(DL-lactide), a stable emulsion would not form without a surfactant being present. The molecular weight distribution plots of the two polymers are superimposed in Figure 13 and they illustrate the development of distinct patterns of degradation for each polymer. Poly(DL-lactide) was

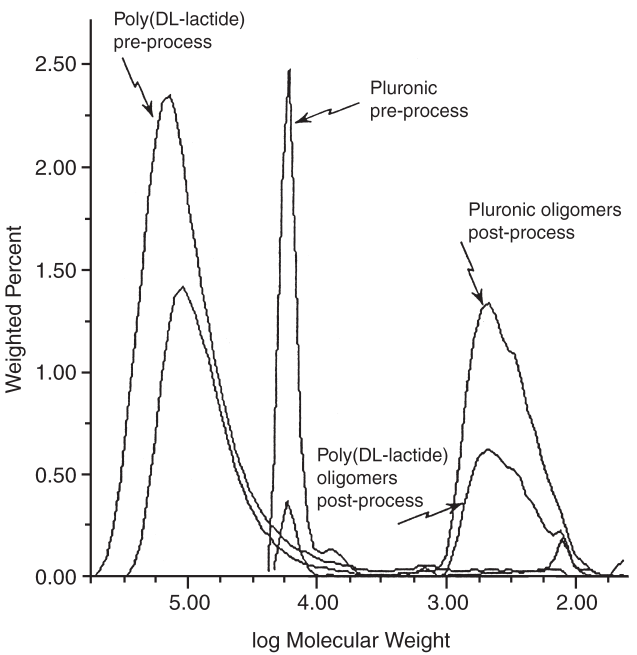



**Figure 13** Molecular weight distribution plot of poly(DL-lactide) and Pluronic® F68 depolymerization during separate ultrasonic flow cell processing in a 30%-to-70% ethyl acetate-to-water emulsion. *Source*: From Ref. 34.

found to degrade by two mechanisms: a shift of the main peak downward and to the right, and, in addition, the formation of a distinct fraction of low-molecular-weight components. The Pluronic F68 degraded directly to a lower molecular weight distribution in the same region as the poly(DL-lactide), with no retention time shift of the main peak or formation of a shoulder on the peak. This pattern of degradation was very different from that seen in the stability study of the dispersion stored at 22°C, which showed a distinct shoulder caused by oxidation of the polyoxyethylene chains to ethylene oxide volatiles. The degradation here was bond breakage, not by random scission of the chains but by an unzipping of the polymer chains, i.e., a depolymerization process. The analysis of GPC molecular weight–normalized distribution plots was an additional methodology the investigators used to evaluate processing effects.

## MECHANOCHEMISTRY OF POLY(DL-LACTIDE) PSEUDOLATEX EMULSIFICATION: EFFECT OF EQUIPMENT TYPE AND PROCESSING TIME

The influence of manufacturing equipment and processing time on the mechanochemistry of poly(DL-lactide) pseudolatexes has been investigated (34). Mecha-

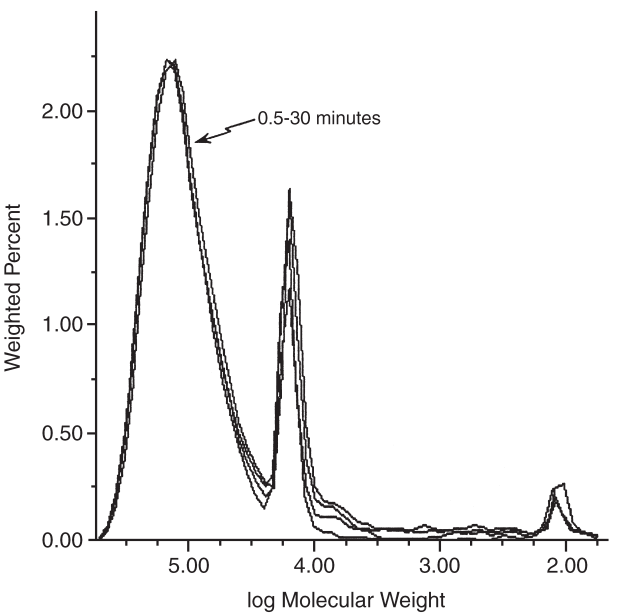



**Figure 14** Influence of emulsification processing time using a rotor/stator mixer on the molecular weight distribution of poly(DL-lactide) pseudolatexes at 0.5, 10, 20, and 30 minutes. *Source*: From Ref. 34.

nochemistry can be broadly defined as a coupling of mechanical and chemical influences at a molecular level. Some examples investigated with poly(DL-lactide) were polymer degradation under shear, and the effects of ultrasonic cavitation on polymers. The generation of GPC-derived normalized distribution plots from processed samples gives a record of pseudolatex molecular weight spectrums, including the identification of multimodal distributions. This analysis was performed to compare poly(DL-lactide) emulsification processes (rotor/stator, ultrasonic, high pressure homogenization, and microfluidization) and to elucidate any differences in the resulting mechanochemistry. Distribution plots for each technique were derived from GPC analysis of processing samples at 0.5, 10, 20, and 30 minutes and placed in an overlay configuration. These results, combined with the analyses given in Figures 10 and 11, help provide an understanding of the mechanochemical processes at work during poly(DL-lactide) pseudolatex manufacture.

The results of calculated average molecular weight shown in Figure 10 for a rotor/stator design showed little change over the entire processing time investigated. This result is confirmed here in Figure 14, with little change seen in the superimposed distribution plots versus processing time. By contrast, Figure 15 demonstrates the degradation occurring from ultrasonic probe processing. The degradation pattern shows a shift to the right (lower molecular weights) of the

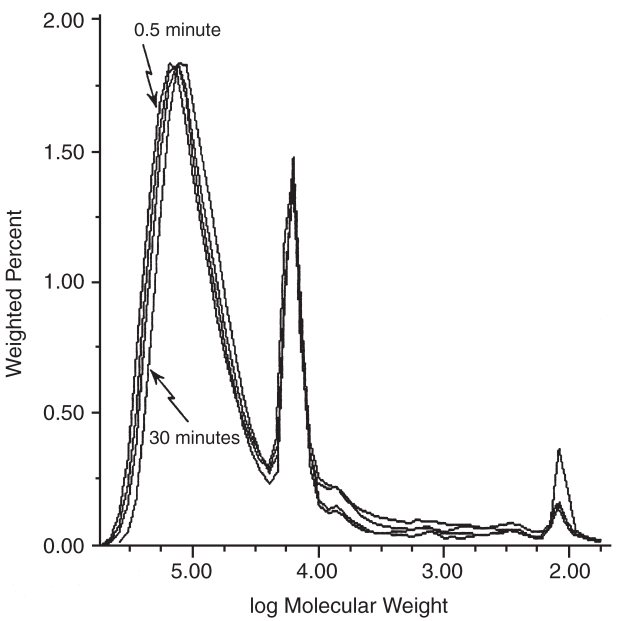



**Figure 15** Influence of emulsion processing time using probe ultrasonification on the molecular weight distribution of poly(DL-lactide) pseudolatexes at 0.5, 10, 20, and 30 minutes. *Source*: From Ref. 34.

main poly(DL-lactide) peak with increasing processing time. The pattern of degradation appears very similar to that caused by hydrolytic degradation of poly(DL-lactide), believed by some investigators to be a first-order random chain scission process (47,48). With ultrasonic processing, the mechanism for polymeric rupture is thought to be a rapid pressure change that accompanies the shock wave radiating from the collapsed cavity. This mechanism will impact the polymer primarily as a function of its chain size and configuration in the solution state.

Molecular weight distribution plots of poly(DL-lactide) pseudolatex undergoing ultrasonic flow cell processing are given in Figure 16. They reveal the appearance of a bimodal distribution with processing time. The most striking result was the appearance of low-molecular-weight components with processing time. This explains the steep decline in average molecular weight illustrated in Figure 10. Processing in the flow cell introduced an additional reaction mechanism to the degradation of the polymers beyond that seen with probe ultrasonic processing. In the standard probe configuration, the directional nature of the sound energy maintains a rapid circulation pattern that acts to limit its residence time in the region directly under the ultrasonic horn. This acoustic streaming effect has been studied in detail, and has been applied to a number of applications (49). In the flow cell configuration however, the emulsion was forced to pass directly between the horn

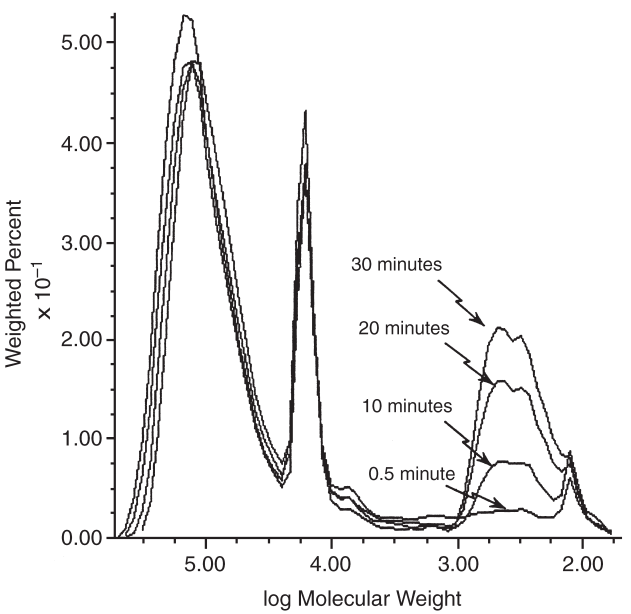



**Figure 16** Influence of emulsification processing time using flow cell ultrasonification on the molecular weight distribution of poly(DL-lactide) pseudolatexes at 0.5, 10, 20, and 30 minutes. *Source*: From Ref. 34.

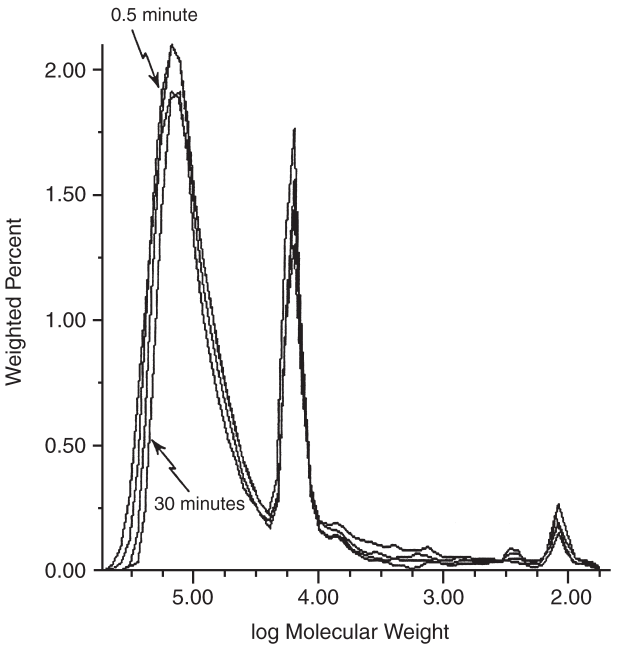



**Figure 17** Influence of emulsion processing with APV Gaulin® high-pressure homogenizer (at 6000 psi) on the molecular weight distribution of poly(DL-lactide) pseudolatexes at 0.5, 10, 20, and 30 minutes. *Source*: From Ref. 34.

and the orifice plate, so the emulsion was systematically exposed to the intense cavitative force and its accompanying high localized heat. The residence time in this environment was not controlled by the acoustic stream, but by the pumping rate through the flow cell.

