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Coatings for Controlled-Release Drug Delivery Systems

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The history of coating of pharmaceutical products goes back many years. For example, Shakespeare refers to gilding (gold-coating) pills. Certainly, even as recently as the 1950s, pharmacists in England and the United States were trained, for example, to coat pills with silver or gold leaf or shellac. To what extent such drug delivery systems provided controlled release is a matter of conjecture. Probably the first reliable coating products were enteric-coated tablets designed to protect acid-labile drugs from degradation in the relatively low pH conditions of the stomach. However, even here there is reason to doubt the efficacy of many of the enteric-coated products that were marketed as recently as the 1960s.

It is probably true that coated pharmaceuticals that can be relied on to provide controlled release are less than 50 years of age. The development of such products has depended, to a very considerable extent, on the availability of chemically modified coatings (especially cellulose derivatives), which are supplied to the pharmaceutical industry as materials of reliable quality. Also, the improvements in coating equipment technology, especially the invention of the Wurster film-coating device, has been essential to the improvement in coating technology.

This review paper focuses on coatings and the method by which coatings can be applied to manufacture controlled-release products. It will be appreciated that coatings are sometimes applied to pharmaceutical products for reasons separate from a desire to modify drug release. For example, coatings are applied to some tablets (e.g., ibuprofen) to mask an unpleasant taste or to improve shelf life stability (e.g., conjugated estrogens). The thrust of this paper is controlled release, although in some instances coatings designed for control of drug release may also confer other benefits, such as improved ease of swallowing tablets for geriatric patients. Thus, in this paper, sugar coating, which is not normally used primarily as a method of control of drug release, receives only minimal attention.

The essential elements of a coated pharmaceutical product are a core (consisting of drug or drug plus excipients) encased by a layer or layers of materials that regulate the rate at which drug is released into the surrounding medium. The primary coating materials, usually polymeric, will often require the addition of other excipients, such as plasticizers, pore formers, or antiaggregation agents, for the product to be conveniently manufactured or for the coating to perform in the desired fashion. It is therefore appropriate to give attention to some of these types of excipients. The demarcation between a coated and a matrix-type pharmaceutical controlled-release product is not always clear. Thus, as Tice and Tabibi have pointed out (1), a microcapsule has its drug "centrally located within the particle where it is encased within a unique polymer membrane. . . . Whereas a microsphere

has its drug dispersed throughout the particle; that is the internal structure of a matrix of drug and polymer excipient."

Obviously, therefore, some of the materials used as coatings to control drug release may also be used for a similar function in matrix-type products. It is also true that some excipients may be used in coated pharmaceuticals for one purpose and be used in other pharmaceuticals to fulfill a different function. Thus, magnesium stearate, most commonly used in pharmaceutical technology as a tablet lubricant, has been used to prevent agglomeration of coated microparticles (2).

FUNDAMENTAL REQUIREMENTS

There are three preeminent requirements for any coating intended for use in controlling the rate of release of drug from a commercially available product:

1. The coating must control the release pattern of the drug such that the release profile (zero order, first-order pulsatile, or other) is within acceptable limits so it complies with the pharmacokinetic and/or pharmacodynamic requirements of the particular drug product.
2. All components of the coating must be acceptable to the relevant regulatory agencies for the route of administration and species for which the product is intended.
3. The coating materials must be commercially available at a reasonable price, reproducibly meeting functionally relevant standards so that process validation can clearly demonstrate that the manufacturing process is fully under control and that the product is likely to show an acceptably low level of batch-to-batch variation.

The first of the above three *desiderata* is not covered in this paper. It is, however, essential before considering specific coating components to give some attention to regulatory concerns.

Regulatory Concerns

There are many polymeric materials that research workers have identified as having potential for control of drug release. Unfortunately, relatively few have been approved for use in either human or veterinary pharmaceutical products. It would be most imprudent for any controlled-release project involving the use of a coating to be initiated without some attention being given to the regulatory status of the components being considered if it is hoped that ultimately a product can be marketed. It would be attractive if a simple list of "acceptable" components could be provided to readers of this paper. However, there are several reasons that prevent the preparation of such a list. The processes of globalization and harmonization are far from being complete. Although significant progress is being made, there are still important differences in the regulatory requirements of the United States, the European Union, and Japan (3–5). Thus what may be acceptable in one jurisdiction is not necessarily acceptable in another.

Even within one jurisdiction, different levels of acceptance may apply to an excipient intended for the oral or intramuscular route or for use in humans or feed animals. Also, of course, the approval of a coating component depends on the quality and quantity of minor constituents. Thus, approval may well be source specific. In the United States, the mechanism of Drug Master Files provides a most useful mode by which the manufacturer of an excipient can establish with the Food and Drug Administration (FDA) a detailed record of test data pertaining to its own marketed product. On authorization by the sponsor of the Drug Master File, FDA personnel can access the file when considering a marketing submission document such as a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) that involves use of the excipient. Information from excipient suppliers as to the current regulatory acceptability of one of their products for administration to humans or animal species by specified routes of administration can be most useful.

In the recent past, there was considerable gloom in the pharmaceutical industry about the possibilities of obtaining regulatory approval for new excipients. The formation of the International Pharmaceutical Excipient Council has raised hopes that in the future this process will be less difficult than previously (6,7).

At the time marketing permission is requested from a regulatory agency such as the FDA, the sponsor is required to demonstrate that the manufacturing process is fully validated (8). Validation of process can only be successful if there are reliable, functionally relevant standards for the raw materials so that batch-to-batch variability of such raw materials is low. This requirement can often create problems for excipients of natural origin, which commonly show considerable batch, seasonal, and source variability. Thus, unless a new coated, controlled-release product is being developed for a nutraceutical for sale through health food stores, which insist on all components being "natural," any group considering a new product is probably well advised to avoid the use of natu-

ral products such as shellac. Although shellac is still used quite substantially in coated products, it is very difficult to obtain reliable, quality material. Substantial batch-to-batch variability of shellac has been the source of difficulties with the FDA because of a lack of sufficiently precise control over drug release.

Sources of Information on Coating Materials and Processes

It is hoped that this paper provides useful coverage of the fundamentals of both coating materials and processes. However, since this field is so vast and also because it is in a state of flux, those readers interested in details on a particular coating material or piece of coating equipment may find it useful to supplement this paper with information derived from other sources.

For general coverage of the selection of formulation and processing factors in the development of coated, controlled-release products, the discussions presented by Rudnic and Kottke (9) and Schwartz and O'Connor (10) are recommended.

It is generally recognized that national pharmacopoeias (e.g., USP, BP, PF, JP) have done an excellent job in setting standards for drug substances. Unfortunately, until quite recently, comparatively little attention had been given by national or professional bodies to developing chemical, physical, or biological standards for excipients, including materials used in coatings; thus, the USP/NF does not have monographs on all the commonly used coating excipients. Although this failing is now recognized, there is still no official compendium that might be used by those seeking standards for pharmaceutical excipients. However, the *Handbook of Pharmaceutical Excipients* (11) has attained quasi-official status in this regard. Although this book is not perfect (some feel that there is an uneven level of treatment in the different monographs, and others feel that additional substances should be included), this text is often used by those seeking standards for excipients.

Another book likely to find increasing use by those looking for specifications for excipients is *Handbook of Pharmaceutical Additives*, written by Ash and Ash (12); it provides a global survey of more than 6000 products that can be accessed by trade name, chemistry, function, and manufacturer. However, for those who become directly concerned with developing a control led-release coated product, there is much to be said for consulting the manufacturers' literature. Although there is considerable variation in the content and detail of such material, much is comprehensive, detailed, and objective. Reputable manufacturers of excipients, because they derive a substantial portion of their income from the pharmaceutical industry, have an obvious interest in disseminating reliable information about their products.

Additional sources of specialized information are provided by consultants or through the services of contract houses, which provide formulation and processing development assistance. The Coating Place in Verona, Wisconsin, is one such organization. Those interested in locating such contract houses may find the Drug Information Association's *Pharmaceutical Contract Support Organizations Register* of value (13).

