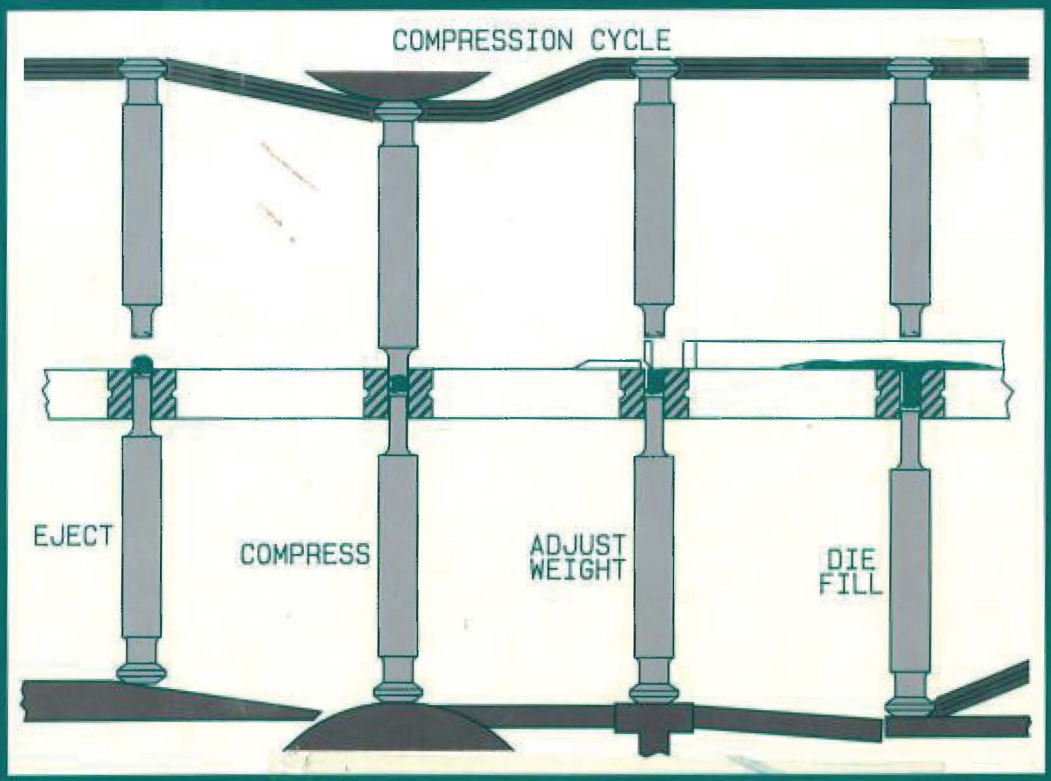
Pharmaceutical Dosage Forms: Tablets Volume 3

Second Edition, Revised and Expanded

Edited by Herbert A. Lieberman, Leon Lachman, and Joseph B. Schwartz



PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes

VOLUME 3

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Changes that have occurred in coating processes reflect a desire to:

Consistently obtain a finished product of high and reproducible quality
Achieve processes in which the economics are maximized, particularly with respect to process times and equipment utilization

While the methods for applying coatings to solid-dosage forms are varied, and some are described elsewhere in this book, this chapter will focus on the processes of sugar coating and film coating, and will discuss these processes with respect to:

Raw materials
Application techniques
Potential problems
Available coating equipment

II. SUGAR COATING

A. Introduction

The process of sugar coating, which has its origins in the confectionery industry, is perhaps one of the oldest pharmaceutical processes still in existence.

Although in recent years modernization of the process with respect to panning equipment and automation has taken place, sugar coating is still considered to be more of an art rather than a science.

While methods (and materials) for coatings date back over 1000 years (early Islam makes reference to pill coatings based on mucillage of psyllium seeds), the current pharmaceutical process of sugar coating originated in the middle of the nineteenth century when sugar as a raw material became plentiful, and the forerunner of modern panning equipment was invented.

Although the tendency is to produce pharmaceutical coating pans from stainless steel, early pans were made from copper because drying was effected by means of an externally applied heat source. Current thinking, even with conventional pans, is to dry the coated tablets with a supply of heated air and to extract the moisture and dust-laden air from the vicinity of the pan.

Although the sugar-coating process has experienced declining popularity in the United States, it is still retained by many companies worldwide, since many advantages can be realized, including:

Raw materials are inexpensive and readily available
Raw materials are widely accepted with few regulatory problems (with the exception of perhaps colors)
Inexpensive, simple equipment can be used
Sugar-coated products are esthetically pleasing and have wide consumer acceptability
The process is generally not as critical (as film coating) and recovery (or rework) procedures are more readily accomplished

However, in spite of the relative simplicity of the sugar-coating process, it does have some potential shortcomings, for example:

- The size and weight of the finished product results in increased packaging and shipping costs
- The brittleness of the coatings renders the coated tablets susceptible to potential damage if mishandled
- The achievement of high esthetic quality often requires the services of highly skilled coating operators
- The final gloss is achieved by a polishing step which can make imprinting difficult
- The inherent complexity (from the standpoint of the variety of procedures and formulations used) of the process makes automation more difficult

In spite of these difficulties, many companies have made excellent use of modern process technology (including automation), so that the requirements of current GMPs, including documentation, are readily achieved with a high degree of reproducibility in the quality and performance of the finished product.

B. Raw Materials Used in Sugar Coating

As expected, the major ingredient used is sugar (sucrose), although this may be substituted by other materials (such as sorbitol) for low calorie/diabetic products (typically in the candy industry). Sugar-coating formulations are for the most part aqueous.

The sugar-coating process consists of various steps, each designed to achieve a particular function. Consequently, a variety of additives may be incorporated into each type of formulation. Examples of such additives are:

- Fillers (calcium carbonate, talc, titanium dioxide)
- Colorants (dyes, aluminum lakes, iron oxides, titanium dioxide)
- Film formers (acacia, gelatin, cellulose derivatives)
- Antiadhesives (talc)
- Flavors
- Surfactants (as wetting agents and dispersion aids)

Although most of the coating formulations used in the sugar-coating process are applied as liquids, some (e.g., dusting powders) are applied dry.

A typical sugar-coating process encompasses five stages:

1. Sealing
2. Subcoating
3. Grossing
4. Color coating
5. Polishing

While each of these stages is varied, the common feature throughout is that the process requires repeated applications of coating liquid, each

application followed by a period during which the tablets are allowed to tumble freely to allow complete distribution of the coating materials, and finally, a drying period when moisture is removed from the coating prior to the next application.

Sealing

Most of the coating formulations used in the sugar-coating process are aqueous, whereas tablet cores are typically porous, highly absorbent, and formulated to disintegrate rapidly when they make contact with water. Consequently, if these cores are not appropriately protected at the outset, ultimate product stability (both physical and chemical) can be seriously compromised. The purpose of sealing is to offer this initial protection, and to prevent some tablet core ingredients from migrating into the coating, and ultimately spoiling the appearance of the final product.