The cavitative mechanism of ultrasonification requires the existence of dissolved gas in the media. Weissler demonstrated this by ultrasonically irradiating polystyrene dissolved in untreated and degassed toluene (50). The polymer was degraded to one-tenth its original molecular weight in the untreated solution, while the degassed solution showed no cavitation or change in molecular weight. If the temperature becomes high enough, thermal and oxidative reactions occur, and can even predominate the polymer degradation. A number of studies have shown that thermo-oxidative processes can occur faster under shear than at the same temperature without shear (51).

Gupta and Deshmukh, in their study of thermal oxidative degradation of polylactic acid, demonstrated that thermal decomposition and oxidative degradation started taking place at 310°C and 321°C (52). In another investigation, they found the thermal oxidative process to be a result of two kinetically independent units; scission at weak links along the chain (most likely the carbonyl

carbon–oxygen bond) followed by depropagation of volatiles initiated at the unstable polymer chain ends produced by the scission of the weak links (53). In the case of the ultrasonic flow cell processing evaluated here, the cavitative forces were responsible for the random scission of main chains, with added thermal oxidative degradation likely occurring at the chain ends as a result of the flow cell's processing design.

Poly(DL-lactide) pseudolatex emulsification was also performed using an APV Gaulin high-pressure homogenizer at 6000 psi (34). The pattern of degradation was very similar to that seen with standard tip ultrasonification. The main poly(DL-lactide) peak was shifted to the right, with little or no presentation of low-molecular-weight components. The overlays are represented in Figure 17.

The Microfluidizer is a high-shear processor that has the capability to process emulsions at very high pressure to cause cavitation. In addition, its unique interaction chamber impinges the product stream upon itself to create an intense turbulent effect. In a laboratory model M-110T Microfluidizer, processing was performed at both 6000 and 12,000 psi. At a pressure of 6000 psi, identical to that of the APV Gaulin, similar results in average molecular weight changes had been seen, as illustrated in Figure 11. The molecular weight distribution overlays represented in Figure 18 confirmed this result. Increasing the processing pressure

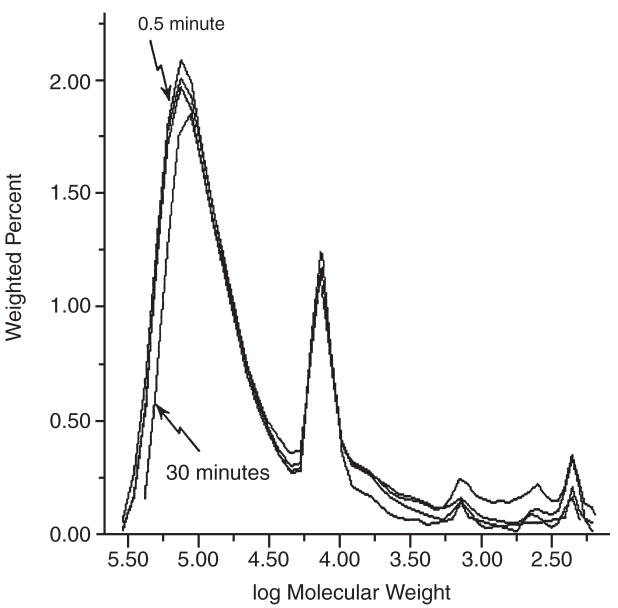



**Figure 18** Influence of emulsification processing time using microfluidization (at 6000 psi) on the molecular weight distribution of poly(DL-lactide) pseudolatexes at 0.5, 10, 20, and 30 minutes. *Source*: From Ref. 34.

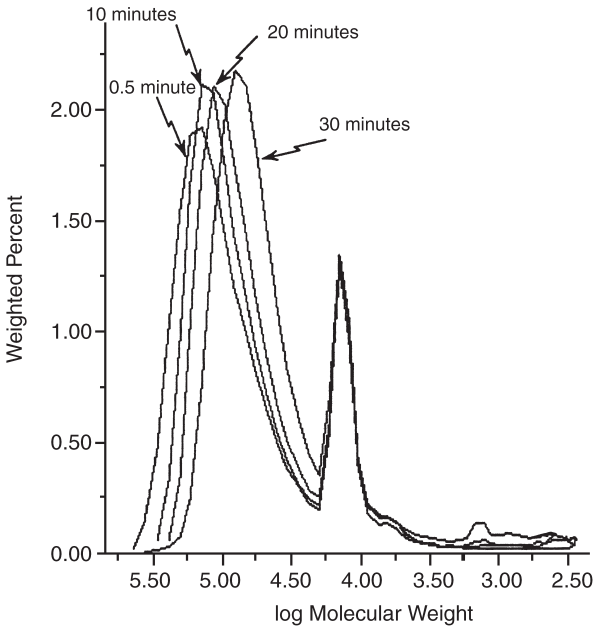



**Figure 19** Influence of emulsion processing time using microfluidization (at 12,000 psi) on the molecular weight distribution of poly(DL-lactide) pseudolatexes at 0.5, 10, 20, and 30 minutes. *Source*: From Ref. 34.

to 12,000 psi, however, as given in Figure 19, fostered more dramatic shifts of the main poly(DL-lactide) peak. The rate of degradation determined by molecular weight averaging in Figure 11 was comparable to that seen by the ultrasonic flow cell in Figure 10, but little generation of low-molecular-weight components accompanied this degradation process.

It is concluded from the comparison of log molecular weight overlays presented in this section that the process by which poly(DL-lactide) pseudolatexes are produced can have a profound and varied influence on the molecular weight distribution of the pseudolatex system. The distinct changes detected with the different processing techniques can be the result of very different mechanochemical reactions. This illustrates the importance of fully characterizing the rate, extent, and type of polymeric degradation occurring during poly(DL-lactide) pseudolatex manufacture.

## PHARMACEUTICAL APPLICATIONS

The release rate of chlorpheniramine maleate from coated pellets was reported to be dependent on the coating level of PLA applied (26). Faster release rates

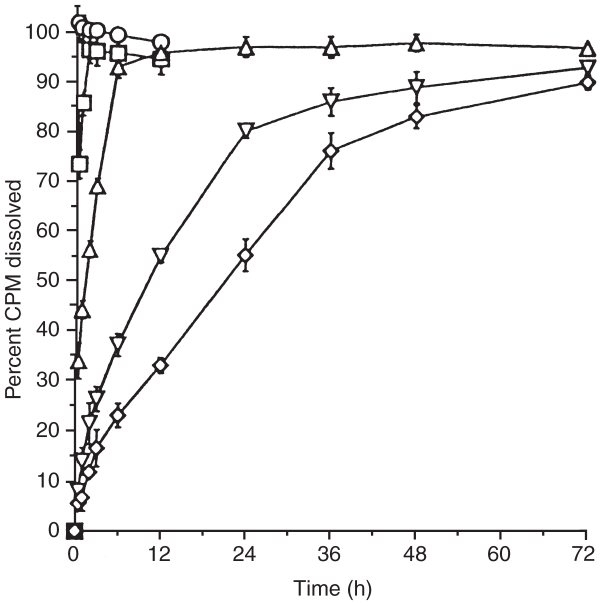



**Figure 20** The influence of coating level (% weight increase) on the dissolution profiles of CPM beads coated with poly(DL-lactide) pseudolatex dispersion, (○) 2%; (□) 4%; (△) 6%; (▽) 8%; (◊) 10%. *Abbreviation*: CPM, chlorpheniramine maleate. *Source*: From Ref. 26.

were obtained when lower levels of polymer were film-coated onto the drug-containing cores, as demonstrated by the preequilibrated samples tested and shown in Figure 20. The release rate was well sustained by the applied film at the 10% polymer weight level, with a near zero-order release seen during the first 24 hours. The initial and subsequent dissolution profiles of these beads are shown in Figure 21, and they display little change in the drug release rate over one-year storage at room temperature. Films were cast from the pseudolatex dispersion, equilibrated, and stored at the same conditions. The films showed no significant change in molecular weight over the one-year storage period, as measured by GPC. The high-molecular-weight of the PLA was responsible for imparting very slow degradation and good mechanical properties to films made from the pseudolatex (26).

Omelczuk and McGinity (4,5) reported on the properties of tablets containing a pseudolatex of a biodegradable polymer. Five molecular weight grades of poly(DL-lactic acid) were incorporated as organic and aqueous pseudolatex binders into matrix tablet formulations containing microcrystalline cellulose and the model drug theophylline. The tablets were thermally treated to temperatures above and below the glass transition temperature ($T_g$) of the PLA. The results of the dissolution studies showed that thermally treating the tablets to temperatures

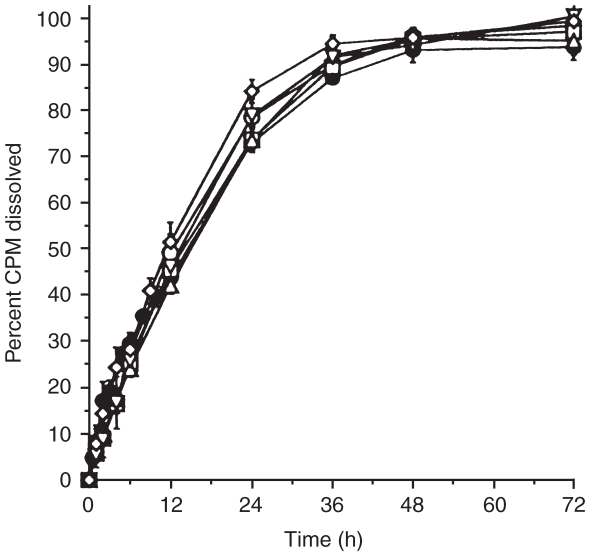



**Figure 21** The influence of storage time on the dissolution profiles of CPM beads coated with poly(DL-lactide) pseudolatex dispersion: (●) time zero; (○) one month; (□) three months; (△) five months; (▽) eight months; (◊) 12 months. *Abbreviation*: CPM, chlorpheniramine maleate. *Source*: From Ref. 26.

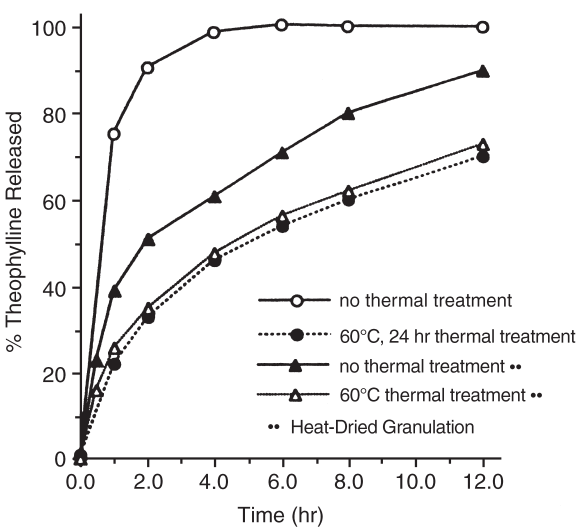



**Figure 22** Effect of thermal treatment on the drug release from tablets utilizing aqueous dispersions on PLA (92,000 $M_w$). *Abbreviation*: PLA, polylactic acid. *Source*: From Ref. 5.

above the $T_g$ of the PLA significantly retarded the matrix drug release, compared to tablets that were not thermally treated, as seen in Figure 22. The retardation in drug release could be attributed to a stronger compact and a more efficient redistribution of the aqueous polymeric dispersion throughout the tablet matrix, based on fundamental principles of annealing. In addition, results from tablet index testing supported the dissolution results. The bonding index of the compact formulations increased after thermal treatment above the $T_g$ of the PLA. GPC and differential scanning calorimetry studies demonstrated that thermal treatment had no significant effect on the molecular weight and the glass transition temperature of PLA alone and in combination with other components of the tablet formulations (4,5).