For those who are interested in becoming current with the most recent research developments in controlled-release coating technology, perusal (manual or computer assisted) of abstracting journals such as *Current Contents* and the primary literature in research journals is, of course, essential. Among those journals particularly likely to publish research or review papers in this area are the following: *Journal of Controlled Release*, *International Journal of Pharmaceutics*, *Drug Development and Industrial Pharmacy*, *Pharmaceutical Research*, *Journal of Microencapsulation*, *Journal of Pharmacy and Pharmacology*, and *Journal of Pharmaceutical Sciences*.

Mechanisms by Which Coatings Can Effect Controlled Release

This brief summary of mechanisms by which coatings and their components can function to control release is only intended so that the properties of the components described below can be related to the overall objective for which the product is designed.

Although there is considerable semantic confusion concerning the various terms (sustained, extended, modified) applied to controlled-release products, the present authors follow Berner and Dinh (14), who state that a controlled-release product "involves control of either the time course or location of drug delivery." The simplest mechanism by which a coating can control temporal aspects of drug release is to apply layers of a single material that can erode, melt, or become permeable at body temperature and thus allow release of drug. By a judicious selection of blends of pellets with varying thicknesses of coating, it may be possible to construct a dissolution profile of the form required for a particular drug. A number of waxes and similar materials are used for controlled-release products that function in this manner, and some of these products have been successfully marketed for many years. Recently, considerable inter-

est has been directed to the use of hot-melt coating methods, some of which incorporate modified, fluidized-bed coaters, to the manufacture of such formulations (15).

Enzymes present in the gastrointestinal tract or elsewhere have considerable potential for exploitation as agents to stimulate the breakdown of the coating of a controlled-release product and thus the release of the drug at an appropriate time after ingestion or at a particular location in the tract. For example, there is evidence that short, linear chains of amylose are resistant to enzymatic attack in the small intestine (16), but can be degraded by colonic microflora. There is thus considerable interest in coating drug delivery systems with a mixture of an appropriate form of amylose and other coating materials, such as ethylcellulose, so that the resultant drug delivery system is capable of releasing drug in the colon. The coatings described by Milojevic and associates (17) may prove to be precursors of coatings that will eventually be commercialized. Also, the possible use of coatings containing azopolymers, which are impermeable in the stomach but are converted to amides in the colon by bacteria, resulting in coating collapse, also may have potential (18).

The variation in pH that occurs as an orally administered drug delivery system moves down the gastrointestinal tract has been very widely used as the trigger to cause the release of drug from enteric-coated drug delivery systems. Polymers, often esters of phthalic acid, used as enteric coatings commonly possess pendanot carboxylic acid groups that are un-ionized in the relatively low pH of the stomach (normally about 1.5 to 4.5), but that ionize and thus repel one another as the pH rises when the delivery system enters the small intestine, thus causing coating disruption.

Diffusion of water from the exterior of the product across the coating, followed subsequently by diffusion in the reverse direction of dissolved drug, is very commonly the major mechanism by which coated products achieve control of drug release. In the least-complicated limit case, the rate of release of drug might be regarded as a simple function of the diffusion coefficient of water or the solvated drug in the polymer, which is regarded as invariant in properties. In reality, such simple conditions rarely exist in commercially available products. Coatings often contain several components in addition to the primary component polymeric species, which provides the backbone of the coating. Some of the secondary coating components may be deliberately added to modify the permeability of the primary polymer by providing channels or pores within the coating (19,20). Other materials, such as plasticizers, although they are added for entirely different reasons, can, in some instances, significantly modify drug-release rates (21). Also, it must be kept in mind that changes in processing variables, such as inlet temperature in a fluidized-bed coater, which may be required during the scale-up from laboratory to pilot scale to manufacturing scale, may result in significant changes to dissolution profiles. Thus, it is wise not to define release rate profiles rigidly for coated, controlled-release products at an early stage of the research and development process.

It should also be kept in mind that the various theoretical models that have been advanced to rationalize the release of drug from coated, controlled-release products are often quite insufficient to predict in vivo dissolution rates reliably and precisely. Although we may find it intellectually convenient to classify coatings in terms of their purported mechanism of control, the reality probably is that in many formulations the actual behavior of the product in the patient is a hybrid of several models, with surface erosion, enzymatic degradation, pH-induced changes, swelling of coating components, and so on all playing roles in the control of drug release. Finally, one must be careful not to fall into the error of assuming that in vitro dissolution tests (even those performed using the flow-through cell) are necessarily always predictive of pharmacokinetic or pharmacodynamic parameters (22).

The osmotic pump approach to the design of coated, controlled-release drug products is one of the most exciting developments that has occurred in controlled-release coating technology. Those interested in this technique should consult the appropriate literature.

Multilamellar coating products, for which there are clear differences in composition of two or more sequentially applied coats, are available and can offer special advantages. For example, Shah, Kearney, and Railkar teach in their patent (23) the use of a core containing drug that is coated with an erodible polymer coating, which, in turn, is surrounded by an enteric-release-type coating. In example 1 of their patent, Shah and his coworkers describe compaction coating of granules with an erodible coating of hydroxypropylmethylcellulose, microcrystalline cellulose, and polyvinyl pyrrolidone. These coated granules were then enteric coated by a spray method with a mixture of hydroxypropylmethylcellulose phthalate and acetylated monoglyceride. The outer coating protects the drug until the small intestine is reached. The inner coating (proximal to the core) is of such a thickness and composition that the drug is released in the colon. Multilamel-

late coatings in which each coating has a different function to perform offer the potential of developing very sophisticated, controlled-release coating systems.

If a coating is prepared around a drug delivery system in which the outermost layer contains a bioadhesive material, then the control of the locus at which drug release will occur becomes possible. A number of materials, including hydroxypropylcellulose, polyacrylic acid, and sodium carboxymethylcellose have been examined for this application (24,25). Bioadhesive coatings have potential for topical buccal, periodontal, gastric, intestinal, ophthalmic, and vaginal delivery (26–29).

MANUFACTURING METHODS FOR THE APPLICATION OF COATING MATERIALS FOR CONTROLLED RELEASE

Although considerable ingenuity has been applied to the development of manufacturing methods that might be used for the application of coating materials for controlled-release products, there are four basic approaches:

1. Pan coating using solvent evaporation
2. Fluidized-bed coating using solvent evaporation
3. Compaction coating
4. Melt coating

For those coating methods that involve the use of a solvent system (i.e., methods 1 and 2), it is convenient to define whether the solvent is aqueous or organic since the selection of solvent not only has regulatory implications (e.g., EPA), but also affects the nature or type of materials used in the coating formulation.

It is possible that other coating methods, such as various types of coacervation, may come to be of greater commercial importance for controlled-release coated products in the future.

Pan Coating

The oldest form of pharmaceutical coating—sugar coating—was an art rather than a science. The basis of the process was, in effect, to use giant "saucepans," which were continually agitated as the "cook" supervised the addition of coating fluid and the subsequent solvent evaporation. Film coating (using cellulosic-type materials for controlled release) naturally evolved from practices and equipment that had been used in sugar coating of tablets.

Conventional coating pans were top-open-ended truncated spheroids mounted on a power unit that allowed the pan to be rotated at an angle of about 45° to the horizontal at a speed of between 20 and 50 rpm. Both the ingress of coating fluid and the egress of solvent vapors were via the top of the pan.

The basic conventional pan design has been substantially improved by a number of modifications that have inter alia improved air flow, throughput, and coating uniformity. Different-shaped pans (cylinders, hexagons, and pear shapes) can offer advantages. Improvement of airflow patterns has been made using side-vented cylindrical pans and perforated pans. In the Hi-Coater (Vector) and Acela-Cata (Thomas), airflow is through the tablet bed and then out of the perforated walls of the pan. The Glatt coater allows airflow with or against the direction in which coating spray is being applied.