Sealing is accomplished by the application of a polymer-based coating (either by ladle or spray techniques) to the surfaces of the tablet cores. Examples of polymers that might be used include shellac, zein, hydroxypropyl methylcellulose (HPMC), polyvinyl acetate phthalate (PVAP), and cellulose acetate phthalate (CAP). These are typically dissolved (at a 15–30% w/w concentration) in an appropriate organic solvent, preferably one of the denatured ethanol products.

While use of shellac has been universal, this polymer can cause problems. One problem results from the fact that shellac can polymerize on storage, causing the solubility characteristics of the coating to change. This problem can either be minimized by incorporating PVP into the shellac formulation [1] or by using one of the other, more stable polymers (such as PVAP).

When using any of the water-insoluble polymers as the basis for a seal-coat formulation, it is important to apply only the minimum quantity of coating needed to give the appropriate protection; otherwise drug-release characteristics may well be affected.

When the seal coat is applied by a ladle technique, detackifiers, such as talc, are often used to minimize the risk of "twinning" or clumping. Overzealous use of talc should be avoided, however, otherwise it might be difficult for the subsequent sugar coat to bond to the surface of the seal coat.

Finally, if the final product is to have enteric properties, this result is usually achieved by using one of the enteric polymers (such as PVAP or CAP) as the basis for the seal coat and ensuring that sufficient coating material is applied.

Subcoating

Subcoating is the first major step of the sugar-coating process and provides the means for rounding off the tablet edges and building up the core weight. It also provides the foundation for the remainder of the sugar-coating process, with any weakness in the final sugar coat often being attributable to weaknesses in the subcoat.

In order to facilitate this buildup, subcoating formulations almost always contain high levels of fillers such as talc, calcium carbonate, calcium sulfate, kaolin, and titanium dioxide. In addition, auxiliary film formers such as acacia, gelatin, or one of the cellulose derivatives may

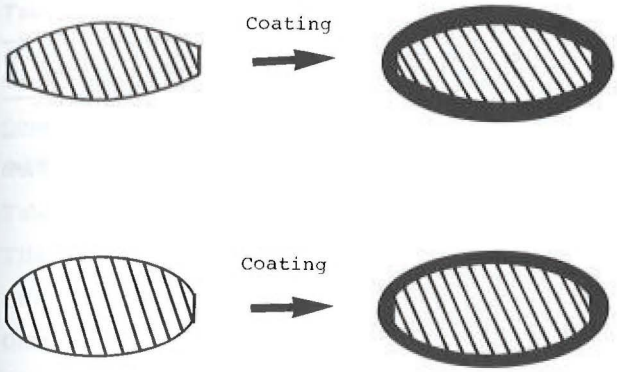

Figure 1 Schematic of examples of acceptable tablet-core shapes for sugar coating.

also be included in order to improve the structural integrity of the coating.

It is important during subcoating to get effective coverage of the coating material over the tablet corners and on the edges if a quality result is to be achieved. To this end, selection of appropriate tablet shapes is important. Certainly, tablet shapes which minimize the corners (such as tablets compacted on deep concave punches or dual radius punches), as shown in Figure 1, can aid in effective coverage. Additionally, it is necessary to minimize tablet edge thickness, otherwise twinning will be more prevalent and incomplete edge coverage (by the coating) is likely to occur (Fig. 2).

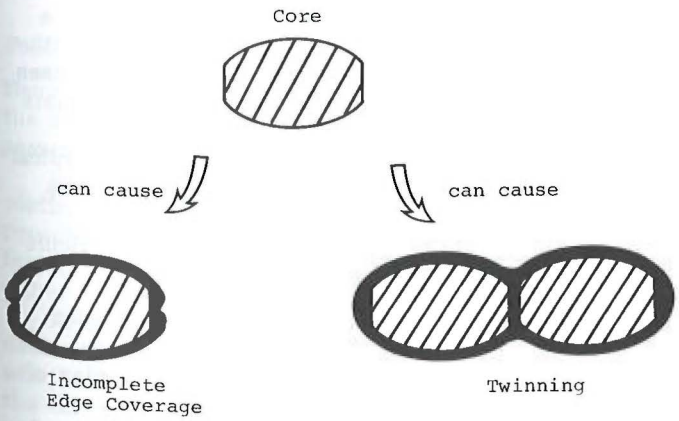

Figure 2 Schematic example of poor tablet core shape for sugar coating. (The twinning problem illustrated is more prevalent when using capsule-shaped tablets.)

Table 1 Examples of Formulations Used in the Lamination Subcoating Process

		I	II
Binder solutions	Gelatin	3.3% w/w	6.0% w/w
	Gum acacia	8.7	8.0
	Sucrose	55.3	45.0
	Distilled water	32.7	41.0
Dusting powders	Calcium carbonate	40.0% w/w	–
	Titanium dioxide	5.0	1.0
	Talc (asbestos free)	25.0	61.0
	Sucrose (powdered)	28.0	38.0
	Gum acacia	2.0	–

Two main approaches to the process of subcoating are often practiced, depending on whether a lamination technique or a suspension subcoat formulation is used. Each has its distinct features and advantages.

LAMINATION PROCESS. The lamination process is perhaps the older of the two techniques used, and involves alternate applications of binder solutions and dusting powder until the required level of coating is achieved. While materials and formulations for binder solutions and dusting powders are varied, some typical formulations are shown in Table 1.

When using the lamination technique it is important to ensure that a careful balance is achieved between the relative amounts of binder solution and dusting powders used. Underutilization of dusting powders increases the risk of sticking and twinning, whereas overdusting can create tablets that have brittle coatings.

While achievement of quality results with the lamination process typically requires employment of skilled operators, there is no doubt that this type of process can permit rapid buildup of the coating.

On the downside, the lamination process can be messy, more difficult to use by less-skilled operators, and more difficult to automate.

SUSPENSION SUBCOATING PROCESS. In simple terms, suspension subcoating formulations result from combining the binder and powder formulations used in the more traditional lamination process. Examples of a typical formulation are shown in Table 2.

Use of the suspension subcoating approach reduces the complexity of the process, allowing it to be used effectively by less-experienced operators, and ultimately facilitates automation of the process.

Table 2 Examples of Suspension Subcoating Formulations

	I	II
Sucrose	40.0% w/w	58.25% w/w
Calcium carbonate	20.0	18.45
Talc (asbestos free)	12.0	–
Titanium dioxide	1.0	1.00
Gum acacia	2.0	–
Gelatin (120 bloom)	–	0.01
Distilled water	25.0	22.29

Grossing (or Smoothing)

In order to manufacture a quality sugar-coated product, it is imperative that the surface of the coating be smooth and free from irregularities prior to application of the color coat.