## SUMMARY

Due to the absence of toxicity, biodegradable polymers have found extensive applications as sutures in surgery and, more recently, as microspheres and nanoparticles for drug delivery. For aqueous pseudolatex dispersions of these polymers to be used in the fabrication of pharmaceutical dosage forms, the stability of the dispersion and the polymer needs to be carefully monitored during long-term storage. In addition, the mechanochemistry underlying different processes used to manufacture the nanoparticulate aqueous dispersion may greatly influence the molecular weight distribution of the polymer. Although no commercial product is currently available, biodegradable dispersions have shown great promise in aqueous film coating applications and also in the preparation of controlled-release matrix tablet formulations. Additional research with these dispersions is needed to fully characterize their properties and exploit their potential in the formulation of unique pharmaceutical dosage forms.

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# 15

# Physical Aging of Polymers and Its Effect on the Stability of Solid Oral Dosage Forms

**Shawn A. Kucera**

*College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*

**Linda A. Felton**

*College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, U.S.A.*

**James W. McGinity**

*College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*

## INTRODUCTION

Film coating is an effective method to modify drug release from tablets and pellets. Aqueous-based coating technology is becoming more popular due to the stringent requirements by environmental and regulatory bodies that restrict the use of organic solvents in production. The formation of thin, transparent films from aqueous-based latex or pseudolatex dispersions occurs with the simultaneous evaporation of water (1,2). Figure 1 is an illustration of film formation from such systems. During the coating process (Stage I), water evaporates from the film-coated substrate at a constant rate. The latex particles begin to pack together and fuse to form a continuous film. As the colloidal particles begin to fuse and coalesce, as seen in Stage II, the rate of water evaporation decreases. By Stage III, film formation is considered complete; however, it is during Stage III that changes occur in the drug-release rate due to physical aging of the polymeric film coating.

Physical aging, or enthalpy relaxation, has been known to polymer scientists for many years. All amorphous polymers show physical aging, where the material

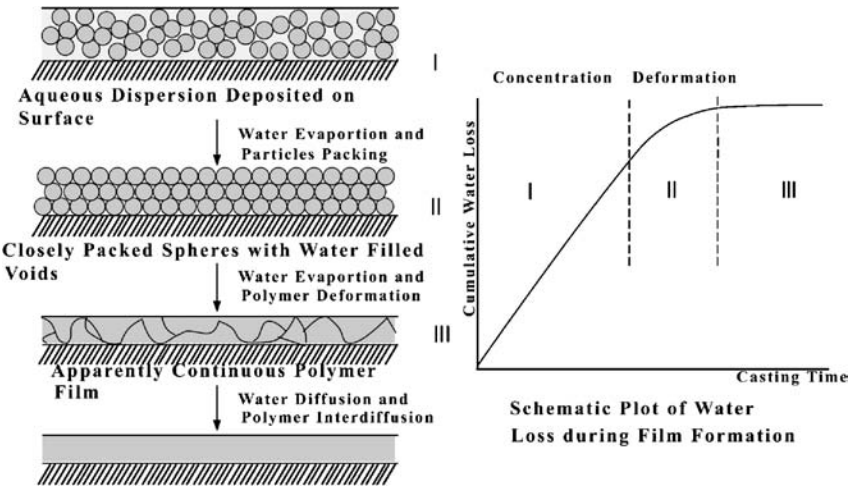


**Figure 1** The formation of thin films from polymeric lattices occurs with the simultaneous evaporation of water.

becomes more rigid, brittle, and dense with time (3). Struik (4) discussed the early work of Simon (5) who had shown that amorphous materials were not in thermodynamic equilibrium at temperatures below their glass transition temperature. The dynamic state is a result of the materials possessing a volume, enthalpy, and entropy that are greater than in the equilibrium state, as shown in Figure 2. The free volume concept states that the transport mobility of particles in a closely packed system primarily depends on the degree of packing, or the free volume. When the

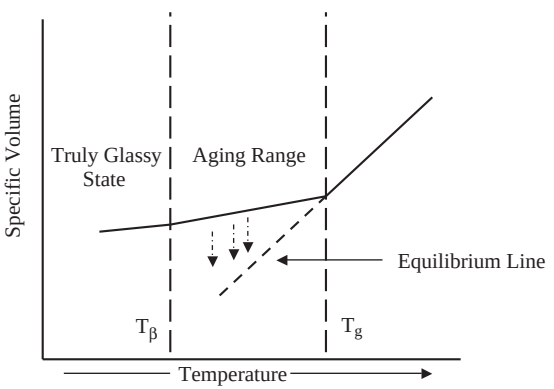


**Figure 2** Graphical representation of the origin of physical aging. $T_g$ is the glass transition temperature of the polymer and $T_\beta$ is the temperature of the highest secondary transition. *Source*: From Ref. 4.

polymer is cooled to some temperature below its glass transition temperature ($T_g$), the mobility will be small, but not zero. At this stage, the free volume is greater than it would be at equilibrium and the volume will decrease slowly (4,6). This contraction is accompanied by a decrease in the polymer chain mobility, which leads to a densification of the polymer, influencing both porosity and tortuosity (6,7).

Diffusion of a drug molecule through a thin film is governed by Fick's first law of diffusion (Eq. 1):

$$Q = \frac{D \times S \times (C_1 - C_2) \times t}{h} \tag{1}$$

where $Q$ (the amount of drug diffused over a period of time, $t$) is a function of $h$, the film thickness; $S$ is the surface area available for diffusion; $C_1$, the concentration of drug in the donor compartment; $C_2$, the concentration of drug in the acceptor compartment, and $D$, the diffusion coefficient of the drug. The physical aging of a polymeric film results in a change in the diffusion coefficient (7,8), which can be shown by the Iyer equation (Eq. 2):

$$D = \frac{D_w \times e}{\tau} \tag{2}$$

where $D_w$ is the diffusion coefficient of the drug in water. $D$ is the diffusion coefficient of the drug and is a function of both the film's porosity, $e$, and tortuosity, $\tau$. As a film ages, it becomes more dense (3), resulting in a decrease in film porosity and an increase in tortuosity, thus causing a decrease in the dissolution rate of drug from film-coated dosage forms over time (7).

This chapter will examine the causes of physical aging of polymers used in the coating of pharmaceutical dosage forms, as well as methods of quantifying this problem and factors that influence aging. The chapter will highlight some research that has been focused on inhibiting physical aging to prevent changes in drug-release rates from coated dosage forms over time.

## METHODS OF QUANTIFYING PHYSICAL AGING

The physical changes in pharmaceutical polymers resulting from aging can be evaluated and quantified by a number of analytical methods, including measurement of the $T_g$, typically done by differential scanning calorimetry (DSC), analysis of mechanical properties or film permeability, dissolution of drug from a coated dosage form, and free volume measurements. The presence of drug crystals on the surface of the coating, which can also indicate polymer aging, can be studied using powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM).

## Mechanical Analysis

When a polymer is cooled below its glass transition temperature, the amorphous material has a higher specific volume, enthalpy, and entropy than the equilibrium state would possess at the same temperature (9). The structural changes in the glassy state due to relaxation of the polymer can manifest changes in the physical properties that are of critical importance to pharmaceutical scientists. These changes include decreases in elongation (7,9,10) and creep compliance (11) as well as increases in elastic modulus (9,10) and tensile stress (7,10,12). These parameters are all quantifiable by examining the physical–mechanical properties of polymeric films as a function of time and storage conditions.

### Unilateral Stress–Strain

A simple method to examine the physical–mechanical properties of polymeric films is by unilateral stress–strain experiments (6,7,10–19). Changes in the internal structures of polymers strongly affect their physical and mechanical properties (20) and the results from stress–strain experiments allow the researcher to gather information on the tensile properties, modulus, and elongation of thin films (7,12). The industry standard for these measurements is published by the American Society for Testing Materials (ASTM) D 882-02: Standard Test Method for Tensile Properties of Thin Plastic Sheeting (21). The specimen to be tested should have a thickness of less than 1.0 mm and a width between 5.0 and 25.4 mm, and should be at least 50 mm longer than the grip separation. The specimens used for the test should have an overall uniform thickness within 10%.

To begin testing, the film specimen is placed in the grips of an instrument such as an Instron testing device (Norwood, MA). One grip of the device is fixed, while the other is allowed to move at a constant rate. As the movable grip is extended, the film is subjected to strain, which is recorded by the instrument with either a tracer/plotter attachment or, as seen in newer equipment, a computer having specialized software packages. These software packages, such as Bluehill (distributed by Instron), allow for the automatic calculation of such parameters as tensile strength at break or maximum load, percent elongation, and the elastic or Young's modulus of a film specimen.

### Creep Compliance

Creep testing is another common method that allows scientists to measure the changes in the physical–mechanical properties of a polymer as it ages (6,11,15,18, 22–28). Creep is the progressive deformation of a material at a constant load. Creep tests measure the dimensional changes that occur over time under a constant static load that is applied to the specimen at a set temperature (29).

The creep of a specimen occurs in three stages, as seen in Figure 3. Following an initial rapid elongation upon application of the load, the creep rate decreases rapidly with time during stage 1. Stage 2 is denoted by the attainment of a steady state with respect to creep rate. Stage 3 is characterized by a rapid increase

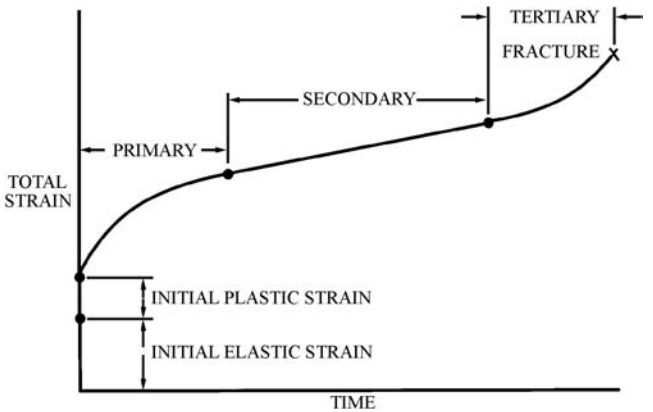


**Figure 3** The creep of a material occurs in three stages. *Source*: From Ref. 29.

in creep rate followed by fracture of the specimen. Graphically, when plotted as a log–log plot, the creep compliance of a material is linear in relation to time (29). During physical aging, creep compliance decreases as indicated by an increase in the slope of creep modulus versus time on a log–log plot.

The industry standard for creep testing is ASTM D 2990-01: Standard Test Methods for Tensile, Compressive, and Flexural and Creep-Rupture of Plastics (29). Specimens for tensile creep measurements should conform to the same standards as those used in unilateral stress–strain experiments. For this experiment,

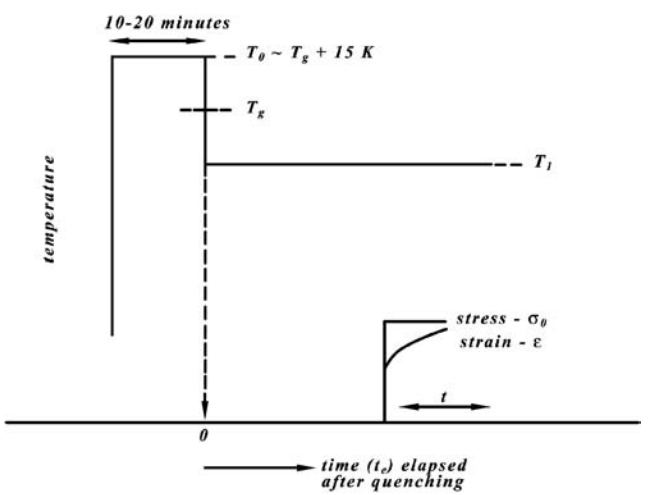


**Figure 4** Temperature versus time scale for a typical creep experiment. *Source*: From Ref. 4.

the film sample is first placed between two clamps. As shown in Figure 4, the sample is then annealed by raising the temperature about 10°C to 20°C higher than the polymer's $T_g$ and cooled or quenched to some predefined temperature below the $T_g$ of the polymer for a period of time, usually a few minutes.