In the old days of manual sugar coating, the coating fluid was ladled into the pan. With modern film coating, the coating is sprayed into the tablet bed, often with the assistance of an air jet. Specialized sword and plough spray devices are available. Modern pan coating certainly represents a great improvement over traditional methods, but there are many in the industry who believe that, for the most reproducible controlled-release coatings showing minimal defects and tablet-to-tablet variability, fluidized-bed methods are probably to be preferred for many formulations.

Fluidized-Bed Coating

The fundamental principle behind fluidized-bed coating in general and the Wurster technique in particular is to suspend tablets in an upward-moving column of warm air during the coating process. This minimizes tablet abrasion and unevenness of film distribution caused by tablet-to-tablet contact. The basic Wurster fluidized-bed coating chamber is essentially cylindrical in shape, with the axis of the cylinder in the vertical plane and the top of the chamber having a convex exterior. Drying air is forced into the base of the cylinder, with the coating materials sprayed by an atomizer into the center of the base of the cylinder. An open-ended inner cylinder acts as a partition to guide the air/flow and the drug delivery units to be coated up the center of the unit, across the inside of the roof, and then down the outer space of the cylinder to the base of the unit, where the spraying and drying cycle recommences. Each time a unit of product reaches the bottom of the coating chamber, it will receive an additional "dose" of coating material. The solvent will be

removed during the period when the unit rises up the center of the chamber and descends down the periphery. The coating is therefore built up in a series of incremental steps; thus, from a processing point of view, although not in terms of composition or function, the coating is multilayered.

This cyclic process of spraying, drying, spraying, and drying performed over a period of time can allow optimum conditions for gradual deposition of a coating of uniform thickness and structure. Batches of product from about 0.5 to 500 kg can be coated, and particles as small as 50 μm up to conventional tablets can be coated on this type of equipment.

The original Wurster design has, in recent years, been significantly improved, for example, by the introduction of an improved spray-nozzle design (Wurster HS) and improved airflow (Swirl Accelerator). There are various types of fluidized-bed coating equipment now commercially available (tangential spray, top spray, etc.). Different operators have their own preferences and, of course, the individual requirements of each controlled-release coating formulation must be considered, as well as equipment availability. Probably for coating controlled-release products with aqueous coatings, bottom or tangential spray equipment is likely to be preferred. A detailed, comprehensive, and authoritative review of Wurster and other fluidized-bed coating technologies has been published by Christensen and Bertelsen (30).

Compression Coating

It is possible to compress a coating around a preformed (relatively soft) core by using a special tablet press (e.g., Drycota by Manesty or Precoter by Killian). The process basically consists of compression of the core to give a relatively soft compact that is then fed into a die of a tablet press that already has received half of the coating material. The core is centered within the die, the remainder of the coating material is added, and the product is then compressed (31). Compaction coating of tablets is not as common as perhaps some of us expected it would be when the equipment was introduced. Perhaps there is still a need for coating mixtures of improved compressibility and flow. Certainly the very high production rates that can be obtained on a tablet press make this coating approach very attractive.

Melt Coating

For those controlled-release coating materials that have a relatively low melting point and have acceptable thermostability, melt coating is possible. Materials applied in this manner include polyglycolyzed glycerides, hydrogenated vegetable oils, glyceride, ethylene glycol polymers, Carnauba wax, and synthetic wax. Top spraying, fluidized-bed-type coaters are probably the most commonly used type of equipment for this purpose, and operating temperatures as high as 200°C–250°C have been employed. Jozwiakowski, Jones, and Franz (32) and Jones and Percel (33) reviewed the processes.

Development of New Controlled-Release Coating Products

If a new controlled-release coating product is developed, it is quite likely that it will use a synthetic polymer applied to the core as an aqueous dispersion rather than using a material of natural origin dissolved in an organic solvent. There are certainly advantages in terms of process validation and likely response from regulatory agencies from the use of aqueous-based coatings of synthetic polymers. However, even with these systems, scale-up from laboratory to pilot scale to manufacturing scale may well require modification of either formulation or processing variables. Even though such changes may seem to be inconsequentially minor, it is still possible that they may cause significant changes in the release profile.

Similarly, changes in formulation or processing variables that may occur during clinical trials can modify the behavior of the product (34). In a marketing approval document submitted to a regulatory agency, it may be necessary to justify reliance on clinical trial results that derive from formulations that are not entirely identical. Also, regulatory agencies require data that demonstrate that the manufacturing process is validated (35). The FDA, for example, will normally require data on at least three production-scale batches before marketing approval is given. It must be kept in mind that a formulation and process that may yield coated products commendably free of coating defects when prepared at the laboratory scale may, at a later point in the development process, exhibit coating defects such as those described by Rowe (36). Rudnic and Kottke (36, p. 379) have presented a useful table to use in diagnosing coating problems.

TRENDS IN THE FORMULATION AND MANUFACTURE OF COATED CONTROLLED-RELEASE PRODUCTS

The trends that are of major importance in the current development of the formulation and manufacture of

coated controlled-release dosage forms may be divided into two categories. First, there are trends common to the manufacture of all types of drug delivery systems; second, there are trends specific to this type of product.

In the first class, we include the following: more rigorous evaluation of data by the FDA before marketing approval is granted; and increasing interest and regulatory concern about validation and optimization. In the second group, we include greater knowledge of, and control over, enteric-coated drug delivery systems, lively interest in coated products for colonic drug delivery, and improvements in both materials and equipment used in controlled-release coated products.

Rigorous FDA Evaluation of Data Before Marketing Approval Is Granted

The so-called generic drugs scandal (37) was a major factor in causing the FDA to become increasingly rigorous in its perusal of requests to market new pharmaceutical products. The introduction of the Application Integrity Policy, designed to discover or discourage fraud, has undoubtedly had significant effects on the research and development process in many companies. The requirement that the FDA District Office conduct a preapproval inspection before a new product can be marketed has caused some dramatic changes in both the pharmaceutical industry per se and contract houses, which perform services to our industry in research, development, manufacturing, or product evaluation.

Optimization, Validation, and Product Evaluation for Coating Formulation and Processing

During the past decade or so, a number of most useful reports have been published that have described various approaches for optimizing the selection of formulation and processing variables for coatings. Johansson, Ringberg, and Nicklasson (38) described the use of sequential, reduced factorial studies of the fluid-bed coating process for organic-solvent-dissolved ethylcellulose. Voight and Wunsch (39) reported an optimization study for the coating of granules by spray coating. Optimization of a Wurster-type spray drying process, including use of different thicknesses of film, was reported by Biaochini and Vecchio (40). Losa and coworkers (41), Bodmeier and Paratakul (42), and Parikh, Porter, and Rohera (43) have also described studies relevant to optimization of coated pharmaceuticals. The paper by Parikh and associates is of special interest to those wishing to optimize and validate the aqueous spray-coating process.

Farivar and coworkers (44) conducted a factorial-design-type optimization study of ethycellulose-coated microcapsules; the study included the evaluation of dissolution as a response parameter. Hsieh, Rhine, and Langer (45) reported concerning a novel approach to coating controlled-release products in which the coating is incomplete (i.e., the drug delivery system has an open, uncoated face). Theoretical and experimental work indicated the potential of this approach. Brook, Douglas, and vanNoort (46) reported about a separate study of the utility of partial coating in order to attain controlled release. Optimization of this approach is possible. The Li team (47) reported interesting studies of the rational development of a diltiazem controlled-release product in which a two-step layering process using a Wurster column is used.

Although there is often overlap between optimization and validation and some workers tend to use the terms almost interchangeably, it is probably useful to maintain a distinction between their meanings. *Optimization* relates to studies of the influence of formulation and processing variables on the properties of a drug delivery system. Such studies often involve the application of empirical mathematical models to defining the interrelationship of such variables. *Validation* has taken on a special regulatory meaning and is now generally used to refer to the process by which the sponsor of an NDA, NADA, or some other marketing approval document tries to convince a regulatory authority, such as FDA, that the formulation and process are under control, that batch-to-batch variability is at an acceptably low level, and that the process is sufficiently robust so that a minor perturbation of any one formulation or processing variable will not have a catastrophic effect on the product. Obviously, therefore, the validation of the coating segment of the manufacturing process will normally involve evaluation of such basic parameters as coating temperature, coating times, equipment loading, and coating composition, together with such other values as may be important for an individual product. Before commencing a process validation study for a coating process, it can be helpful to examine published reports of other workers. However, some caution is advisable. Studies that might have been deemed acceptable by regulatory agency A in 1990 will not necessarily be regarded as acceptable by regulatory agency B in 1999.