While the requisite smoothness may be achieved during the application of the subcoat, it is not unusual to find that further smoothing (prior to color coating) is necessary. Depending on the degree of smoothing required, the smoothing coating may simply consist of a 70% sucrose syrup, often containing titanium dioxide as an opacifier/whitening agent, and possibly tinted with other colorants to provide a good base for subsequent application of the color coat.

If a substantial amount of smoothing is required, as in the case in which the subcoat tablets have a pitted surface, other additives (such as talc, calcium carbonate, corn starch) may be used in low concentrations to hasten the smoothing process.

Color Coating

Many would agree that color coating is one of the most important steps in the sugar-coating process because of the immediate visual impact that is associated with overall quality.

Use of appropriate colorants, which are dissolved or dispersed in the coating syrup, allows the desired color to be achieved. Two basic approaches to coloring sugar-coating syrups exist, each giving rise to differing coating techniques. These two approaches involve the use of either water-soluble dyes or water-insoluble pigments.

Prior to the 1950s, soluble dyes were used extensively to achieve the desired color. This technique was handled by an experienced coater, who had acquired his skill over many years of work experience. Much of the color coating required 2 or 3 days, and unless handled properly, resulted in tablets that were nonuniform in color or mottled, since the soluble dye can migrate to the surface during drying. Additionally, color

reproducibility from batch-to-batch was not predictable, and light sensitivity with subsequent fading was also a problem when using dyes.

The use of insoluble, certified lakes has virtually replaced the soluble dye in pharmaceutical tablet coating. Lakes have several advantages; namely, color migration on drying is eliminated, since lakes are insoluble, light stability is improved, mottled tablets are a rare occurrence, and coating time is substantially shortened. While lakes are insoluble, they are not totally opaque. Consequently, coloring properties can be optimized by combining lakes with opacifiers such as titanium dioxide. The most efficient process for color coating involves the use of predispersed, opacified lake suspensions. By varying the ratios of lake and opacifier, various shades can be produced.

DYE-COATING PROCESS. The features of a typical sugar-coating process that utilizes water-soluble dyes as colorants include:

Sequential application of coating syrups containing specific dye concentrations (typically, as coating progresses, dye concentrations in the syrup may be increased until the target color is achieved)
Addition of a quantity of colored syrup (at each stage) that is sufficient to just wet the *total* tablet surface, followed by gentle drying to achieve requisite smoothness and prevent color migration
Employment of relatively low concentrations of colorant (necessary to achieve final color uniformity), resulting in a requirement to make anywhere up to 50 separate color syrup applications (particularly for dark colors)

There is no doubt that in the hands of a skilled operator the quality of sugar-coated tablets that employ the dye-coating method are difficult to match (this is particularly true from the standpoint of "cleanliness," depth, and "brilliance" of the final color).

However, such a process is not without its difficulties, namely:

Color migration problems (resulting from either underdrying or too rapid a drying) are commonplace.
Color variability, across the surface of individual tablets, which occurs as the result of unevenness of the subcoat layer and transparency of the color coat.
Tablet-to-tablet color variability which may result because the transparent coloring system has not been uniformly distributed.
Batch-to-batch color variation which is likely to occur because of variability in the total quantity of color applications made, or as a result of small differences in amount of colorant weighed out for each batch (water-soluble dyes produce very intense colors and a little goes a long way).
The process is time consuming (because of the slow drying required and the need to make so many individual color applications).

PIGMENT-COATING PROCESS. Pigments have demonstrable advantages over water-soluble dyes, two important ones being:

1. Lack of solubility in aqueous media (which eliminates color migration on drying)
2. Superior light stability

However, because pigments are discrete, insoluble particles, careful attention must be paid to the pigment-dispersion process. Hence, the popularity of commercially available pigment-dispersion concentrates.

Some of the major characteristics of sugar-coating formulations and processes when pigment colorant systems are used include:

- Use of a single-color concentration throughout the color-coating process, thus making it easier to achieve the target end color (in order to obtain a different color, it is necessary to vary the ratios of the lake pigments with respect to the opacifier, titanium dioxide)
- Achievement of batch color uniformity after only a few applications of colored syrup (often color development is complete after eight to 10 applications, and the remaining five to seven applications are simply used to smooth off the tablet surface)
- Reduced drying times resulting from the fact that the insoluble colorants do not migrate on drying, and thus can be dried more rapidly
- Overall shortened color-coating process as a result of reduced number of color applications and shortened drying times

One should, however, be aware of what some might construe to be disadvantages with pigment coloring systems and the associated coating process:

- Colorants derived from pigments (especially when lakes are used in combination with titanium dioxide) are generally not as bright or clean-looking as those obtained with soluble colorants.
- If the pigment color-coating process is rushed, it is relatively easy to produce rough tablets that are difficult to polish.
- There is a need to ensure that pigments are effectively dispersed in the coating syrup (certainly, pigment color concentrates eliminate this problem), otherwise color "specking" might be a problem.
- Since most pigment coloring systems contain lakes (which are typically acidic), it is inadvisable to keep coating systems hot for any length of time once the color has been added; otherwise excessive amounts of invert sugar will be formed.

With the exception of the first of these problems, all the others can easily be avoided, and thus advantages of the pigment coating process tend to prevail, making it the process of choice.

Summarizing these advantages, they are:

- Greater ability to get a uniform color on the surface of each tablet
- Greater batch-to-batch color uniformity
- Significant reduction in thickness of the color coat
- Significant reduction in processing time

Polishing (Glossing)

Since freshly color-coated tablets are typically dull (i.e., they have a matte surface finish), it is necessary to polish them in some way to achieve the gloss that is typical of finished sugar-coated tablets.

While methods to achieve a desirable gloss tend to vary considerably, it is generally recommended that tablets should be trayed overnight (prior to polishing) to ensure that they are sufficiently dry. Excessively high moisture levels in tablets submitted for polishing will:

Make achievement of a good gloss difficult
Increase the risk of "blooming" and "sweating" over longer periods of time

Glossing or polishing can be carried out in various types of equipment (e.g., canvas- or wax-lined pans), including that used for applying the sugar coating itself (which is more typical in automated processes).

Polishing systems that may be used include:

Organic-solvent-based solutions of waxes (beeswax, carnauba wax, candelilla wax)
Alcoholic slurries of waxes
Finely powdered mixtures of dry waxes
Pharmaceutical glazes (typically alcohol solutions of various forms of shellac, often containing additional waxes)

Printing

If sugar-coated tablets are to be further identified with a product name, dosage strength, or company name or logo, this has to be accomplished by means of a printing process.

Typically, such printing involves the application of a pharmaceutical branding ink to the coated tablet surface by means of a printing process known as offset rotogravure.

Sugar-coated tablets may be printed either before or after polishing, with each approach having its advantages and disadvantages. Printing prior to polishing enables the ink to adhere more strongly to the tablet surface, but any legend may subsequently be removed by either friction or as a result of contact with organic solvents during the polishing process. Printing after polishing avoids the problem of print rub-off during polishing, but branding inks do not always adhere well to the waxed tablet surface. Adhesion of printing inks can be enhanced by application (prior to printing) of a modified shellac, preprint base solution.