## Membrane Permeability

Measuring the vapor permeability of a film as a function of time and aging conditions has been previously used to qualitatively analyze physical aging in thin polymeric films (7,11,12,14,16,25,30–38). As the film undergoes further gradual coalescence, its permeability to a gas will decrease due to increases in film density and tortuosity. As physical aging progresses, a decrease in water vapor transmission rate is typically observed.

The water vapor transmission rate is the steady flow of water vapor per unit time through a unit area under specific conditions of temperature and humidity (39). A useful guideline is the ASTM E 96/E 96 M-05. The guideline describes two methods for determining the moisture vapor permeability of a thin film. One method, known as the desiccant method, involves placing a thin polymer film over the opening of a cup containing anhydrous calcium chloride as a desiccant. The film is secured and the apparatus is placed in a constant-temperature, constant-humidity environment. The cup is weighed periodically and a graph of weight versus time is plotted. The second method is called the water method, where the cup contains a saturated salt solution of a known relative humidity (RH) rather than a desiccant. With this method, the permeability of the film is evaluated by quantifying the transfer of water vapor from the cup through the specimen to a controlled atmosphere over time.

The rate of water vapor transmission can be calculated using Equation 3:

$$WVT = \frac{G}{tA} \tag{3}$$

where $WVT$ is the water vapor transmission in g/hr m$^2$, $G/t$ is the slope of the line from the weight gain versus time plot, and $A$ is the surface area of the film. These data can be used to calculate the permeability of a thin film. Permeability is simply the arithmetic product of permeance and thickness, where permeance is the rate of water vapor transmission through the film as a function of vapor pressure differences between the two surfaces. Permeance is a performance measure of the film, whereas permeability is a property of the material. The permeance of the film can be calculated using Equation 4:

$$Permeance = \frac{WVT}{\Delta p} = \frac{WVT}{S(R_1 - R_2)} \tag{4}$$

where $S$ is the saturation vapor pressure at test temperature, $R_1$ is the RH at the source (in the chamber for the desiccant method and in the cup for the water method), and $R_2$ is the RH at the vapor sink. The permeability of the film is calculated by multiplying the thickness of the film by its permeance.

## Free Volume Measurements

### Ellipsometry

Ellipsometry is an optical technique for measuring the dielectric properties (i.e., refractive index) of thin films (35–37,40–42). Huang and Paul first reported on the use of ellipsometry in monitoring the physical aging of thin glassy films by changes in refractive index (40). This method has the advantage that no damage is done to the film specimen, allowing the same sample to be examined throughout an aging study.

The Lorentz–Lorenz parameter ($L$) is derived from the Lorentz–Lorenz equation (Eq. 5) (40):

$$L = \frac{n^2 - 1}{n^2 + 2} = \frac{\rho\, N_{av}\, \alpha}{3\, M_0\, \varepsilon_0} \tag{5}$$

The equation shows that the refractive index ($n$) is directly related to $\rho$, the density of the polymer, where $N_{av}$ is Avogadro's number, $\alpha$ is the average polarizability of the polymer repeat unit, $M_0$ is the molecular weight of the polymer repeat unit, and $\varepsilon_0$ is the permittivity of free space.

The Lorentz–Lorenz parameter (Eq. 5) can also be related to the density of a polymer by Equation 6 (41):

$$L = \rho C \tag{6}$$

where $\rho$ is the density of the material and $C$ is a material constant from the bulk values of refractive index and density at 25°C (41). The fractional free volume, $f$, at any time is then determined by Equation 7 (41):

$$f = \frac{V - V_0}{V} = 1 - \rho\, V_0 = 1 - \frac{L}{C}\, V_0 \tag{7}$$

where $V = 1/\rho$ is the specific volume at that aging time, $V_0$ is the occupied volume of the polymer computed from the van der Waals volume of the polymer, $V_w$, by the Bondi method, where $V_0 = 1.3V_w$ (41).

## Positron Annihilation Spectroscopy

Another method used to quantify the changes in free volume due to the physical aging of polymeric films is by the use of positron annihilation spectroscopy (PALS) (18,43–46). This method is able to measure the free volume as well as the free volume distribution in a polymeric film (18,43,47). The positron is a particle that has the same properties as an electron but with an opposite charge. When a positron and an electron meet, it is likely that a positronium atom will form (47). There are two possible positronium "states" that can exist: the para-positronium (*p*-Ps) and the ortho-positronium (*o*-Ps). While the *p*-Ps state has a very short life of about 125 ps (47) in a vacuum, the *o*-Ps has a relatively long lifetime of about 142 ns (47) under the same conditions and a lifetime of about 1 to 10 ns in a polymer (43). When the *o*-Ps atom annihilates, three gamma rays are emitted, which can be detected to determine the lifetime of the particle.

In a PALS experiment, a radioactive sample of $^{22}$NaCl (23,43,47) is used to inject lone positrons into the polymer sample. The lifetime of the positron in the sample ($\lambda$) is therefore due to the electron density at the location of the positron according to Equation 8 (43):

$$\lambda = C \int \rho_+ \rho_- \, dV \tag{8}$$

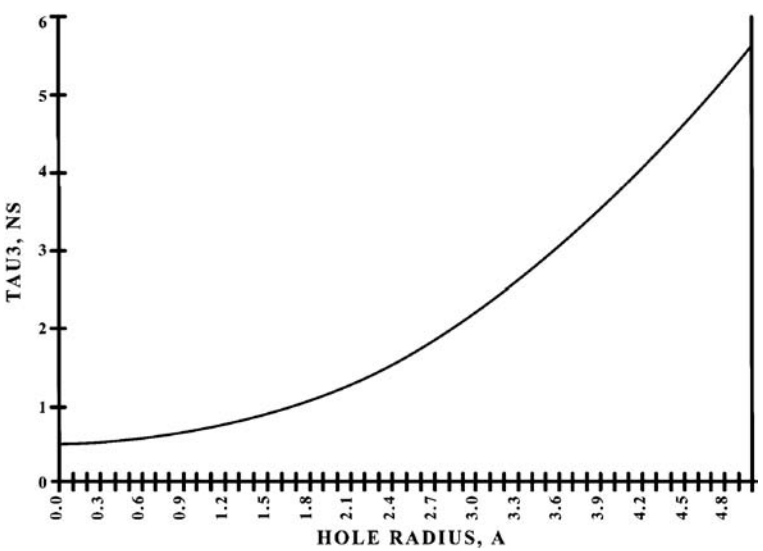


**Figure 5** *ortho*-Positron lifetime versus hole radius according to Equation 9. *Source*: From Ref. 23.

where $C$ is a constant and $\rho_+$ and $\rho_-$ are the positron and electron densities, respectively. The lifetime of the *o*-Ps particle (in nanoseconds), $\tau$, is described by Equation 9 (43,44,47):

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \tag{9}$$

where $R$ is the radius of the spherical free volume holes and $\Delta R$ represents the thickness of the electron layer, which is a constant of 1.656 Å (23,47). Thus, there is a direct correlation between the lifetime of the *o*-Ps and the size of the free volume voids in the polymer matrix, as seen in Figure 5 (23).

## Thermal and Microscopic Analysis

DSC is a common analytical method used to determine various polymer properties, including melting temperature, degree of crystallinity, $T_g$, and enthalpy of transition. The technique is widely used to investigate excipient–polymer interactions

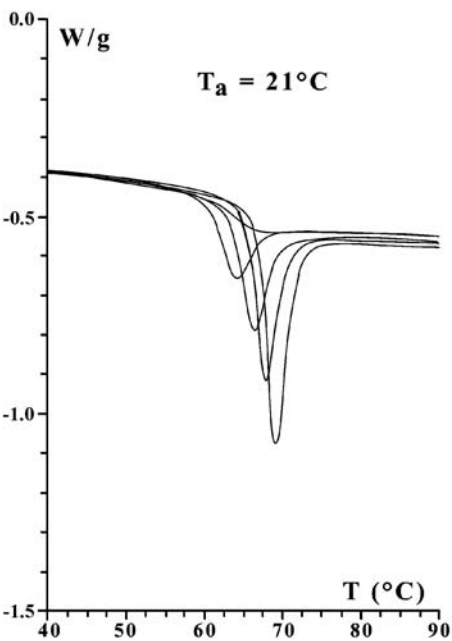


**Figure 6** Heat flux (W/g) versus temperature $T$ for an organic powder coating physically aged at 21°C. From left-hand to right-hand side: ageing times, $t_a$ = 0, 7, 24, 63, and 159 days. *Source*: From Ref. 48.

and evaluate the effectiveness of plasticizing agents in polymeric films. A film sample and a reference are heated at a programmed rate and more energy is absorbed (or emitted) in the sample during a phase change. The energy or heat flow is plotted against temperature or time, and software programs are used to determine the desired property. During physical aging, there is a decrease in enthalpy or enthalpy of relaxation, which can be measured by DSC. This parameter is commonly used to study physical aging and can be determined by integrating the endothermal peak present in the $T_g$ region during the initial scan (48). As the polymer ages, both the peak size and the temperature corresponding to its maximum will increase (18,48), as seen in Figure 6.

Polymer films may contain various additives such as endogenous emulsifiers, active pharmaceutical ingredients, or excipients that either improve processability or modify drug release from the coated dosage forms. In some cases, the polymer may be stored at a temperature above the $T_g$. At this point, the specific volume of the polymer is large as is the molecular mobility of the polymer, and it is possible for the additive components to crystallize during storage. Techniques such as DSC, PXRD, and SEM can be used to scan the polymeric films to determine if crystal growth is present.

## VARIABLES THAT INFLUENCE PHYSICAL AGING

### Plasticizers

Plasticizers reduce the intermolecular attractions between polymer chains to increase the flexibility of the resulting film and enhance the formation of thin films from aqueous lattices. The selection of a plasticizer is of the utmost importance when formulating a coating dispersion. Plasticizers must remain in the film, exhibiting little or no tendency for migration or volatilization. Moreover, plasticizers must be compatible with the polymer. Using a plasticizer that is incompatible with an aqueous latex can result in poor film formation and instabilities with respect to drug release over time during storage.

**Table 1** Effect of Aging on Eudragit® RL and RS 100 Films Plasticized with 0.5% Glyceryl Triacetate

| Film | Age (days) | Decrease in plasticizer content (%) | Decrease in elongation at break (%) | Change in permeation rate (%) |
|---|---|---|---|---|
| Eudragit RL | 180 | 52 | 15 | +31 |
| Eudragit RS | 180 | 48 | 39 | -53 |

*Source*: From Ref. 31.