Dietrich and Brausse (48) reported concerning a validation study in which the effects of spray-drying temperature, air velocity, and relative humidity on release rates

of a controlled-release coated product were explored. The starting point for any current validation study should be the definition of all functionally relevant attributes of the raw materials. Depending on the individual excipient, the USP/NF, *Handbook of Pharmaceutical Excipients*, or manufacturer's data may well provide most, if not all, of what is needed in this respect. However, depending on the nature and function of the excipient, it also may be prudent for the manufacturer of the drug delivery system to consider the use of additional test methods for the excipients, intermediates, or final product. Such test methods may not only be useful during process validation, but may also be of value in routine testing of marketed product or during troubleshooting. For test data to be submitted to the FDA, it is, of course, essential that the data be derived by objective test methods applied in accordance with an acceptable standard operating procedure (SOP). Thus, manual flexing of a cast polymer film between the two hands of an experienced polymer technologist, although perhaps of use in troubleshooting of a plasticization problem, is not likely to be regarded as a test of pivotal value for documentation submitted to the FDA.

Microscopic examination of films, either cast or in situ in the drug delivery system, can provide useful data on the fine structure of the coating that may well be related to function. For example, Hasirci and Kamel (49) used optical and scanning electron microscopy to demonstrate the pore structure of a hydrophobic tablet coat. Evaluation of pharmaceutical polymer films using a confocal laser scanning microscope (50) may well become of increasing importance. Gopferich, Alsonso, and Langer (51) have published a most useful paper describing the use of a variety of techniques—polarized light microscopy, electron microscopy, specialized chemical analysis, and elemental analysis—to characterize coating structure. Pourkavoos and Peck (52) characterized coated tablets using thermogravimetric analysis, differential scanning calorimetry, and mercury intrusion porisimetry.

Zhou and coworkers (53) described an approach for determining tablet coating distribution from the weight distribution of uncoated and coated tablets. The authors indicate the potential value of the method in scale-up and validation studies.

Fukimore and associates (54) published a most interesting paper in which a computer simulation of agglomeration in a Wurster coating process is described. Results were compared with experimentally generated data. Voigt and Wunsch (55) reported the use of equipment for evaluating drug release from film-coated pellets. Wu, Jean, and Chen (56) used scanning electron microscopy in their investigation of the relationship between coating structure and dissolution rate. Murthy and Ghebre-Sellassie (57) investigated dissolution stability of coated pharmaceuticals. Pathak and Dorle (58) examined dissolution of coated microcapsules; their results indicate that the release mechanism does not follow a simple process. Lee and Liao (59) presented an interesting theoretical study of the effect of coating deformation on dissolution. Dissolution studies of a coated theophylline product were the subject of a report by Lavanisifar and coworkers (60).

Malamataris and Pilpel (61) studied compaction properties of coated products using the Heckal and the Cooper and Eaton equations to assist in the interpretation of the data. Since there is an increasing interest in the use of drug delivery systems that consist of controlled-release coated microcapsules incorporated into compressed tablets (that can, if desired, also be coated), there is substantial value in examining compaction behavior of coated products. The combination of multiparticulate drug delivery and a compressed tablet yields a hybrid product that can have the advantages of the reliable controlled delivery of coated microcapsules and the convenience, stability, and patient acceptability of compressed tablets (62). Although there is not a large amount of experimental data that pertain directly to the resistance of polymer-coated microcapsules to coating fracture during the process of tablet compaction, it seems likely that the following factors are of importance in delineating the extent of such fracture:

1. Shape, size, and other characteristics of the particles to be coated
2. Composition and thickness of the polymer coating applied to the particles
3. Nature of the tablet matrix and the ratio of coated particles to total tablet weight
4. Compression force applied when the tablet is produced

Chang and Rudnic (63) have shown that not all controlled-release coatings applied to cubic KCl crystals are equally resistant to compaction fracture.

Enteric-Coated, Controlled-Release Products

During the past decade or so there have been significant advances in the reliability of enteric coatings and their sensitivity to the pH at which drug is released. Agyilrath and Banker (64) indicated that the various factors

that influence the dissolution of enteric coatings are the following:

1. The pK_a of the polymer
2. Total free carboxylic acid content of the polymer
3. Nature of the core material
4. Ionic strength of the dissolution fluid
5. Coating thickness
6. Presence or absence of plasticizers and other non-enteric components in the coating layer

Porter and Ridgeway (65) used x-ray crystallography in an investigation of two enteric-coating polymers, cellulose acetate phthalate and polyvinyl acetate phthalate which were found to be essentially amorphous in nature. Lin and Kawashima (66) reported on the development of an enteric-coated formulation using cellulose acetate phthalate. Malfertheiner and coworkers (67) described clinical evaluation of some enteric-coated aspirin products. The topic of how effective enteric-coated aspirin is in preventing blood loss caused by ulceration of the gastrointestinal tract is still a subject of lively interest.

Ebel and associates (68) have applied an empirical mass transfer model for enteric coat dissolution that uses in vivo dissolution data to characterize the pH-dependent solubility properties of the polymer film and estimation of a mass transfer coefficient. The authors presented data comparing predicted and experimentally determined mass transfer coefficients.

Taniguchi, Tanahashi, and Fujii (69) described enteric coating of an enzyme. Lin and coworkers (70) reported the enteric coating of a vaccine using cellulose acetate phthalate as the coating material. Kiriyama and colleagues (71) reported on the bioavailability of a tripeptide protease inhibitor, which was enteric coated by hydroxypropyl methylcellulose phthalate. Duodenal absorption appears satisfactory. Arica and coworkers (72) described successful enteric coating and evaluation of diclofenac sodium.

Coated Pharmaceuticals for Colonic Delivery

The controlled release of drugs in the colon has, in recent years, become a topic of great interest to many pharmaceutical scientists. This interest derives primarily from two causes. First, there is a desire to develop therapies that allow specific delivery of drugs to the colon for the treatment of such conditions as ulcerative colitis. Second, the exciting possibility of using the colon as a portal of entry for polypeptides and small proteins into the vascular system has stimulated many research groups to work in this field. (There are, of course, many matrix-type approaches also being examined for colonic drug delivery.) In above sections of this paper, some references to coated drug delivery systems designed for drug release in the colon were given (16–18,23). The references given hereafter are samples of some of the many varied strategies being employed for coated products for colonic drug delivery.

Van-den-Mooter, Samyn, and Kinget (73) published two papers that deal with the use of copolymers of 2-hydroxyethylmethacrylate (HEMA) and methylmethacrylate (MMA), and terpolymers of HEMA, MMA, and methacrylic acid were synthesized in the presence of an azobenzene derivative for use as coatings for pharmaceutical products designed for colonic drug delivery. In vivo testing of the coating was reported. Ashford and Fell (74) published a useful review of oral delivery of drugs to the colon.

Niwa and coworkers (75) described an ethylcellulose capsule that only ruptures and allows the drug within to be released when a swellable polymer, such as low-substituted hydroxypropyl cellulose, has expanded so much as to destroy capsule integrity. The lag time during which the pressure within the capsule is developing is such that the drug is released in the colon. The release time of the drug was mainly dependent on the thickness of the capsule.

Wakerly and associates (76) investigated the use of film coatings consisting of ethylcellulose and pectin for colonic drug delivery. In vitro dissolution studies in a flow-through cell indicate the potential of this approach. Gardener and coworkers (77) reported on the use of a pig model for studying colonic drug delivery systems.