C. Application Techniques

Application of sugar coatings to pharmaceutical tablets has long been considered one that requires a significant amount of skill on the part of the operator. While this philosophy has a lot of truth in it, and while it is certainly difficult for untrained operators to achieve quality results, the employment of special techniques (such as the use of suspension subcoat formulations and coatings colored with proprietary pigment dispersions) makes quality results achievable even for less-skilled operators.

While many different types of coating formulation (Sec. II.B) will be applied during the coating process, similarities in application exist for each of them.

The basic application procedure in each case involves three steps in sequence:

1. Application of an appropriate volume (sufficient to completely cover the surface of every tablet in the batch) of coating liquid to a cascading bed of tablets
2. Distribution of the coating liquid uniformly across the surface of each tablet in the batch
3. Drying of the coating liquid once uniform distribution is achieved

Specific details of actual procedures adopted may vary from company-to-company. However, the ultimate goal in each case is to ensure that the coating is uniformly distributed throughout the batch. Although this goal may be facilitated by the manner in which the coating liquid is applied, and by manual stirring of the wet tablets to help eliminate "dead spots" (regions in the tablet bed that are difficult to reach with the coating liquid), the main mechanism for distribution of the coating liquid relates to the shearing action that occurs as tablets cascade over one another.

For the greatest period of time, sugar-coating liquids were applied manually by allowing premeasured quantities of coating liquid to be poured across the moving tablet bed. In recent times, there has been a greater reliance on mechanical dosing techniques, involving the use of spray guns or dosing "sparges" (Fig. 3).

One of the major misconceptions concerning the use of mechanical dosing techniques, particularly spray guns, is that they can exert a major influence on uniformity of distribution of the sugar-coating liquid. Again, it is important to emphasize that the main factor controlling distribution of the coating liquid relates to contact between the cascading tablets, and transfer of liquid from one tablet to another as the result of this contact. Thus, particularly when using spray guns, it is not necessary to finely atomize the coating liquid in order to ensure effective distribution of that liquid. Indeed, excessive atomization can cause "fogging" where much of the coating liquid can end up on the walls of the pan rather than on the tablets. Consequently, many advocates for the use of spray guns simply allow the liquid to stream from the nozzle. For this reason, use of a device similar to that shown in Figure 3 can be equally effective and less expensive than using spray guns.

Summarizing, since coating uniformity is achieved as the result of tablet-to-tablet transfer of liquid coating material, it is not necessary for each tablet to pass through the zone of application (which is a necessity in the film-coating process). Factors which influence coating uniformity in the sugar-coating process are that:

The coating material remains fluid until it is spread across the surface of every tablet in the batch.

Sufficient volume of coating liquid is applied to ensure that every tablet in the batch is capable of being wetted (thus liquid volumes may have to be changed as the process progresses in order to reflect changes in tablet size and drying conditions).

The coating pan exhibits good mixing characteristics, particularly so that dead spots are avoided (many coating pans of conventional design, i.e., the traditional pear-shaped design, may have to be modified by inclusion of mixing baffles, otherwise mixing may have to be augmented by manual stirring of the tablets by the operator).

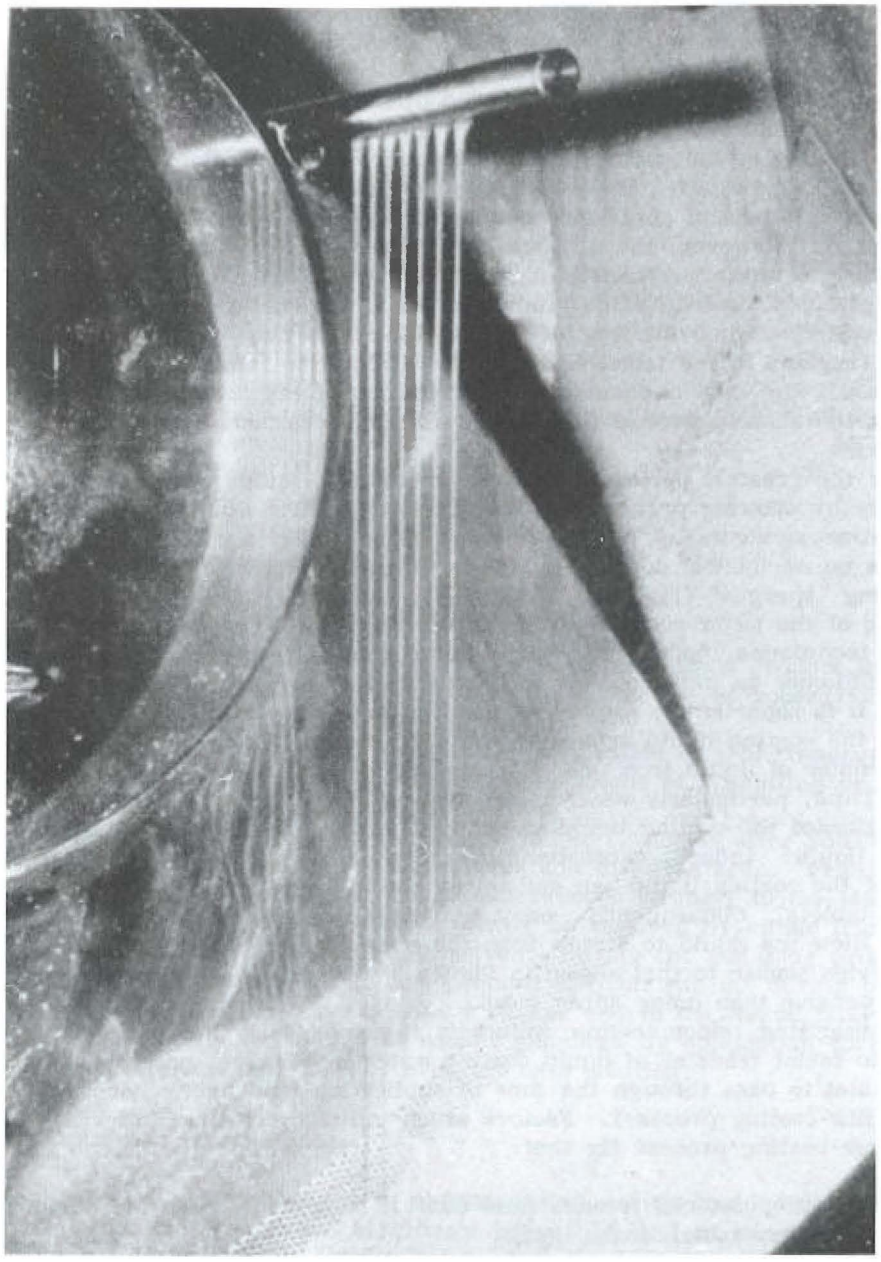

Figure 3 Figure showing a dosing sparge for sugar coating.