Once incorporated, the plasticizing agent should remain in the polymeric matrix in order to produce a stable film. The permeability and mechanical strength of Eudragit RS and RL films were found to be a function of the plasticizer remaining in the film, as shown in Table 1 (31). Both films exhibited a decrease in plasticizer content after six months of storage at 25°C/0% RH and a concomitant decrease in the elongation at break. In contrast, the permeability of

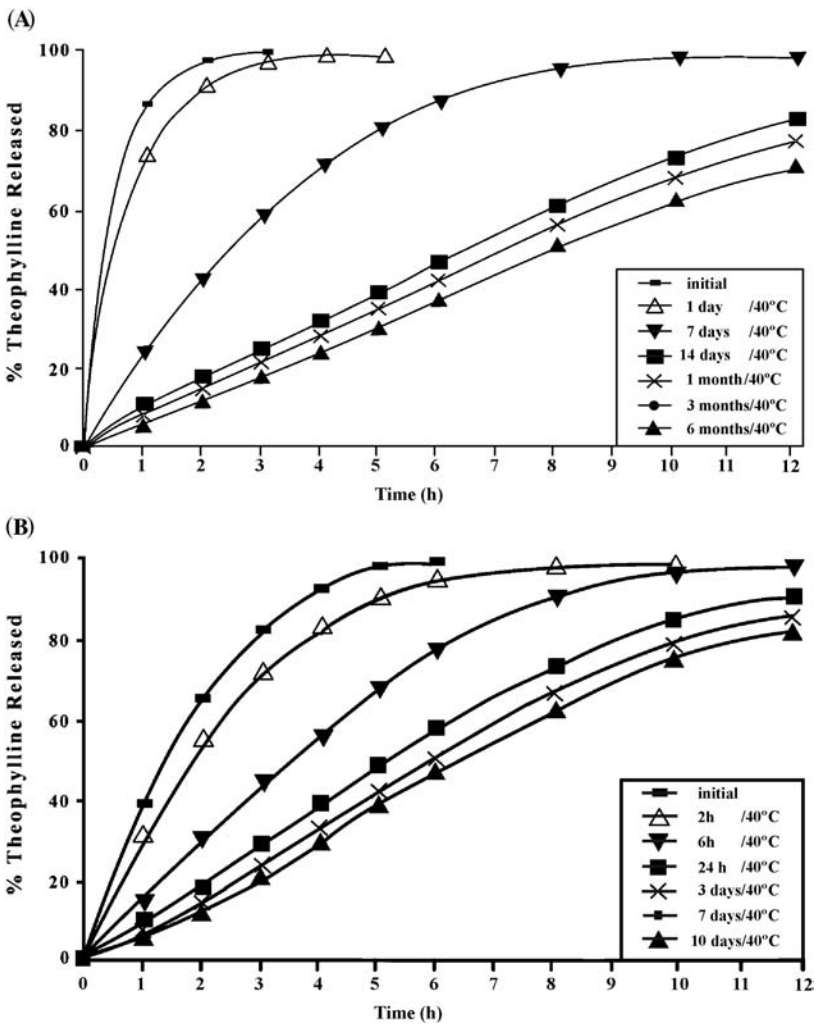


**Figure 7** Changes of drug-release profiles after storage (40°C, 50% RH) of pellets coated with Eudragit® RS 30 D containing 5% Pharmacoat® 505 and (**A**) 10% TEC and (**B**) 20% TEC (9.9% and 10.5% coating level respectively). *Abbreviations*: RH, relative humidity; TEC, triethyl citrate. *Source*: From Ref. 49.

RS films decreased during this time period, while the RL films demonstrated an increase in permeability. These results were attributed to the volatilization of the plasticizer. The loss of plasticizer was less critical for the more hydrophilic RL polymer, with the void space being quickly filled by the permeant solution, thus resulting in an increase in permeation.

The addition of a proper amount of plasticizer to the coating dispersion is also of considerable importance. The incorporation of an inadequate amount of plasticizer in the formulation can result in polymer films that are brittle or that require longer curing times to exhibit stable films. The degree of coalescence of latex particles at the end of the coating process is a function of the concentration of plasticizer in the formulation, with higher concentrations of plasticizer producing enhanced or more complete film formation. In one study, theophylline release from pellets coated with Eudragit RS 30 D containing 5% Pharmacoat 606 and 10% or 20% triethyl citrate (TEC) as a plasticizer was investigated (49). As shown in Figure 7, the time to achieve a stable drug-release rate at storage conditions of 40°C and 50% RH ranged between 6 months and 10 days, depending on plasticizer concentration.

## Curing and Storage Conditions

After completion of the coating process, coated dosage forms are often stored at elevated temperatures to promote further gradual coalescence of the film, a process known as curing. Curing of film-coated dosage forms is an important component in the film-formation mechanism of thin films from aqueous lattices. The film-formation process from these aqueous dispersions relies on capillary forces to draw together and deform the latex particles and is influenced by the amount of water in the polymeric film. As the amount of water in the polymer film increases, the $T_g$ of the film is lowered, resulting in an increased mobility of the polymer chains, which in turn enhances the further coalescence of the latex particles. As the humidity of the environment is decreased, the amount of water in the polymeric film is reduced, and consequently the capillary forces that facilitate film formation are not present.

Although the presence of water can help to enhance the coalescence of polymeric films during curing, high levels of humidity during storage can destabilize the films, leading to changes in the drug-release rate over time. Water will function as a plasticizer in film-coated dosage forms and enhance coalescence of polymeric films during storage, which will generally result in a decrease in the drug-release rate.

Both curing temperature and curing time significantly affect the drug-release rate, but curing temperature is of greater consequence (50–52). As illustrated by Figure 8, there is a decrease in the dissolution rate of diphenhydramine from pellets coated with a 10% weight gain of Eudragit NE 30 D at all three curing temperatures investigated. The decrease in the release rate of the product stored

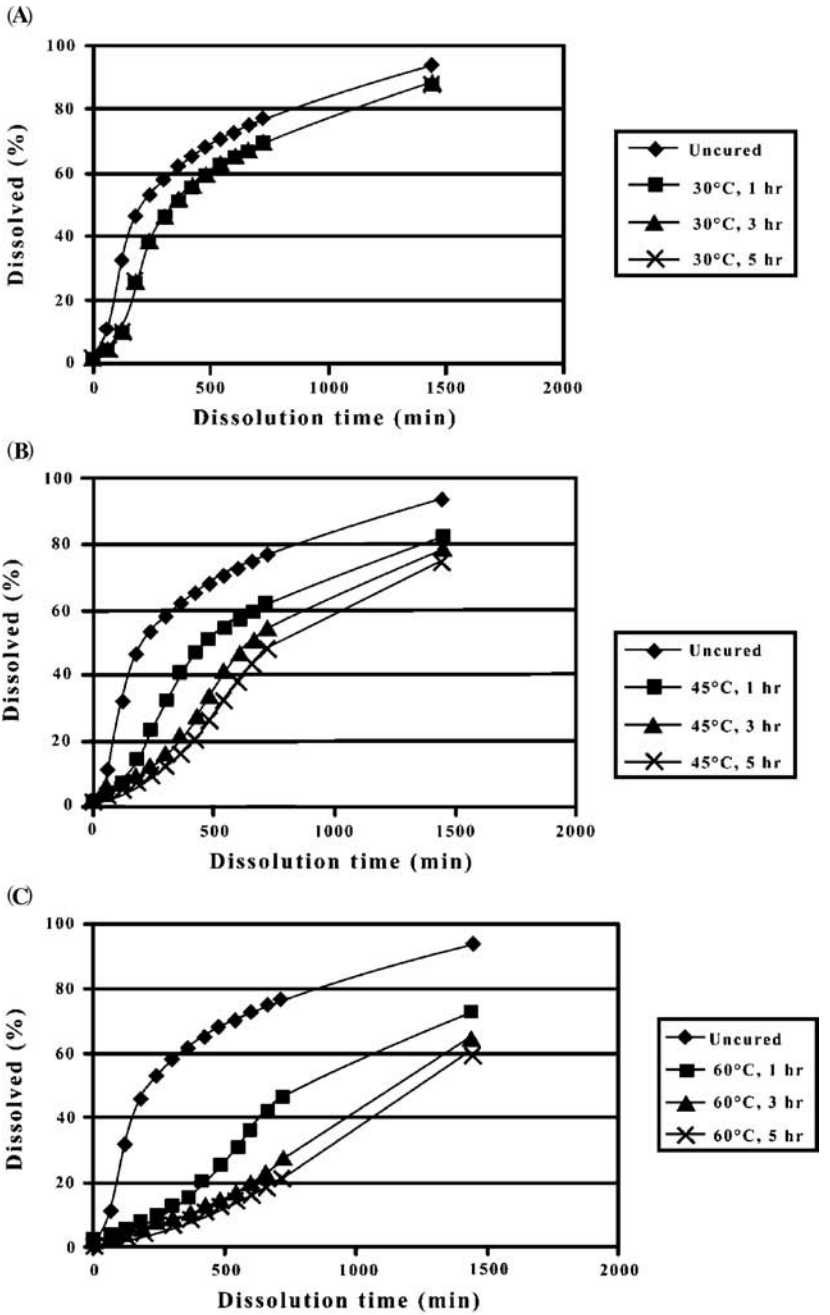


**Figure 8** The dissolution profiles of diphenhydramine HCl pellets coated with 10% Eudragit® NE 30 D and cured at (**A**) 30°C; (**B**) 45°C; (**C**) 60°C. *Source*: From Ref. 51.

at 30°C was small (when compared to other temperatures) and not significantly affected by length of curing time. However, as temperature and storage time were increased, the changes observed in the dissolution rate were amplified. It is suggested that in order for the polymer to achieve a stable energetic state, energy is required to overcome existing barriers that cause the stable state to be kinetically disfavored. At higher temperatures, more polymer molecules can overcome this energy barrier and reach the stable state, which is reflected by a slower drug-release rate. On the other hand, at lower curing temperatures, fewer molecules can achieve the stable state, meaning that changes in drug release would be expected to occur slowly over time until this stable state is reached.

Changes in drug release during curing have also been reported for high-glass-transition-temperature polymers, such as ethylcellulose, in dosage forms coated with Aquacoat® ECD. Physical instabilities in the coating can cause cracking and chipping of the film coating; however, researchers attributed these problems to an increase in the water content of the films rather than a decrease (32). Incomplete film formation and further gradual coalescence during storage of dosage forms coated with Aquacoat will cause instability in the drug-release rate. In contrast to the stability problems seen in acrylic polymers, uncured Aquacoat ECD films actually exhibited an increase in drug dissolution rate (Fig. 9). Faster drug release may be caused by brittle films or the formation of microruptures in the film coat during storage (53). For films cast from an organic solution, there is a significant shift in creep compliance as aging progresses, indicating a decrease in the free volume of the film and increased compaction of the polymer structure.

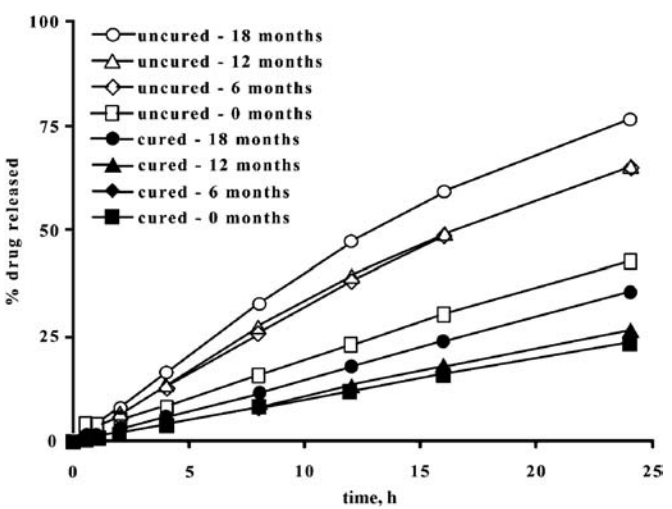


**Figure 9** Influence of storage time on the theophylline release from uncured and cured (one hour; 60°C) Aquacoat®/ATBC-coated pellets (high-dose pellets) in 0.1N HCl. *Abbreviation*: ATBC, acetyl tributyl citrate. *Source*: From Ref. 53.