Developments in Materials and Processing

Published studies, from both academia and industry, clearly indicate that much energy and skill are being devoted to improving existing coating materials and processing methods, as well as exploring the potential of new materials and coating techniques. Fukimore and coworkers (78) described the potential of aqueous coats of ethylacrylate methymethacrylate 2-hydroxyethyl methacrylate copolymer. Park, Cohen, and Langer (79) presented a most interesting report that describes the use of aqueous coatings of an adsorptive water-soluble polymer, polyethyleneimine, for control of protein release.

Bhagat and associates (80) described a novel coating process that leads to the formation of a uniform defect-free coating. This coating process, termed "diffusion controlled interfacial complexation," involves a chemical reaction as part of the coating process. The technique can be applied to tablets that may be characterized by zero-order release.

Ramade (81) presented a review of the role of polymers in drug delivery that contains some useful data for any worker considering testing polymers for inclusion in drug delivery systems. Bianchini and Vecchio (82) described the coating of dose units prepared by extrusion-spheronization. Pourkavoos and Peck (83) reported on the mechanism and extent of sorption of water following aqueous film coating. Ashton and coworkers (84) described the design and evaluation of a coated drug delivery device intended for implantation in the eye. Deasy (85) described, in a helpful review article, some recent advances in the design and evaluation of coated products.

Coating of pharmaceuticals as a method of ensuring reproducible controlled release has come of age. The uncertainties about reliability of the natural-origin raw materials used for coating have been replaced by quiet confidence in the standardization of the synthetic materials now commonly used. The difficulties that were encountered during the conversion from organic solvents to water have been resolved, and prospects for future developments are good.

What factors should be taken into account when a pharmaceutical research and development group selects a formulation and processing strategy for a controlled-release product? More specifically, what are the advantages of coated, vis-à-vis noncoated, products? It is not possible to give a precise answer to this question that is of general applicability. Obviously, the physicochemical, pharmacokinetic, and pharmacoeconomic attributes of the drug substance, together with such factors as the formulation group's experience in previous controlled-release projects, and the availability of equipment and patents may all play legitimate roles in this type of decision. It would certainly be unreasonable to claim that coated controlled-release approaches should always be selected in preference to noncoated methods. However, there are certain strong advantages of coating procedures that do merit careful consideration:

1. The supply of a variety of reliable-quality excipients that are acceptable to regulatory agencies
2. A successful track record of products being taken from research and development pilot-scale to large-scale manufacturing with, in many cases, surprisingly few problems
3. Manufacturing methods that normally do not require the fabrication of any new manufacturing equipment, but rely on well-tested manufacturing methods, which in many instances, are readily validated
4. The availability of a remarkably flexible range of formulation and processing variables that can be used to custom build controlled-release profiles for a plethora of purposes

MATERIALS USED IN CONTROLLED-RELEASE PRODUCTS

The following section presents data on some of the more common materials used in pharmaceutical controlled-release coatings. It is not represented that this list is a comprehensive statement of all materials ever proposed for use in such products. Generally, the materials listed below are used for one or more of three main functions: (1) provision of the backbone structure of the coating, (2) facilitation or control over transport of drug across the membrane, or (3) plasticization of the coating. Coatings may well contain other components, such as colors or antioxidants, but specific attention is not given to components with a primary function that is not covered by one of the above three categories. The functions of the first two classes are self-evident; however, it is appropriate to define what is meant by a plasticizer since this term is sometimes used as a "catchall" to cover any excipient other than the primary coating material regardless of the function the excipient is expected to fulfill in the coating.

A plasticizer, in terms of its functional definition, is an excipient, usually a low molecular weight organic solvent, added to coating material to assist in the processing by rendering the film more flexible. It is believed that such materials act by lowering the polymer glass transition temperature. Plasticizers must be compatible, in terms of solubility parameter, with the polymer to which they will be added to make it more flexible. Thus, plasticizers are not general purpose, but must be chosen from materials that have been shown to be useful for a particular polymer.

Examination of the substances listed below indicates that a substantial number of the materials are cellulose derivatives. The review of chemically modified cellulose by Kumar and Banker (86) provides most useful back-

Table 1

Materials Listed as Components in Controlled-Release Coating

Enteric coatings
A. Cellulosic
1. Cellulose acetate phthalate, CAP*
2. Hydroxypropylmethylcellulose phthalate, HPMCP*
B. Noncellulosic
3. Methacrylic acid polymers*,†
4. Polyvinylacetate phthalate, PVAP
5. Shellac*
Non enteric coatings
A. Cellulosic
6. Ethylcellulose, EC*
7. Hydroxyethylcellulose, HEC*
8. Hydroxypropylmethylcellulose, HPMC*
9. Methylcellulose, MC*
10. Sodium caroboxymethylcellulose, NaCMC*
B. Noncellulosic
11. Carnauba wax*
12. Castor oil*
13. Cetyl alcohol*
14. Ethylene vinyl acetate copolymer
15. Hydrogenated vegetable oils*
16. Polyvinyl alcohol*
17. Silicon-based polymers
Plasticizers
18. Benzyl benzoate*
19. Chlorobutanol*
20. Dibutyl sebacate*
21. Diethyl phthalate*
22. Glycerol*
23. Polyethylene glycol*
24. Sorbitol*
25. Triacetin*
26. Triethyl citrate*

* Monograph in USP/NV.

† Also used as nonenteric coatings.

ground data in this area. Also, for more detailed information on polymers used in controlled drug delivery, the book edited by Tarcha (87) is likely to be of value. For those excipients listed in the USP/NF, it is appropriate to check standards given in this official compendium. The materials listed below are presented in a sequence that relates to function and alphabetical order. Materials 1 through 5 are polymers used for enteric coating, 6 through 17 are materials used as primary or secondary components in coating controlled-release pharmaceuticals, and 18 through 26 are plasticizers (see Table 1). The list of suppliers for the various materials is not necessarily exhaustive. An asterisk by the name of an excipient indicates that the material has a monograph in USP23/NF18.

1. *Cellulose acetate phthalate (CAP).** CAP is a cellulose ester referred to as Cellacephate in the BP and as Cellulosi acetas phthalus in the Ph. Eur. It is soluble at pH values above about 6.0 and thus will tend to release drug toward the distal end of the small intestine. CAP is soluble in acetone and ethyl acetate. Plasticizers, such as triacetin or castor oil, are usually incorporated into this polymer. CAP is approved for oral use in the United States and the European Union. It has been reported that CAP may be incompatible with ferrous sulfate, ferrous chloride, silver nitrate, and other inorganic salts. Also, since CAP has free carboxylic acid, incompatibilities with acid-sensitive drugs (e.g., omeprazole) are possible. Application from aqueous dispersion may be possible (88). Suppliers include Eastman Kodak and FMC.

2. *Hydroxypropylmethylcellulose: phalate (HPMCP).** HPMCP is a monophthalic ester of hydroxypropylcellulose. The NF specifies two grades: 200731 and 220824. The BP refers to HPMCP as Hypromelluse Phthalate, and the Ph. Eur. refers to it as Methylhydroxypropylcellusoi Phthalus. It normally releases drug in the proximal part of the small intestine. Shin-Etsu (89) markets three grades that vary in molecular weight (higher values generally yield tougher films) and the pH at which drug release normally occurs (from about 5.0 to 5.5). Plasticizers, such as castor oil, diacetin, diethyl and dibutyl phthalate, and polyethylene glycols, are commonly used with this polymer. Aqueous coating is possible (90). HPMCP is approved for oral use in the European Union, United States, and Japan. Possible incompatible agents include strong oxidizing agents. Also, inclusion of more than about 10% titanium dioxide as a color may adversely affect physical stability or gastric resistance of the film coat. This material is also made by Eastman.