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D. Problems in Sugar Coating

In any coating process, a variety of problems may arise. Often such problems may be related to formulation issues that have been compounded by those associated with processing.

Problems with Tablet Core Robustness

The attritional effects of any coating process on tablet cores is well understood. Consequently, tablet cores must be sufficiently robust to resist the stress to which they will be exposed during coating.

With this in mind, particular attention must be paid to important tablet physical properties such as hardness (diametral crushing strength), friability, and lamination tendency. Failure to address these issues is likely to result in a situation in which tablet fragmentation occurs during the coating process.

Tablet fragmentation is not only a problem from the standpoint that the broken tablets will obviously not be saleable (and thus would have to be inspected out), but additionally, the broken fragments may typically become "glued" (because of the adhesive nature of the coating fluids) to the surface of undamaged tablets (Fig. 4); thus spoiling a significant portion of the batch.

Quality Problems with Finished Tablets

CHIPPING OF COATINGS. Sugar coatings are inherently brittle and thus prone to chipping if mishandled. Addition of small quantities of polymers (such as cellulosics, polyvinyl pyrrolidone, acacia, or gelatin) to one or more of the various coating formulations often helps to improve structural integrity, and thus reduces chipping problems.

Excessive use of insoluble fillers and pigments tends to increase the brittleness of sugar coatings, and thus should be avoided where possible.

CRACKING OF THE COATING. Tablet cores that expand, either during or after coating, are likely to cause the coating to crack (Fig. 5). Such expansion may result from moisture absorption by the tablet core, or may be caused by stress-relaxation of the core after compaction (a phenomenon which is known to occur, for example, with ibuprofen). Moisture sorption can be minimized by appropriate use of a seal coat, whereas expansion due to postcompaction stress relaxation can be resolved by extending the time between the compaction event and commencement of sugar coating.

NONDRYING COATINGS. Inability to dry sugar coatings properly, especially those based on sucrose, is often an indicator that excessive levels (greater than 5%) of invert sugar is present. Inversion of sucrose is exacerbated by keeping sucrose syrups at elevated temperatures under acidic conditions for extended periods of time. Such conditions occur when sugar-coating solutions containing aluminum lakes are kept hot for too long, or such sugar-coating formulations are constantly being reheated to redissolve sugar that is beginning to crystallize out.

TWINNING (OR BUILDUP OF MULTIPLES). By their very nature, sugar-coating formulations are very sticky, particularly as they begin to

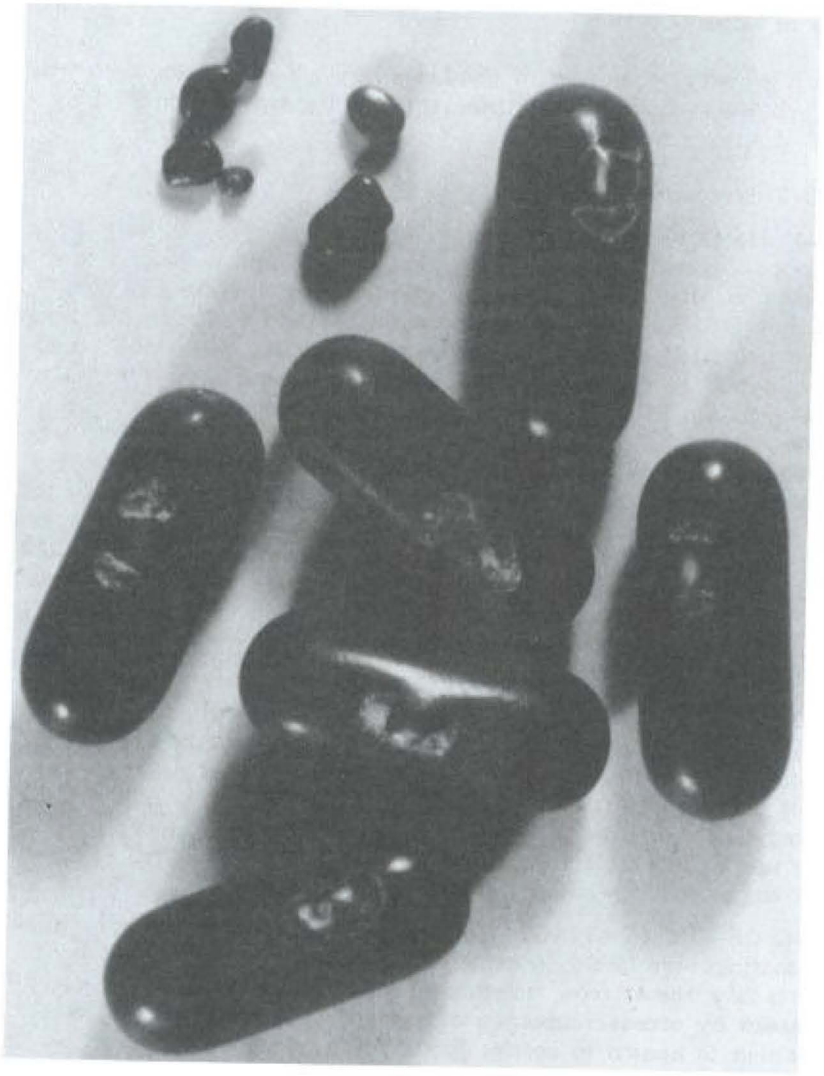

Figure 4 Figure showing how broken tablets can ruin a whole batch of product in sugar coating.

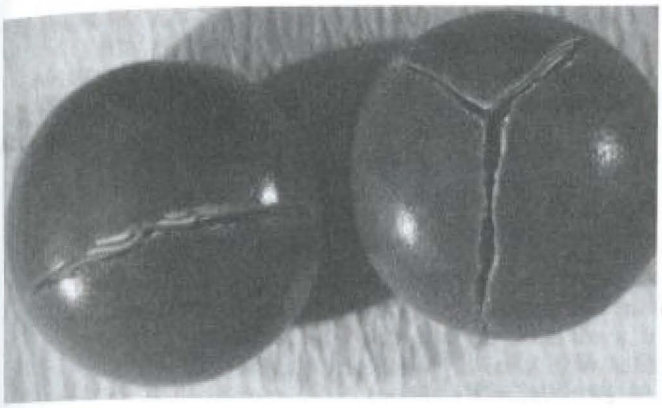

Figure 5 Sugar-coated tablets with cracked coating.

dry, and allow adjacent tablets to stick together. Buildup of multiples really becomes a problem when the tablets being coated have flat surfaces (as shown in Fig. 2) which can easily come into contact with one another. This can be particularly troublesome with high-dose, capsule-shaped tablets that have high edge walls. Appropriate choice in tablet punch design can be effectively used to minimize the problem.