These changes were also responsible for a reduction in the water vapor permeability coefficient as a function of aging time (11). For aqueous-based films, a decrease in free volume was noted as a result of further gradual coalescence of the pseudolatex particles (14).

## Endogenous Excipients

The presence of endogenous excipients in aqueous coating systems is often necessary to stabilize the dispersion during storage. In other cases, excipients are used in the emulsion polymerization process of aqueous lattices, as is the case of non-

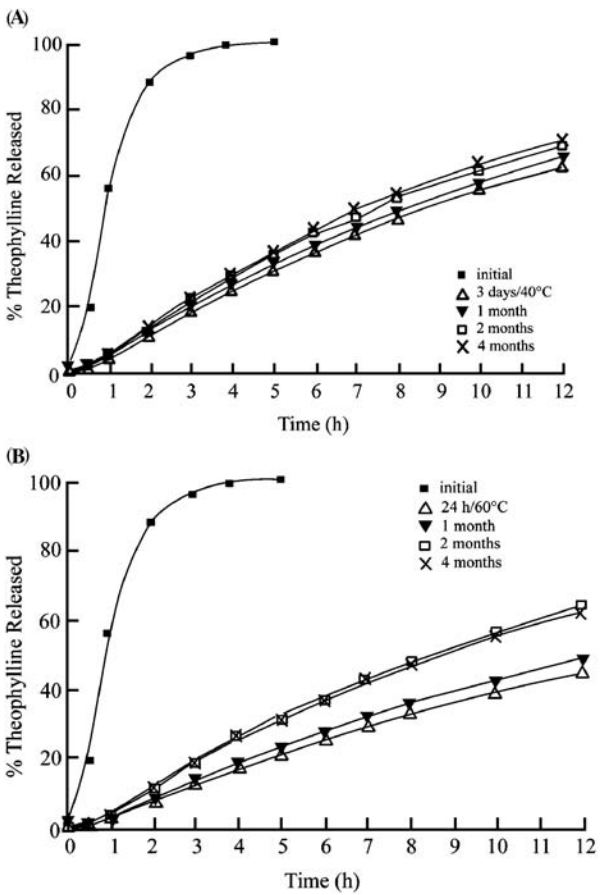


**Figure 10** Evolution, during storage at 25°C/50% RH (one, two, and four months) of theophylline release profiles from Eudragit® NE 30 D–coated pellets previously cured for (**A**) three days at 40°C/50% RH, and (**B**) 24 hours at 60°C/50% RH. *Abbreviation*: RH, relative humidity. *Source*: From Ref. 54.

oxynol 100 in Eudragit NE 30 D dispersions. However, the presence of this emulsifier can lead to serious stability issues, such as an increase in drug dissolution rate during storage, as shown in Figure 10 (54). Due to the relatively high melting point of the surfactant (~60°C), it is possible for the material to crystallize within the film during storage at room temperature. Studies have shown that crystallization of the surfactant affects the dissolution rate of the drug from coated dosage forms (54). Further gradual coalescence and drug release from coated pellets were influenced by increasing amounts of nonoxynol 100 in the coating dispersions (55). When a commercially available Eudragit NE 30 D dispersion (1.5% nonoxynol 100) was used to coat pellets, the drug-release rate diminished by 10% over two months of storage at room temperature, while a decrease of only 5% was observed when the nonoxynol 100 concentration was 5%. However, when the surfactant concentration was increased to 10%, there was first a decrease in the dissolution rate of the drug as a result of the initial swelling of the polymer, after which the dissolution rate increased. This phenomenon was the result of further coalescence of the polymer, which decreased the drug-release rate, coupled with the dissolution of surfactant crystals, which caused large pores in the film and enhanced the release of the drug (55).

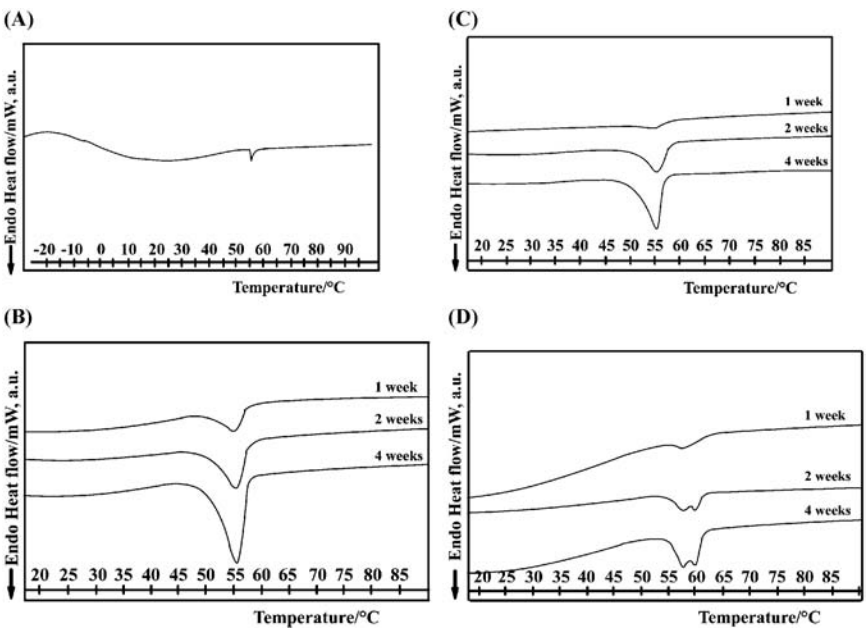


**Figure 11** DSC curves of fresh films (**A**). DSC curves of films stored at (**B**) 25°C/60% RH; (**C**) room temperature/<35% RH; (**D**) 40°C/75% RH. *Abbreviation*: RH, relative humidity. *Source*: From Ref. 56.

The crystallization of nonoxynol 100 in Eudragit NE 30 D free films has also been followed via calorimetric studies (55). These studies showed the melting point of nonoxynol 100 as a single endothermic peak at around 55°C for freshly cast films of Eudragit NE 30 D. The films were stored at ambient conditions (25°C/<35% RH), 25°C/60% RH, and 40°C/75% RH and analyzed using DSC at periods of one, two, and four weeks. As time progressed, all films showed an increase in the magnitude of the melting point endotherm of nonoxynol 100 (Fig. 11), indicating crystal growth of the surfactant in the film, which agrees with earlier data published by Lin and Augsburger (54). The study also concluded that lower temperatures caused a higher degree of crystallization of the emulsifying agent.

Positron annihilation lifetime spectroscopy was used to measure the distribution of free volume holes in cast films of Eudragit NE 30 D with and without

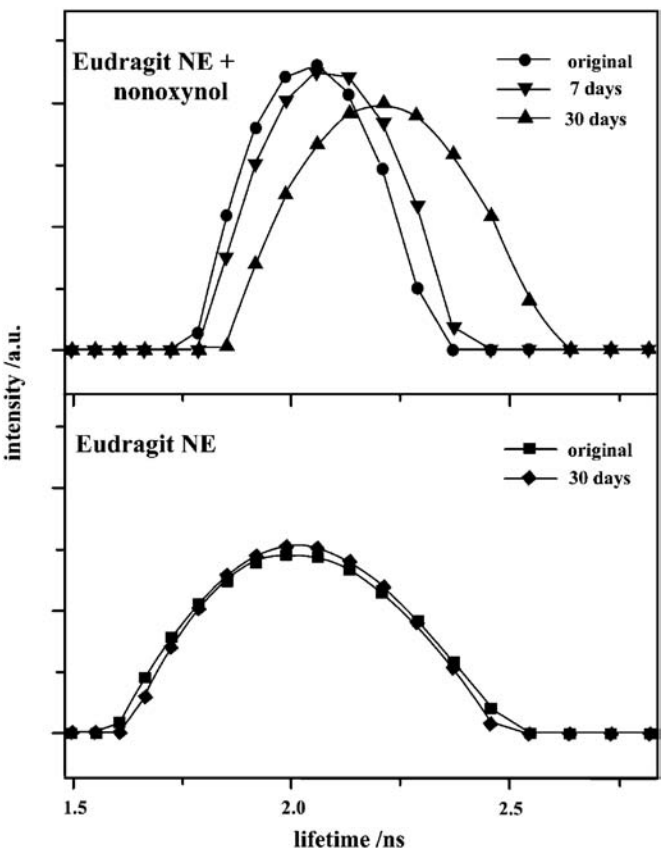


**Figure 12** The effect of storage on Eudragit® NE films with and without nonoxynol 100. The relative pressure of water was 0.75 (RH = 75%) in every case. *Abbreviation*: RH, relative humidity. *Source*: From Ref. 43.

nonoxynol 100 (43). Figure 12 shows that when the emulsifying agent was not present in the film, the size distribution of free volume holes remained unchanged when stored for 30 days at 25°C/75% RH. When nonoxynol 100 was present in the film, however, the size distribution of the free volume holes narrowed and was more uniform following initial sample preparation. During one month' of storage at conditions of high humidity, water initiated an absorption–dissolution transition in these films, and the size distribution of the free volume holes in the polymer increased. This report confirms earlier studies (51,55,56) that indicated that nonoxynol 100 affects the long-term stability of Eudragit NE 30 D films.

## METHODS USED TO STABILIZE/PREVENT AGING

### Increased Plasticizer Concentration

Plasticizers lower both the glass transition temperature and the minimum film-formation temperature of the polymer. Furthermore, the degree of coalescence of latex particles at the completion of the coating process increases as the amount of plasticizer in the formulation increases, due to the plasticizer's ability to weaken polymeric intermolecular attractions, thus allowing the polymer molecules to move more readily, increasing the flexibility of the polymer. For example, theophylline pellets coated with a formulation containing Eudragit RS 30 D, 5% Pharmacoat 606, 50% talc, and 30% TEC showed virtually no change in dissolution rate upon storage, as shown in Figure 13 (49).

While liquid plasticizers can be lost through evaporation during storage, solid-state plasticizers have the distinct advantage of remaining in the film throughout the life of the dosage form. Studies have been conducted in which nonpareil beads were coated with Eudragit RS 30 D containing 40% ibuprofen as the active ingredient and a solid-state plasticizer (57). The coated beads were cured at 40°C

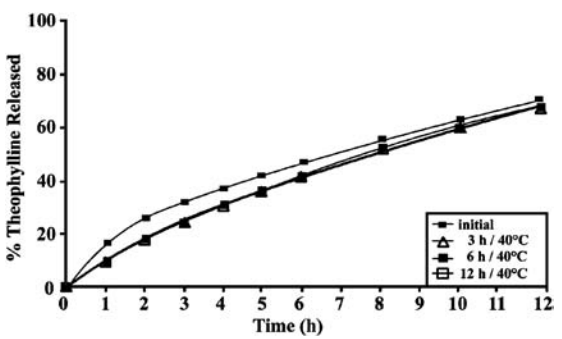


**Figure 13** Changes of drug-release profiles after storage (40°C, 50% RH) of pellets coated with Eudragit® RS 30 D containing 5% Pharmacoat® 606 and 30% TEC (11.2% coating level). *Abbreviations*: RH, relative humidity; TEC, triethyl citrate. *Source*: From Ref. 49.