3. *Methacrylic acid polymer and other polymeric methacrylates.* There are three grades specified in NF18 of these materials, which are often referred to as polymeric methacrylates or Eudragit®. (Polyacrylates in NF18 are listed under Ammonio methacrylate copolymer and methacrylic acid copolymer.) Eudragit E, which is soluble below pH 5.0, is used as a nonenteric coating. Eudragit L100-55 is used as an enteric coating for drug release at a pH of above 5.5; NE 30 D is used as a permeable, controlled-release coating; RL 30 D is used in controlled-release coating for which a high permeability film is required. The manufacturer of Eudragit has published

a guide to the use and properties of the whole range of Eudragits (91). Aqueous enteric coating is possible with Eudragit. By blending different grades of Eudragit, the formulator may be able to control release pH from about 5.5 to 7.0 and also the permeability of the film at constant pH (92). Lehman presented authoritative reviews of polymethacrylate coating systems (93). Ghebre-Sellassie (94) reviewed the use of aqueous dispersions of Eudragits for controlled release. Eudragits have been used in topical, oral, parenteral, ophthalmic, and other types of pharmaceutical products.

4. *Polyvinylacetate phthalate (PVAP).** PVAP is a reaction product of phthalic anhydride and partially hydrolyzed polyvinyl acetate. As an enteric film coating, it releases drug at pH values above about 5.0, so absorption may occur throughout the small intestine. It is approved for oral use in the European Union and the United States. Trade names include Opaseal®, pHthalvin®, and Sureteric®. The Colorcon literature (95) provides quite specific advice on processing conditions using, for example, an Acela-Cota. Porter (96) described aqueous film coating using PVAP.

5. *Shellac.** Shellac is obtained from a gummy exudation produced by female insects, *Laccifer lacca kerr*. Commercially, it is available in several grades (bleached, orange, white, etc.). Although its precise composition is both unknown and variable, its main component is a resin. The quality of this material shows significant variation with respect to both source and storage time. The pH at which drug is released is about 7.0, which may well be somewhat too high for most enteric-coated products. Unless there is some specific requirement that an enteric coating shall be "natural," this material is *not* recommended for anyone developing a new product. Depending on the grade, it is acceptable for oral use in the European Union, United States, and Japan. Suppliers include Classic Flavors, H.E. Daniel, Ikeda, and Ruger.

6. *Ethylcellulose (EC).** EC is a cellulose ether derivative that has three hydroxy groups available for substitution. It is sometimes referred to as cellulose ethyl ether. Grades with differing degrees of substitution and/or molecular weight are available commercially. This polymer is virtually insoluble in water, but is freely soluble in organic solvents. Higher viscosity grades (e.g., Ethocel® 100) tend to produce tougher films. The permeability of ethylcellulose films can be increased by adding materials such as hydroxypropyl cellulose, polyethylene glycol, and the hilce (97,98). Plasticizers used with ethylcellulose include dibutylphthalate, diethylphthalate, dimethylphthalate, benzyl benzoate, cetyl alcohol, castor oil, and corn oil. Oxidative degradation can be reduced by adding stabilizers such as octyl phenol or butylated hydroxyphenol. An ultraviolet light absorber, such as 2,4-dihydroxybenzophenone (at about 0.7%) has also been used as a stabilizer. Aqueous dispersions such as Aquacoat® (FMC) and Surelease® (Colorcon) are available. The Surelease literature (99) contains a number of cookbook-type recipes. Ethylcellulose is accepted for oral use in many parts of the world. Suppliers include Colorcon, FMC, Dow, and Hercules.

7. *Hydroxyethylcellulose (HEC).** HEC, Ph. Eur. Hydroxyethylcellulosum, is cellulose 2-hydroxyethyl ether. This water-soluble polymer, available under such trade names as Cellosize® and Natrosol®, which is available in several grades (100), is approved for oral use in the European Union, United States, and elsewhere. Suppliers include Allchem, Amerchol, Aqualon, Sumisho, and Union Carbide.

8. *Hydroxypropyl methylcellulose (HPMC).** HPMC Hypromelose, BP; Hydroxypropylcellulosum, Ph. Eur.) is cellulose 2-hydroxypropyl methyl ether. HPMC is an excellent water-soluble film former; low-viscosity grades (e.g., Methocel® HG, Dow) are commonly used in controlled-release coated pharmaceuticals. It is approved for oral and topical use in the European Union, United States, and Japan. The *Handbook of Pharmaceutical Excipients* (11) reports that it may be incompatible with oxidizing agents, metallic salts, and ionic organics (101). Suppliers include Aldrich, Dow, Aqualon, Cortaulds, and Hercules.

9. *Methylcellulose (MC).** MC (Methylcellulosum, Ph. Eur.) is cellulose methyl ether. It is soluble in water and organic solvents and is used in a number of controlled-release coated products (102). It is approved (at varying levels) in the European Union, United States, and Japan for use in oral, topical, buccal, vaginal, and parenteral pharmaceutical preparations. This material can be obtained from Dow.

10. *Sodium carboxymethylcellulose (NaCMC).** NaCMC (Carboxymethylcellulose sodium, USP/NF; Carmelose sodium, BP; Carboxylmethylcellulosum natricum, Ph. Eur.) is the sodium salt of cellulose carboxycellulose ether. NaCMC is soluble in water and polar organic solvents (103). A number of different grades are commercially available with different degrees of substitution and viscosity. NaCMC is approved in the European Union, United States, and Japan for dental, oral, topical, and parenteral use. Suppliers include Hercules and Cortaulds.

11. *Carnauba wax.** This material, sometimes referred to as Brazil wax or sera canauba, is a gummy exu-

date obtained from the Brazilian wax palm. It is photolabile. It has been accepted (for different purposes) for inclusion in foods and/or oral pharmaceuticals in the European Union, United States, and Japan. Suppliers include Spectrum, Ruger, Aldrich, and Penta. Sterotex® is a trade name.

12. *Castor oil.** There is an NF monograph (Hydrogenated Castor Oil) for this material in which it is defined as mainly consisting of the triglyceride of hydrosteric acid. It has been used in topical and oral pharmaceutical products in the European Union, United States, and Japan.

13. *Cetyl alcohol.** The NF monograph defines cetyl alcohol as containing not less than 90.0% of cetyl alcohol with the remainder consisting of related alcohols. It is referred to as Alcohol Cetylicus in Ph. Eur. The *Handbook of Pharmaceutical Excipients* (11) states that cetyl alcohol is incompatible with oxidizing agents and also suggests that it may cause allergic reactions. Cetyl alcohol has been used in topical and oral pharmaceutical products in the European Union, United States, and Japan. Suppliers include Aldrich, Proctor and Gamble, Ruger, and Spectrum. This material is marketed under a number of trade names, including Dyhdag®, Lanette®, and Nacol®.

14. *Ethylene vinylacetate copolymer.* This material, sometimes referred to as EVA copolymer, is used as a coating material in transdermal products in the United States. Suppliers include Allied Signal, Bayer, and Focus.

15. *Hydrogenated vegetable oils.** Oils derived from cottonseed, palm, and soy bean are covered by this title. Trade names include Lubritab®, Sofisan®, and Sterotex®.

16. *Polyvinyl alcohol.** This material is commercially available in at least three different viscosity grades. It is used in the United States in ophthalmologic, parenteral, topical, and oral products.

17. *Silicon-based polymers.* These relatively new materials for use in controlled-release coatings are presently attracting considerable attention. They can be applied as a coating from aqueous dispersions (104).

18. *Benzyl benzoate.** Benzyl benzoate, which has been accepted for oral use in both the United States and United Kingdom, has been used as a plasticizer for several cellulosic-type films. Suppliers include Ruger, Aldrich, and Spectrum.

19. *Chlorobutano.** Chlorobutanol has many uses in pharmaceutical technology, including plasticizing some cellulose esters and ethers. It has been widely used in topical, oral, and parenteral pharmaceutical products throughout the world. Suppliers include R.W. Greef, Aldrich, and Ruger.

20. *Dibutyl sebacate.** This plasticizer is used in a number of oral products. Suppliers include Union Carbide and Unitex.

21. *Diethyl Phthalate.** This material has been used as a plasticizer (in the range 10–30%). It is included in oral products in the United Kingdom and United States. Suppliers include Allchem, Diahachi Chemical, Eastman, Aldrich, and Spectrum.