UNEVEN COLOR. Because it has a major impact on final tablet appearance, the color-coating stage of the sugar-coating process is critical to ultimate tablet quality.

Uneven distribution of color, particularly with the darker colors, is often visually apparent, and thus a major cause of batch rejection. Many factors may contribute to this type of problem, including:

Poor distribution of coating liquids during application. This may be caused by poor mixing of tablets in the coating process, or failure to add sufficient liquid to coat completely the surface of every tablet in the batch.

Color migration of water-soluble dyes while the coating is drying.

Unevenness of the surface of the subcoat when using dye-colored coatings. This unevenness causes a variation in thickness of the transparent color layer that is perceived as different color intensities.

"Washing back" of pigment-colored color coatings. While pigments do not migrate on drying, if excessive quantities of coating liquid are applied during the coloring process, there is a tendency for the previously applied (and dried) color layers to be redissolved and distributed nonuniformly; thus giving rise to nonuniform appearance. This problem is particularly noticeable for formulations predominantly colored with aluminum lakes where the level of opacifying pigments (such as titanium dioxide) is low (i.e., dark colors).

Excessive drying between color applications. This can cause erosion of the color layer and contributes to unevenness in the color coat.

"BLOOMING" AND "SWEATING." Residual moisture (in finished sugar-coated tablets) can often be a problem. Over a period of time, this moisture can diffuse out and affect the quality of the product. Moderate levels of moisture egress cause the polish of the product to take on a fogged appearance, a phenomenon often termed blooming. At higher levels (of moisture egress), the moisture may appear like beads of perspiration on the tablet surface. This second phenomenon, often called sweating, can be much more serious, since tablets stored in closed containers will ultimately stick together.

Obtaining appropriate levels of moisture in the sugar coating is conducive to good polish characteristics (polishing can be difficult if the tablets are too dry) and avoidance of sweating and blooming. Thus, great care has to be taken with the drying stage at the end of each application of coating liquid as well as to selection of appropriate racking/drying of tablets prior to polishing.

"MARBLING." One of the secrets to achieving a high-quality, sugar-coated product is to ensure that color is uniformly distributed in the color layer, and at the same time at the end of the application of the color coating that a smooth coating surface (prior to polishing) is obtained.

Failure to achieve the requisite smoothness often results in a marbled appearance on polishing. This problem occurs as the result of the collection of wax in the small surface depressions (Fig. 6) of a rough coating and is particularly evident with darker colors.

Recovery of Reject Sugar-Coated Tablets

Owing to the amount of material applied as a coating in the sugar-coating process, it is not appropriate to grind up reject sugar-coated tablets for recompaction. One potentially viable recovery procedure (although one not without its difficulties because of handling problems) is to wash off the sugar coating by carefully dipping the coated tablets (held on a screen)

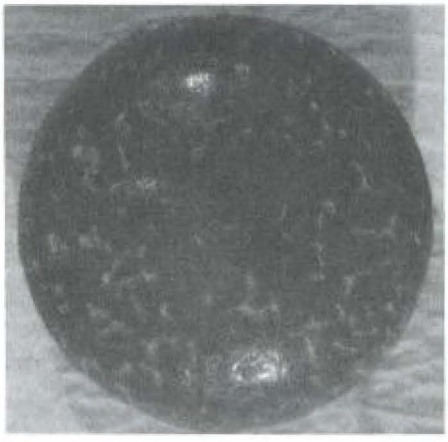

Figure 6 Figure showing marbled appearance on the surface of sugar-coated tablets resulting from wax buildup during polishing of rough tablets.

into a water bath until sufficient coating is removed such that on subsequent refinishing, the desired quality is achievable. Once the requisite quantity of coating is removed, the tablets can be dried by tumbling in a coating pan under a warm air stream (50°C). Such a procedure must obviously be validated to ensure that overall product quality is not compromised for the sake of improving visual quality.

III. FILM COATING

A. Introduction

Film coating is quite a complex process that draws on technologies associated with polymer chemistry, industrial adhesives and paints, and chemical engineering. The process of film coating can be simplified to represent one that involves the application of thin (in the range of 20–200 μm), polymer-based coatings to an appropriate substrate (tablets, beads, granules, capsules, drug powders, and crystals) under conditions that permit:

- Balance between, and control of, the coating liquid addition rate and drying process
- Uniformity of distribution of the coating liquid across the surface of product being coated
- Optimization of the quality (both visual and functional) of the final coated product

While film coatings can be applied by manual ladling techniques, they now almost always utilize a spray-atomization technique.

In the spray-application process, bulk coating liquids are finely atomized and delivered in such a state that droplets (of coating liquid) retain sufficient fluidity to wet the surface of the product being coated, spread out, and coalesce to form a film. Because of the highly adhesive (or "tacky") nature of partially dried droplets, it is imperative that the droplets of coating liquid dry almost instantaneously the moment they contact the surface of the substrate; otherwise sticking and picking will occur. Hence, there is a need to strike an appropriate balance between liquid application rate and the drying process. A simplified schematic of the film-coating process is shown in Figure 7.

Because of the rapid drying that typically takes place during the application of film coatings, uniformity of distribution of the coating is controlled both by uniformity of application of the coating liquid (i.e., the number of spray guns used, types of spray patterns used, and fineness of atomization of coating liquid) and the uniformity of mixing (controlled by pan speed, baffle design, tablet size and shape) of the product being coated. Unlike sugar coating, it is not desirable in film coating to have partially dry coating material being transferred from one tablet to another, since this would create imperfections in the coating that would be readily evident at the end of the coating process. However, this does not mean that the tumbling action (of tablets, etc.) in a coating process has no effect on ultimate coating structure. On the contrary, Rowe [2] has described how the high shear developed at the tablet surface (as the result of the mutual rubbing together of adjacent tablets) can promote sufficient flow of the coating (which induces a leveling effect) to achieve better cohesion within the film.

Table 12 Common Plasticizers Used in Conventional Film Coating

Class	Examples
1. Polyhydric alcohols	Propylene glycol
	Glycerol
	Polyethylene glycols
2. Acetate esters	Glyceryl triacetate (Triacetin)
	Triethyl citrate
	Acetyl triethyl citrate
3. Phthalate esters	Diethylphthalate
4. Glycerides	Acetylated monoglycerides
5. Oils	Castor oil
	Mineral oil

Use of triacetin as a plasticizer in aqueous formulations, although less popular, may have certain advantages when trying to improve the moisture-barrier properties of the film coating. This effect has recently been confirmed by data presented by Johnson et al. [41].

Colorants

Any of the approved colorants discussed earlier would be suitable for use in conventional film coatings, although preference is usually shown for insoluble colorants (pigments).

C. Modified-Release Film Coatings

Film-coating techniques can be effectively used to modify the release of the active ingredient from a pharmaceutical solid-dosage form.