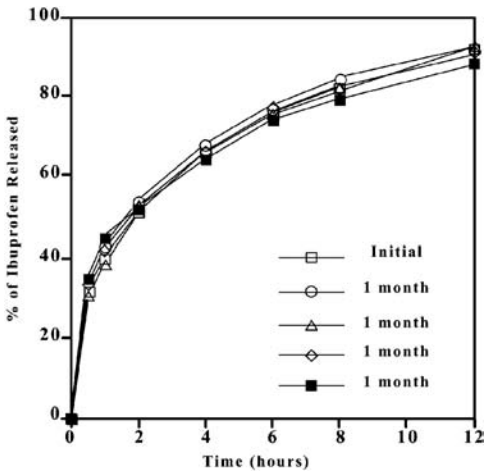


**Figure 14** Effect of storage time at 23°C on the dissolution rate of ibuprofen from nonpareil beads coated with 10% Eudragit® RS 30 D polymer containing 40% ibuprofen ($n = 6$). *Source*: From Ref. 56.

for a period of 24 hours and then stored at 23°C and 0% RH. No significant difference was found between the initial drug-release rate and the drug-release profiles of the stored samples (Fig. 14). The authors reported that the presence of ibuprofen in the coating also served as an antiadherent, preventing the agglomeration of pellets during the coating process and subsequent storage.

## Curing and Storage

The conditions at which dosage forms are cured, as well as stored, can have a significant effect on the stability of the polymeric film. When dosage forms are cured at high temperatures, the time required to reach a fully coalesced film decreases in comparison to curing at lower temperatures (53). At temperatures above the $T_g$ of the film, the mobility of the polymer chains increases and latex coalescence is accelerated, so that films are nearly completely coalesced when removed from the coating apparatus.

Humidity in the environment during storage can significantly influence drug release from coated dosage forms. Water vapor in the atmosphere that is adsorbed by the polymeric films can act as a plasticizer, increasing the molecular mobility of the polymer and aiding in the densification and further coalescence of the polymer. In the case of acrylic films cast from organic solutions (10), the time required for a fully coalesced film to form was shown to be longer than for the same film cast from an aqueous system. Curing of these films at low-humidity conditions under vacuum was not effective in removing the solvent from the films; however, higher-humidity conditions were found to facilitate solvent removal.

## Addition of High-Glass-Transition Temperature Polymers

The addition of a miscible, high-glass-transition polymer is another method that has been shown to stabilize drug release from sustained release coatings. Stabilization occurs when the molecular mobility of the polymer film decreases on increasing the $T_g$ of the polymer blend. High-glass-transition-temperature polymers also serve as a framework to resist the densification and further coalescence of a continuous phase with a much lower glass transition temperature. As an example, Eudragit L 100-55 was found to be miscible with Eudragit RS 30 D (58), and although the enteric polymer increased the drug-release rate from coated theophylline pellets as the pH of the dissolution media increased, the product exhibited no physical aging when stored at 40°C, i.e., a static drug-release profile over time (Fig. 15). Another study (59) showed that the addition of 16.7% Eudragit L 30 D-55 to Eudragit NE 30 D decreased the tackiness of the films and, when cured

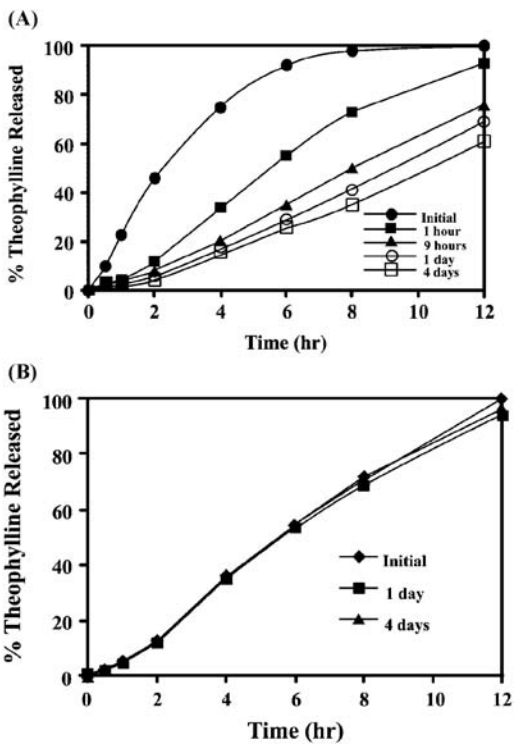


**Figure 15** Influence of storage time at 40°C on the release of theophylline from pellets coated with (**A**) 12% Eudragit® RS 30 D plasticized with 17.5% TEC and (**B**) 12% Eudragit RS 30 D/L 100-55 (3:1) plasticized with 17.5% TEC, overcoated with 2% Eudragit RD 100. Dissolution performed in pH 7.4 phosphate buffer medium using the USP method 2 ($n = 6$). *Abbreviations*: RH, relative humidity; TEC, triethyl citrate. *Source*: From Ref. 59.

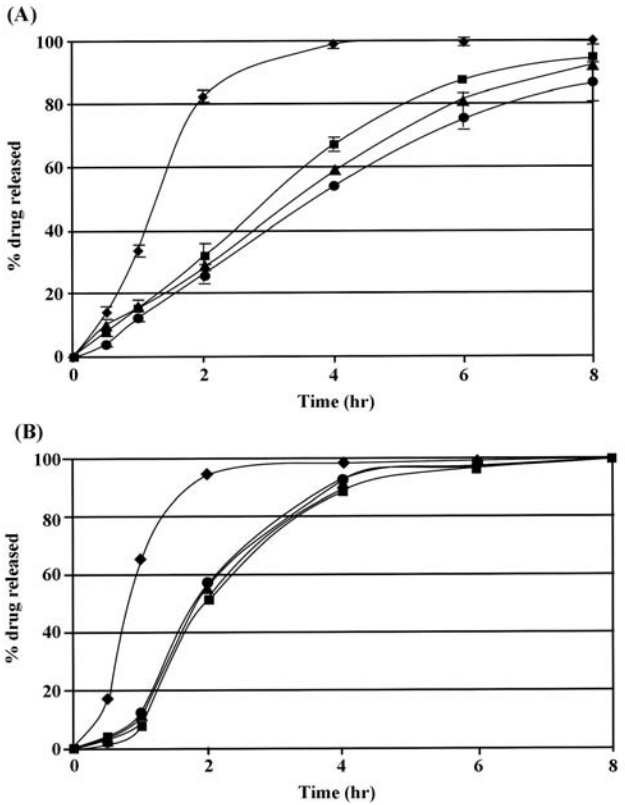


**Figure 16** (**A**) Influence of curing time on the release of PPA-HCl from pellets coated with Eudragit NE 30 D, stored at 60°C (USP 24, apparatus 2, 500 mL of pH 1.2 HCl, 37°C, 100 rpm, $n = 3$): ◆, initial; ■, 4 hr; ▲, 24 hr; ●, 72 hr. (**B**) Influence of curing time on the release of PPA-HCL from pellets coated with Eudragit NE 30 D containing 16.7% Eudragit L 30 D-55 stored at 60°C: ◆, initial; ■, for 4 hr; ▲, for 10 hr; ●, for 24 hr, □, for 5 days. *Abbreviation*: PPA, phenylpropanolamine. *Source*: From Ref. 59.

at 60°C, the drug-release rate of the coated pellets stabilized after four hours of storage (Fig. 16).

## High Solids Content

Talc is traditionally used as an antitacking agent in the coating formulation and is usually present at concentrations of 50% to 100%. Generally, the addition of higher amounts of talc is seldom used, because the high solids content could alter drug release from the dosage form. However, it has been shown that the inclusion of up to 200% talc can be used to successfully formulate coated pellets with a sustained drug-release rate (60). When this amount of talc was added to a 95:5 blend

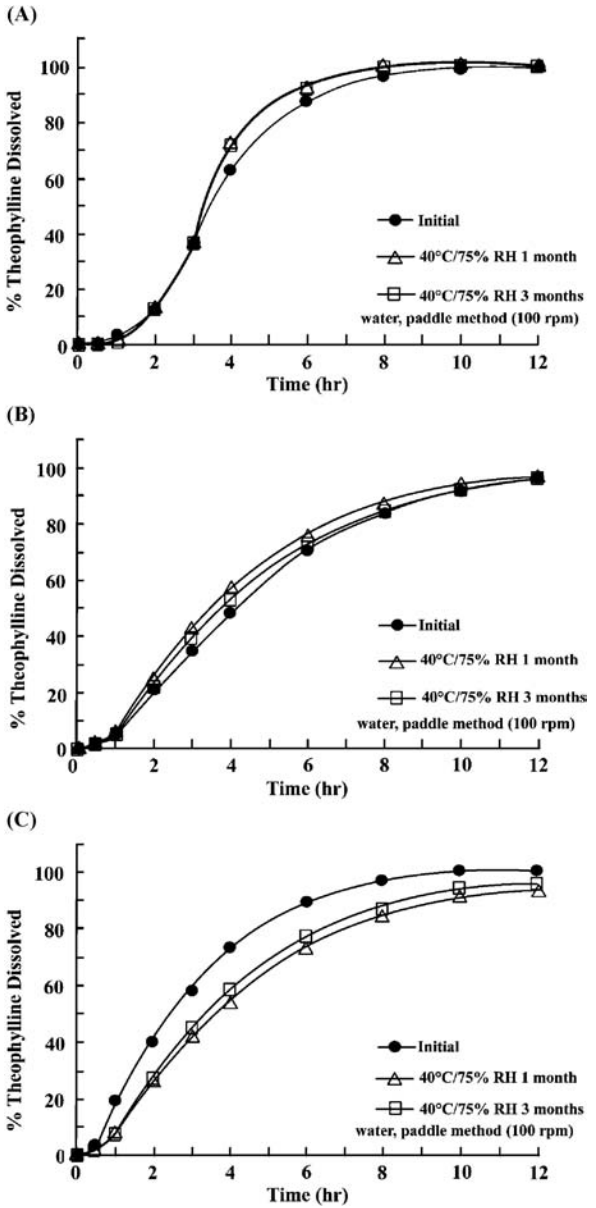


**Figure 17** Stability of theophylline release rate from pellets coated with Eudragit® RS/RL containing 200% talc after storage at 40°C/75% RH with (**A**) 10% TEC, (**B**) 20% TEC, and (**C**) 30% TEC. *Abbreviations*: RH, relative humidity; TEC, triethyl citrate. *Source*: From Ref. 60.

of Eudragit RS/RL 30 D plasticized with TEC, the acrylic polymer functioned as an effective binder for the talc, resulting in a continuous film coat. Although film formation was incomplete, the coating still provided a sustained release of the drug. The high talc content of the films also resulted in no agglomeration of the coated pellets during curing at 60°C or storage at 40°C/75% RH in open containers. The authors stated that the addition of 10% or 20% TEC to the coating formulation resulted in dosage forms that were physically stable and showed no significant change in drug-release rate during storage for three months (Fig. 17).