22. *Glycerol (glycerin).** This multipurpose excipient has been used as a plasticizer. It is used in many types of pharmaceutical products throughout the world. Suppliers include Ruger, Asland, Croda, Compton and Knowles, Proctor and Gamble, and Ellis and Everard.

23. *Polyethylene glycol.** Polyethylene glycol (also known as Macrogol) is commercially available in a variety of molecular weight ranges. It is widely used in many parts of the world in parenteral, topical, and oral pharmaceutical products. Suppliers include BASF, Dow, duPont, Texaco, and Union Carbide.

24. *Sorbitol.** Sorbitol has many pharmaceutical uses, including plasticization. It is available in many different grades and is included in many oral pharmaceutical products used in many parts of the world. Suppliers include Aldrich, ICI, Penta, Ruger, and Spectrum.

25. *Triacetin.** This plasticizer has been included in oral pharmaceuticals in both the United Kingdom and United States. Suppliers include Aldrich, Eastman, and Ruger.

26. *Triethyl citrate.** This plasticizer has been used in oral pharmaceuticals, including coated products prepared using aqueous coating methods. Suppliers include Aldrich, Penta, H. E. Daniels, and Sharon. Hydagen® is a trade name for this material.

REFERENCES

1. T. R. Tice and S. E. Tabibi, *Treatise on Controlled Drug Delivery* (A. Kydonieus, ed.), Marcel Dekker, New York, 1991, p. 320.
2. Controlled Release Potassium Chloride, U.S. Patent 4,863,743, issued September 1989, inventors D. Hsiao and T. Chou, assignee Key Pharmaceuticals, Kenilworth, NJ.
3. A. C. Cartright and B. R. Matthews (eds.), *International Pharmaceutical Product Registration*, Ellis Horwood, New York, 1994.
4. G. E. Peck. Food and Drug Laws that Affect Drug Product Design, Manufacture, and Distribution, in *Modern*

Pharmaceutics, 3rd ed. (G. S. Banker and C. T. Rhodes, eds.), Marcel Dekker, New York, 1995, chap. 19.
5. B. A. Matthews, European Aspects of Regulation of Drug Products, in *Modern Pharmaceutics*, 3rd ed. (G. S. Banker and C. T. Rhodes, ed.), Marcel Dekker, New York, 1995, chap. 20.
6. A. Merrill, Pharmaceutical Technology, 34–40 (December 1995).
7. Information on IPEC may be obtained from Louis Blecher at (201) 628-3231.
8. I. R. Berry and R. A. Nash, *Pharmaceutical Process Validation*, 2nd ed., Marcel Dekker, New York, 1994.
9. E. M. Rudnic and M. K. Kottke, Tablet Dosage Forms, in *Modern Pharmaceutics*, 3rd ed. (G. S. Banker and C. T. Rhodes, eds.), Marcel Dekker, New York, 1995.
10. J. R. Schwartz and R. E. O'Connor, Optimization Techniques and Pharmaceutical Formulation and Processing, in *Modern Pharmaceutics*, 3rd ed. (G. S. Banker and C. T. Rhodes, eds.), Marcel Dekker, New York, 1995.
11. *Handbook of Pharmaceutical Excipients*, 2nd ed., Royal Pharmaceutical Society of Great Britain, London, and American Pharmaceutical Association, Washington, DC, 1994.
12. M. and I. Ash (compilers), *Handbook of Pharmaceutical Additives*, Gower, Aldershot, England, 1995.
13. *Pharmaceutical Contract Support Organizations Register*, Drug Information Association, Washington, DC, 1996.
14. B. Berner and S. Dinh, in *Treatise on Controlled Drug Delivery*, (A. Kydonieus, ed.), Marcel Dekker, New York, 1991, p. 2.
15. A. S. Achanta, P. S. Adusmili, K. W. James, and C. T. Rhodes, Drug Dev. Ind. Pharm., 23, 441–450 (1997).
16. R. L. Botham, V. J. Morris, T. R. Noel, S. G. Ring, H. N. Englyst, and J. H. Cummins, in *Gums and Stabilizers for the Food Industry*, (G. O. Phillips, P. A. Williams, and D. J. Wedlock, eds.), Oxford University Press, London, 1994, pp. 187–195.
17. S. Milojevic, J. M. Newton, J. H. Cummings, G. R. Gibson, R. L. Botham, S. G. Ring, M. Stockham, and M. C. Allwood, J. Controlled Release, 38, 75–84, 85–94 (1996).
18. M. Saffran, G. S. Kumar, C. Savariar, J. C. Burnham, F. Williams, and D. Neckers, Science, 233, 1081 (1986).
19. M. Donbrow and D. Y. Samuelov, J. Pharm. Pharmacol., 32, 461–470 (1979).
20. Dry Sustained Release Theophylline Oral Formulation, U. S. Patent 4,587,118, issued May 6, 1986, inventor C. M. Hsiao, assignee Key Pharmaceutical, Miami, FL.
21. T. A. Wheatley and C. R. Steuernagel, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd ed. (J. W. McGinity, ed.), Marcel Dekker, New York, 1997, p. 50.
22. USP 23/NF18, United States Pharmacopoeial Convention, Rockville, MD, 1994, 1793–1799.
23. Colon-targeted Delivery System, U. S. Patent 5,482,718, issued January 9, 1996, inventors N. H. Shah, W. P. Kearney, and A. Railkar, assignee Hoffman-LaRoche, Nutley, NJ.
24. V. Lenaerts and R. Gurny, *Bioadhesive Drug Delivery Systems*, CRC Press, Boca Raton, FL, 1990.
25. H. R. Chueh, H. Zia, and C. T. Rhodes, Drug Dev. Ind. Pharm., 21, 1725–1748 (1995).
26. A. Joglekar, C. T. Rhodes, and M. Danish, Drug Dev. Ind. Pharm., 17, 2103–2153 (1991).
27. N. A. Pappas and J. J. Sahlin, Biomaterials, 17, 1553–1561 (1996).
28. P. Ashton, D. I. Blandford, P. A. Pearson, G. J. Jaffe, D. F. Martin, and R. B. Nusseblatt, J. Ocal. Pharmacol. 10, 691–701 (1994).
29. J. G. Needleman, Br. Dental J., 170, 405–408 (1991).
30. F. N. Christensen and P. Bertelsen, Drug Dev. Ind. Pharm. 23, 451–463 (1997).
31. E. M. Rudnic and M. K. Kottke, Tablet Dosage Forms, in *Modern Pharmaceutics*, 3rd ed. (G. S. Banker and C. T. Rhodes, eds.), Marcel Dekker, New York, 1995.
32. M. J. Jozwiakowski, D. M. Jones, and R. M. Franz, Pharm. Res., 7, 1119–1135 (1990).
33. D. M. Jones and P. J. Percel, in *Multiparticulate Oral Drug Delivery* (I. Ghebre-Sellassie, ed.), Marcel Dekker, New York, 1994, pp. 113–142.
34. D. C. Monkhouse and C. T. Rhodes (eds.), *Drug Products for Clinical Trials*, Marcel Dekker, New York, 1997.
35. I. R. Berry and R. A. Nash, *Pharmaceutical Process Validation*, 2nd ed., Marcel Dekker, New York, 1994.
36. R. C. Rowe, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd ed. (J. W. McGinity, ed.), Marcel Dekker, New York, 1997, chap. 12.
37. M. R. Hamrel, Clin. Res. Drug Reg. Affairs, 14, 139–154 (1997).
38. M. E. Johansson, A. Ringberg, and M. Nicklasson, J. Microencap., 4, 217–222 (1987).
39. R. Voigt and G. Wunsch, Pharmazie, 40, 772–776 (1985).
40. R. Biaochini and C. Vecchio, Boll. Chim. Farm., 128, 373–379 (1989).
41. C. Losa, L. Marchal-Heussler, F. Orallo, J. L. Villo-Jato, and M. J. Alonso, Pharm. Res., 10, 80–87 (1993).
42. R. Bodmeier and O. Paratakul, Pharm. Res., 11, 882–888 (1994).
43. N. H. Parikh, S. C. Porter, and B. D. Rohera, Pharm. Res., 10, 535–534 (1993).
44. M. Farivar, H. S. Kas, L. Omer, and A. A. Hineal, J. Microencap. 10, 309–317 (1993).
45. D. S. Hsieh, W. D. Rhine, and R. Langer, J. Pharm. Sci., 72, 17–22 (1983).