While modern pharmaceutical technology makes possible the design of dosage forms that exhibit modified time of release or rate of release (or both) of the active ingredient, a plethora of terminology (relating to these kinds of dosage forms) exists that confuses formulators, prescribers, and consumers alike.

The *United States Pharmacopeia/National Formulary* (USP/NF) has simplified this terminology somewhat by defining a modified-release dosage form as one in which "the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. . . ."

Under this umbrella definition, the USP/NF recognizes two types of modified-release dosage form:

1. Extended release: One that permits at least a twofold reduction in dosing frequency as compared to the situation in which the drug is presented as a conventional dosage form (extended-release dosage forms are often called sustained-release or controlled-release dosage forms)
2. Delayed release: One that releases the active ingredient at some time other than promptly after administration (an enteric-coated product is an example of this type of dosage form)

Enteric Film Coatings

By definition, enteric coatings are those which remain intact in the stomach (and exhibit low permeability to gastric fluids), but break down readily once the dosage form reaches the small intestine. The prime uses of such coatings are:

To maintain the activity of drugs that are unstable when exposed to the gastric milieu (e.g., erythromycin and pancreatin)
To minimize either nausea or bleeding that occurs with those drugs that irritate the gastric mucosa (e.g., aspirin and certain steroids)

Early approaches to preparing enteric-dosage forms involved treating gelatin capsules with formalin or coating tablets with shellac. Both of these approaches were unreliable, since the solubility of the membrane (which is responsible for the enteric effect) can be unpredictable. Modern enteric coatings are usually formulated with synthetic polymers that contain ionizable functional groups that render the polymer water soluble at a specific pH value. Such polymers are often referred to as polyacids.

Examples of commonly used enteric-coating polymers (including those introduced more recently) are listed in Table 13. Since many of these polymers are esters, they may be subject to degradation (as a result of hydrolysis) when exposed to conditions of elevated temperature and humidity. Such hydrolysis can result in a substantial change in enteric properties.

While many of the polymers shown in Table 13 have been used for many years in enteric-coating formulations, the special aqueous-solubility requirements for an enteric polymer have delayed thr routine employment of *aqueous* enteric-coating technology. More recently, various systems of aqueous enteric coating have been introduced, and examples are shown in Table 14. As these examples suggest, many of the coating systems exist as dry powders, with the coating liquid being prepared shortly before use by dispersing (or dissolving) the polymer in water. The reason for supplying many enteric coating systems as dry powders is to avoid problems of poor stability (due to hydrolysis) when these polymers are exposed to water for extended periods.

Very little information (one exception being that for PVAP) [42] is given regarding the stability of many of these polymers once converted into aqueous dispersions.

The performance of enteric-coated dosage forms has often been open to question. Certainly, much of the uncertainty can be related to the earlier common use of "natural" polymers (such as shellac) and simplistic coating procedures. The use of synthetic, predictable polymers and the adoption

Table 13 Examples of Enteric-Coating Polymers

Polymer	Comments
Cellulose acetate phthalate (CAP)	Subject to hydrolysis (high)[b]
Cellulose acetate trimellitate (CAT)	Subject to hydrolysis[b]
Polyvinyl acetate phthalate (PVAP)	Subject to hydrolysis (low)[b]
Hydroxypropyl methylcellulose phthalate (HP)	Subject to hydrolysis (medium)[b]
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	Subject to hydrolysis (low)[b]
Poly (ME-EA) 1:1[a]	–
Poly (MA-MMA) 1:1[a]	Relatively high dissolution pH
Poly (MA-MMA) 1:2[a]	Relatively high dissolution pH

[a]MA, methacrylic acid; EA, ethylacrylate; MMA, methyl methacrylate.

[b]When exposed to conditions of elevated temperature and humidity.

of modern processing technology should have done much to dispel these concerns. However, problems still exist today. Unfortunately, many of the factors that can dramatically effect the performance of enteric coatings have long gone unrecognized. Ozturk et al. [43] recently presented information on some of the important factors that can influence the behavior of enteric coatings. These factors include:

- The nature of the drug in the dosage form (the presence of aspirin, for example, can greatly influence dissolution of the coating).
- The quantity of coating applied (application of excessive quantities of coating can substantially delay release of drug from the dosage form).
- The presence of imperfections in the coating (fissures or "pick" marks will destroy the integrity of the coating).
- The dissolution pH of the polymer used in the coating.
- The effect of in vitro test conditions (dissolution of the coating, and ultimate drug release, can be affected dramatically by the pH and ionic strength of the test solutions and the agitation rate).

Finally, while most enteric product are in tablet form, it has been demonstrated that enteric-coated tablets are influenced significantly by gastrointestinal (GI) transit. Focus has thus begun to shift toward using enteric-coated pellets or granules, which can give greater reproducibility [44] (with respect to release and absorption of drug).

Sustained-Release, or Controlled-Release, Film Coatings

Film-coating techniques to produce sustained-release dosage forms have been utilized since the late 1940s, when SmithKline used a pan-coating

Table 14 Examples of Aqueous Enteric-Coating Systems

Product	Form	Polymer	Comments
Eudragit L 30 D	Latex dispersion	Poly (ME-EA) 1:1[a]	System essentially contains only the polymer
Eudragit L-100-55	Spray-dried latex	Poly (ME-EA) 1:1[a]	Requires dispersing in water with addition of alkali System only contains polymer
HP-F	Dry powder	HP	Requires dispersing in water System only contains polymer
Coateric	Dry powder	PVAP	Complete system Requires dispersing in water with addition of ammonia
Aquateric	Spray-dried pseudolatex	CAP	System essentially contains only polymer Requires dispersing in water
HPMCAS	Dry powder	HPMCAS	System contains only polymer Requires dispersing in water
CAP	Dry powder	CAP	System contains only polymer Requires dissolving in water with aid of alkali (ammonia)
CAT	Dry powder	CAT	System contains only polymer Requires dissolving in water with aid of alkali (ammonia)

[a]MA, methacrylic acid; EA, ethacrylic acid.

Table 15 Examples of Coating Materials Used in Sustained-Release Film-Coating Formulations

Coating material	Membrane characteristics
Fats and waxes (e.g., beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol)	Permeable and erodible
Shellac	Permeable and soluble (at high pH)
Zein	Permeable and soluble (at high pH)
Ethylcellulose	Permeable
Cellulose esters (e.g., acetate)	Semipermeable
Silicone elastomers	Permeable (when PEG added)
Acrylic esters	Permeable

process to apply various mixtures of fats and waxes (dissolved in organic solvents) to drug-loaded beads. Since that time, a variety of materials and coating processes have been used for the same purpose. Drug release from such sustained-release products is moderated by the film coating which acts as a membrane that allows infusion of GI fluids and the outward diffusion of dissolved drug. In some instances, the release process may be augmented by a coating that slowly dissolves (e.g., shellac), or is subject to digestion by enzymes (e.g., fats and waxes).