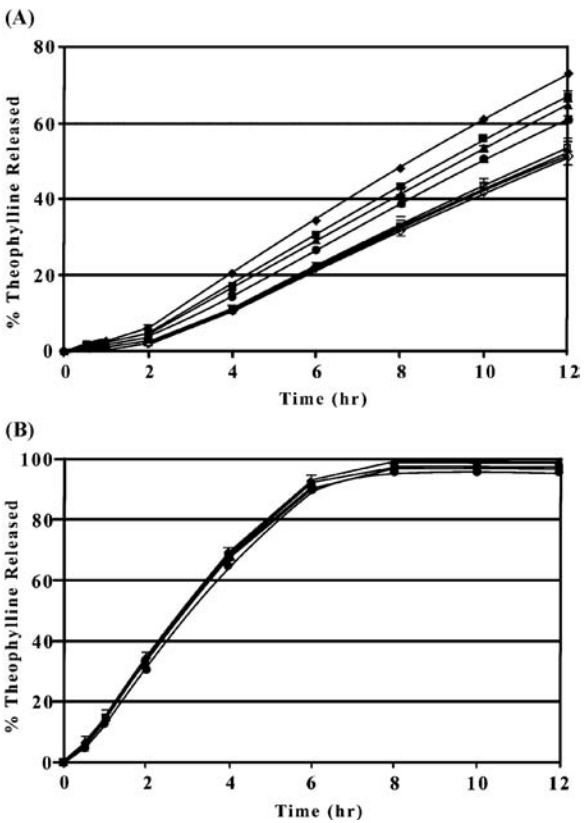


**Figure 18** (**A**) Influence of storage time on the release rate of theophylline from pellets coated with Eudragit® RS 30 D stored at 25°C/60% RH in open high-density polyethylene containers (USP 26 apparatus 2, 900 mL, 50 mM phosphate buffer, pH 7.4, 37°C, 50 RPM, $n = 3$): ◆, initial; ■, 1 week; ▲, 2 weeks; ●, 4 weeks; ◊, 4 months. (**B**) Influence of storage time on the release rate of theophylline from pellets coated with Eudragit® RS 30 D containing 10% HEC stored at 25°C/60% RH in open HDPE containers (USP 26 apparatus 2, 900 mL, 50 mM phosphate buffer, pH 7.4, 37°C, 50 RPM, $n = 3$): initial, 1 week, 2 weeks, 4 weeks, 4 months. *Abbreviations*: RH, relative humidity; HDPE, high-density polythylene. *Source*: From Ref. 7.

### Addition of Immiscible, Hydrophilic Excipients

Hydrophilic, water-soluble polymers have found use in stabilizing sustained-release polymers in coating applications. It has been shown that these excipients form boundaries that inhibit the further coalescence of the functional polymer. For example, hydroxyethylcellulose (HEC) has been shown to stabilize the release rate of theophylline from pellets coated with Eudragit RS 30 D (7). Theophylline pellets coated with the acrylic polymer plasticized with 20% TEC showed a decrease in drug-release rate during storage at 25°C/60% RH (Fig. 18A). Cast films of the same formulation showed an increase in tensile strength and a decrease in water vapor transmission rate during storage over one month. The addition of 10% HEC to the coating formulation (Fig. 18B), however, stabilized the drug-release profiles of the coated pellets stored at the same conditions. Likewise, no changes were observed in the physical–mechanical properties or the water vapor transmission rate of the cast films containing HEC. Atomic force microscopy was used to characterize the surface morphology of the cast films. Films of Eudragit RS 30 D (Fig. 19A) exhibited a smooth, regular surface where all latex particle boundaries had disappeared. In contrast, a rough surface was observed for acrylic films containing 10% HEC (Fig. 19B). The hydrophilic polymer had surrounded the hydrophobic acrylic latex particles and prevented the further coalescence and densification of the film. The HEC allowed the film structure to be retained during storage and stabilized the permeability and mechanical properties of the film.

Albumin was investigated to stabilize drug release from Eudragit RS/RL 30 D films (12). The addition of 10% albumin resulted in the destabilization of the film, exhibiting significant aging during a three-month period, as demonstrated by substantial changes in drug release over time (Fig. 20). This was attributed to

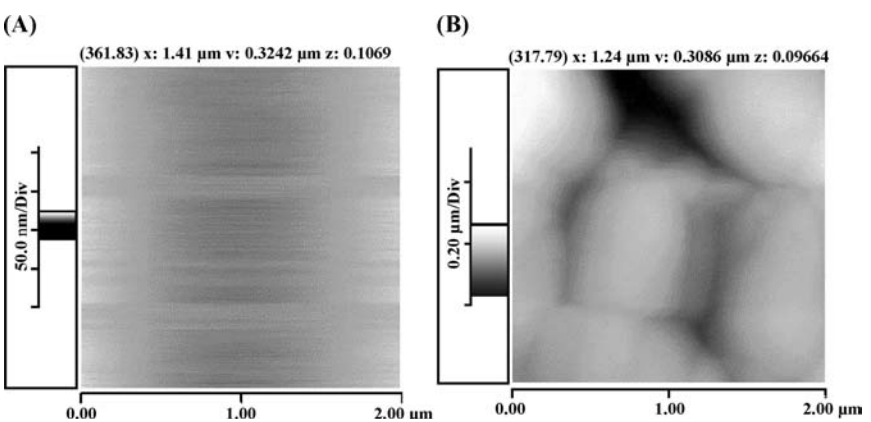


**Figure 19** AFM image of cast polymeric films: (**A**) Eudragit® RS 30 D and (**B**) Eudragit® RS 30 D containing 10% HEC. *Abbreviations*: AFM, atomic force microscopy; HEC, hydroxyethylcellulose. *Source*: From Ref. 7.

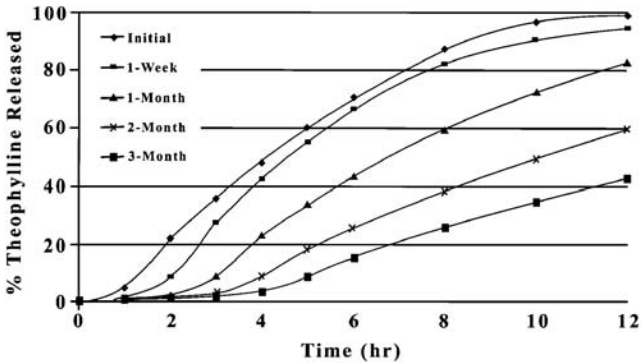


**Figure 20** The influence of albumin on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in open containers ($n = 3$). *Abbreviation*: RH, relative humidity. *Source*: From Ref. 12.

the intermolecular interactions between the protein and polymer. The pH of the dispersion was above the isoelectric point of the albumin, resulting in attractive forces between the quaternary ammonia groups on the polymer and the negatively charged protein. This destabilization was also the result of increased water absorption by the polymeric film. However, when the Eudragit dispersion was first acidified to a pH of 2.5 and then the albumin was added, there was no change in drug release when the coated dosage forms were stored at both 40°C/75% RH

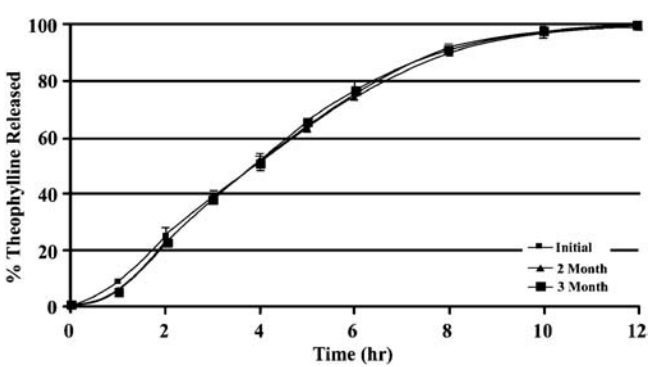


**Figure 21** The influence of dispersion pH (2.5) on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D (15% WG) containing 10% albumin and stored at 40°C/75% RH in hermetically sealed HDPE containers with desiccant ($n = 3$). *Abbreviations*: RH, relative humidity; HDPE. *Source*: From Ref. 12.

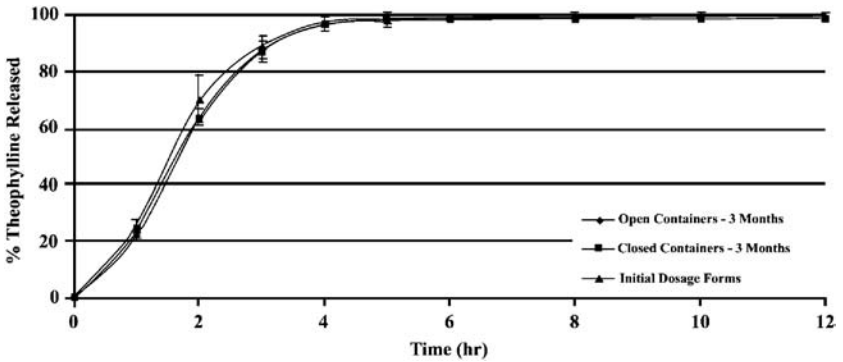


**Figure 22** The effect of gelatin on the release of theophylline from pellets coated with Eudragit® RS/RL 30 D containing 10% gelatin and stored at 40°C/75% RH in open and closed containers ($n = 3$). *Abbreviation*: RH, relative humidity. *Source*: From Ref. 12.

(Fig. 21) and 25°C/60% RH in aluminum-induction-sealed high-density polyethylene containers. Electrostatic forces between the positively charged species, as well as the elimination of moisture, were responsible for the stabilization. In the same study, gelatin was also investigated as a possible protein to stabilize drug release. Although 10% gelatin in the coating dispersion did prevent aging effects, the drug-release rate was noticeably faster than when albumin was used in the films (Fig. 22). The increase in drug-release rate was attributed to the hydration of the gelatin in the film, resulting in areas of high diffusion.

## SUMMARY

Physical aging is a phenomenon that affects all polymers. Simply utilizing alternative coating systems or polymers is not the solution to formulations that exhibit these stability issues. The subject has been extensively discussed in the chemical engineering literature and is an important consideration during formulation development for pharmaceutical scientists. The physical aging of polymers has been shown to cause changes in the physical–mechanical, permeability, and drug-release properties of polymeric films due to a densification and decrease in free volume of the polymer as it relaxes to an equilibrated thermodynamic state. Since the coating of oral dosage forms with aqueous polymeric lattices is one of the simplest and most widely used methods for controlling drug-release rates, the stability of these coated dosage forms is of the utmost importance. Aging has been shown to be influenced by factors such as humidity and temperature during storage as well as excipients in the coating formulation. A number of techniques have been used to stabilize polymeric films and prevent aging. Care must be taken to both plan for and identify potential aging issues during the early stages of product development. This includes determining the mechanism or mechanisms of desta-

bilization, identifying the most appropriate stabilizer for the coating formulation, and ensuring that the coated dosage forms are cured to a point that film formation from the aqueous latex is complete.

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### about the editors...

JAMES W. MCGINITY is Professor of Pharmacy, College of Pharmacy, the University of Texas at Austin, received his B.Pharm. degree from the University of Queensland, Brisbane, Australia, and graduated with his Ph.D. degree in Physical Pharmacy from the University of Iowa, Iowa City. Dr. McGinity's current research includes film coating technology, hot melt extrusion, materials science, tablet technology, and modified release drug delivery systems. A keynote speaker at over 50 international conferences, Dr. McGinity has published more than 160 peer-reviewed articles, written over 25 book chapters in the field, and has been issued 23 U.S. patents. He is an AAPS Fellow, has refereed for many influential journals, and is on a select number of editorial boards, including *Drug Development and Industrial Pharmacy, Pharmaceutical Development and Technology,* and *The European Journal of Pharmaceutics and Biopharmaceutics.*

LINDA A. FELTON is an Associate Professor of Pharmaceutics at the University of New Mexico, Albuquerque. She earned a B.S. in Pharmacy and a Ph.D. in Pharmaceutics from the University of Texas at Austin. Her research interests are focused on polymeric film coating technology, modified release systems, and topical/transdermal drug delivery. She has presented her work at national and international conferences and has published extensively in peer-reviewed journals. Dr. Felton is a reviewer for a number of pharmaceutical journals, and an editorial board member of *Drug Development and Industrial Pharmacy*. Dr. Felton has a joint appointment with the Department of Veteran's Affairs Cooperative Studies Program where she oversees the formulation development of clinical trials materials. She is a current member of AAPS, CRS, ISPE, and AACP.

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Telephone House
69-77 Paul Street
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