46. I. M. Brook, C. W. Douglas, and R. vanNoort, Biomaterials, 7, 292–296 (1986).
47. S. P. Li, R. G. Felt, L. C. Di-Paulo, M. K. Huang, and R. O. Williams, III, Pharm. Res., 12, 1338–1342 (1995).
48. R. Dietrich and R. Brausse, Arzneimittelforcshung, 38A, 1210–1219 (1988).
49. V. M. Hasirci and I. L. Kamel, Biomaterials, 9, 42–48 (1988).
50. K. Carlsson, P. E. Danielsson, R. Lenz, A. Liljeborg, L. Majlof, and N. Ashland, Optics Lett., 10, 53–55 (1985).
51. A. Gopferich, M. J. Alsonso, and R. Langer, Pharm. Res., 11, 1568–1574 (1994).
52. N. Pourkavoos and G. E. Peck, Pharm. Res., 10, 1212–1218 (1993).
53. J. Zhou, T. Williams, H. Swopes, and T. Hale, Pharm. Res., 13, 381–386 (1996).
54. Y. Fukimore, H. Ichikawa, K. Jono, Y. Takeuchi, and T. Fukuda, Chem.-Pharm. Bull. Tokyo, 40, 2159–2163 (1992).
55. R. Voigt and G. Wunsch, Pharmazie, 41, 114–117 (1986).
56. J. C. Wu, W. J. Jean, and H. Chen, J. Microencap., 11, 507–518 (1994).
57. K. S. Murthy and I. Ghebre-Sellassie, J. Pharm. Sci., 82, 113–126 (1993).
58. Y. V. Pathak, and A. K. Dorle, J. Microencap., 7, 185–190 (1990).
59. D. J. Lee and Y. C. Liao, J. Pharm. Sci., 84, 1366–1373 (1995).
60. A. Lavanisifar, R. Ghalandari, Z. Ataei, M. E. Zolfaghari, and S. A. Mortazavi, J. Microencap., 14, 91–100 (1997).
61. S. Malamataris and N. Pilpel, J. Pharm. Pharmacol., 35, 1–6 (1983).
62. M. K. Kottke, G. Stetsko, S. E. Rosenbaum, and C. T. Rhodes, J. Geriatric Drug Ther., 5, 77–92 (1990).
63. R. K. Chang and E. M. Rudnic, Int. J. Pharm., 70, 261–270 (1991).
64. G. A. Agyilrath and G. S. Banker, in *Polymers for Controlled Drug Delivery*, (P. J. Tarcha, ed.), CRC Press, Boca Raton, FL, 1991, p. 37.
65. S. C. Porter and K. Ridgeway, J. Pharm. Pharmacol., 35, 341–344 (1983).
66. S. Y. Lin and Y. Kawashima, Pharm. Res., 4, 70–74 (1987).
67. P. Malfertheiner, A. Stanescu, W. Rogatti, and H. Ditschuneit, J. Clin. Gastroenterol., 10, 269–272 (1988).
68. J. P. Ebel, M. Jay, and R. M. Beihn, Pharm. Res., 10, 233–238 (1993).
69. M. Taniguchi, S. Tanahashi, and M. Fujii, Appl. Microbiol. Technol., 33, 629–632 (1990).
70. S. Y. Lin, Y. L. Tzan, C. J. Lee, and C. N. Weng, J. Microencap., 8, 317–325 (1991).
71. A. Kiriyama, M. Sugarhara, Y. Yoshikawa, Y. Kiso, and K. Takada, Biopharm. Drug Dispos., 17, 125–134 (1996).
72. B. Arica. M. Y. Arica, H. S. Kas, A. A. Hineal, and V. Hasirci, J. Microencap., 13, 699 (1996).
73. G. Van-den-Mooter, C. Samyn, and R. Kinget, Pharm. Res., 11, 1737–1741 (1994) and 12, 244–247 (1995).
74. M. Ashford and J. T. Fell, J. Drug Target., 2, 241–257 (1994).
75. K. Niwa, T. Takaya, T. Morimoto, and K. Takada, J. Drug Target., 3, 83–89 (1995).
76. Z. Wakerly, J. T. Fell, D. Atwood, and D. Parkins, Pharm. Res., 13, 1210–1212 (1996).
77. N. Gardener, W. Harisign, R. Spiller, N. Farraj, J. Wiseman, H. Horbury, and L. Illum, J. Pharm. Pharmacol., 48, 688–693 (1996).
78. Y. Fukimora, Y. Yamaoka, H. Ichikawa, Y. Takeuchi, T. Fakuda, and Y. Osako, Chem. Pharm. Bull. Tokyo, 36, 3070–3078 (1988).
79. T. G. Park, S. Cohen, and R. Langer, Pharm. Res., 9, 37–39 (1992).
80. H. R. Bhagat, R. W. Mendes, E. Mathiowitz, and H. N. Bhargava, Pharm. Res., 8, 576–583 (1991).
81. V. V. Ramade, J. Clin. Pharmacol., 30, 10–23 (1990).
82. R. Bianchini and C. Vecchio, Farmaco, 44, 645–654 (1989).
83. N. Pourkavoos and G. E. Peck, Pharm. Res., 10, 1363–1371 (1993).
84. P. Ashton, D. L. Blandford, P. A. Pearson, G. J. Jaffe, D. F. Martin, and R. B. Nussenblatt, J. Ocul. Pharmacol., 10, 691–701 (1994).
85. P. B. Deasy, J. Microencap., 11, 487–505 (1994).
86. V. Kumar and G. S. Banker, Drug. Dev. Ind. Pharm., 19, 1–32 (1993).
87. P. J. Tarcha, ed., *Polymers for Controlled Drug Delivery*, CRC Press, Boca Raton, FL, 1991.
88. A. M. Ortega, Ph.D. thesis, Purdue University, West Lafayette, IN, 1977.
89. Shin-Etsu Chemical Company, technical literature on HPMCP, 1993.
90. N. A. Muhammad, W. Boisvert, M. R. Harris, and J. Weiss, Drug. Dev. Ind. Pharm., 18, 1787–1797 (1992).
91. Rohm. Pharma. GmBh, Eudragit literature, 1990.
92. K. O. R. Lehman, Drug Dev. Ind. Pharm., 12, 265–287 (1986).
93. K. O. R. Lehman, in *Aqueous Polymeric Coating for Pharmaceutical Dosage Forms*, 2nd ed. (J. W. McGinity, ed.), Marcel Dekker, New York, 1997, chap. 4.
94. I. Ghebre-Sellassie, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd ed. (J. W. McGinity, ed.), Marcel Dekker, New York, 1997, chap 7.
95. Colorcon, Sureteric®, West Point, PA, 1995.

96. S. C. Porter, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd ed. (J. W. McGinity, ed.), Marcel Dekker, New York, 1997, chap. 9.
97. Dow Chemical Company, *Ethocel*, 1993.
98. Dow Chemical Company, *Ethocel Bibliography*, 1993.
99. Colorcon, Surelease technical literature, West Point, PA, 1990.
100. B. Kovacs and G. Merenyi, Drug Dev. Ind. Pharm., 16, 2302–2333 (1990).
101. G. Banker and G. Peck, Drug Dev. Ind. Pharm., 7:693–716 (1981).
102. N. M. Sanghavi, P. R. Kamath, and D. S. Amin, Drug Dev. Ind. Pharm., 16, 1843–1848 (1990).
103. G. Banker, G. Peck, E. Williams, D. Taylor, and Pirakitkulr, Drug Dev. Ind. Pharm., 8, 41–51 (1982).
104. L. C. Li and G. E. Peck, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd ed. (J. W. McGinity, ed.), Marcel Dekker, New York, 1997, chap. 14.