As with enteric coatings, most formulators today prefer to use synthetic polymers that have more predictable properties. A list of many of the coating materials used in sustained-release film coatings is shown in Table 15.

Various pharmaceutical forms may be used as substrates for sustained-release film coatings. These may generally be classified as:

Tablets
Multiparticulates (e.g., drug-loaded beads, granules, crystals, powders, drug/ion-exchange resin complexes)

While both general types of substrates are in current use, the preference now shows a trend toward multiparticulate systems which are perceived to have advantages such as minimization of risk of dose dumping (should membrane rupture occur) and optimization of GI transit.

Although multiparticulates (especially drug-loaded beads) were once commonly film coated in pans, the wide variety of multiparticulate systems coated today often requires specialized processing techniques that involve the use of fluid-bed coating equipment.

As with other types of film coating, great interest has been shown in using aqueous-coating technology for sustained-release products. Although aqueous coating systems capable of producing sustained-release film coatings were first introduced in the early 1970s, aqueous sustained-release film coating is still not yet widely practiced. Such coating systems

CAT Dry powder Requires dissolving in water with aid of alkali (ammonia)
CAT System contains only polymer Requires dissolving in water with aid of alkali (ammonia)

[a]MA, methacrylic acid; EA, ethacrylic acid.

Table 16 Examples of Aqueous Polymeric Dispersions for Sustained-Release Film Coating

Material	Polymer	Comments
1. Surelease	Ethylcellulose	Aqueous polymeric dispersion contains requisite plasticizers Addition of lake colorants should be avoided because of alkalinity of dispersion
2. Aquacoat	Ethylcellulose	Pseudolatex dispersion Requires addition of plasticizers to facilitate film coalescence
3. Eudragit NE 30 D	Poly(ethylacrylate-methyl methacrylate) 2:1	Latex dispersion No plasticizers required unless improved film flexibility is desired
4. Eudragit RL 30 D	Poly(ethylacrylate-methyl methacrylate)triethyl ammonioethyl methacrylate chloride 1:2:0.2	Aqueous polymeric dispersion No plasticizers required unless improved film flexibility is desired
5. Eudragit RS 30 D	Poly(ethylacrylate-methyl methacrylate)triethyl ammonioethyl methacrylate chloride 1:2:0.1	Aqueous polymeric dispersion No plasticizers required unless improved film flexibility is desired
6. –	Silicone elastomer	Requires addition of PEG

typically consist of aqueous dispersions of water-insoluble polymers (Table 16) which form films by a process of coalescence of submicron polymer particles. This process can be greatly affected by conditions used in the coating process, and variable results (as they relate to ultimate drug-release characteristics) can often be attributed more to lack of control over the coating process (or choice of inappropriate processing parameters) rather than to any variability in the aqueous dispersion used.

A useful description of the use of aqueous sustained-release film-coating systems has been given elsewhere [3].

Irrespective of the coating materials or types of coating systems used, most formulators prefer to prepare simple membranes that modify drug release by diffusion. Some rather unique approaches, however, have also

Table 17 Factors Influencing Drug Release from a Sustained-Release Film-Coated Dosage Form

Parameter	Influenced by
1. Surface area	Size, size distribution, and surface topography of material being coated
2. Diffusion coefficient	Formulation of film coating
	Structure of coating
	Nature of drug
3. Drug-concentration gradient across membrane	Initial drug loading
	Drug content inside the membrane at any intermediate time
	Agitation rate (which influences drug concentration on outside of membrane)
4. Membrane thickness	Size, size distribution, and surface topography of material being coated
	Quantity of coating material applied (related to theoretical quantity of coating to be applied, and coating efficiency)

been used that result in the creation of incomplete film coatings. One such approach is exemplified by the simple osmotic pump in which a delivery orifice is formed in the otherwise intact film coating by means of laser drilling [45]. Alternatively, a microporous membrane may be formed by the inclusion within the film structure of various water-soluble, powdered ingredients that may subsequently be leached out so as to enhance drug release. This approach has been described by, among others, Lindholm and Juslin [46].

Sustained-release dosage forms from which drug release is moderated by an applied film coating are often called reservoir systems. Drug release from such systems can often be described by application of Fick's first law of diffusion [47].

The rate of drug release through the membrane is *directly* proportional to surface area, diffusion coefficient, drug solubility in and drug concentration gradient across the membrane, and inversely proportional to membrane thickness. Factors which have an impact on these parameters are listed in Table 17.

With respect to drug-release characteristics, variable results may ensue through inability to effectively control many of these influencing factors. For example:

Variations (from batch-to-batch) in size and shape of the core material (to be coated) would certainly cause variations in surface area and coating thickness.

Variations in coating structure may well result from variable processing conditions that cause picking or spray drying (particularly with organic-solvent-based coating solutions) and incomplete coalescence with aqueous polymeric dispersions, and general variation in process efficiencies (which influence uniformity of distribution, and overall quantity applied, of the coating material)

D. Application Techniques in Film Coating

As in sugar coating, film-coating liquids can be applied either by manual ladling techniques or by means of spray atomization. However, in recent years, manual ladling procedures have waned in popularity and are not extensively practiced today. Some pigmented, shellac-based film-coating systems are available that facilitate ladle application, and the technique may also be used for applying certain types of enteric coatings and sustained-release coatings based on shellac.

Far more popular are techniques that utilize the spray-atomization process, which allows coating liquids to be applied in a much more controlled and reproducible manner. This precision is especially important when applying aqueous-coating formulations where liquid delivery and distribution must be carefully matched to the drying conditions developed in the process.

Three basic types of spray-atomization processes (which will be described in more detail later in this chapter) are:

1. Airless spray techniques: Because of high delivery rates, these are typically reserved for production-scale film-coating processes where organic-solvent-based coating liquids are to be applied.
2. Air-spray techniques: Typically used in small-scale coating processes and all those involving aqueous-coating systems.
3. Ultrasonic spray techniques: Still considered to be experimental techniques owing to certain limitations imposed by the rheology of the coating liquids.

E. Problems in Film Coating

Film coating, as with sugar coating, is a process that subjects the product being coated to a significant amount of stress. Unavoidable attritional effects demand that both the product being coated and the coating itself be formulated with appropriate mechanical properties if problems associated with fragmentation (of the cores) and erosion (of the cores and coating) are to be avoided.

The replacement of organic solvents with water (as either solvent or vehicle) has also increased the complexity of the process. Water has a significantly higher latent heat of vaporization (than the previously used organic solvents), and thus greater attention must be paid to monitoring (and preferably controlling) the drying conditions in the aqueous process.

Finally, the interaction between a film coating and its substrate is extremely complex. Core characteristics such as porosity, surface rugosity, and surface energy can hinder or enhance wetting by the coating liquid. Viscosity and surface tension of the coating liquid are also factors that influence the inital wetting process (of the substrate by the coating liquid).