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Factors in the development of oral controlled-release dosage forms

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In recent years, several pharmaceutical products have been introduced as oral controlled-release dosage forms, both as tablets or capsules and as oral suspensions. The advantages of oral controlled-release dosage forms are well known: fewer administrations, greater therapeutic effect, and fewer side effects. A recent series of articles reviewed the various sustained-release delivery systems;[1] this paper focuses on the methods of manufacture, with emphasis on formulating and processing oral controlled-release dosage forms.

METHODS OF DOSAGE FORM DEVELOPMENT

Today there are essentially four general methods or principles used to develop oral controlled-release dosage forms: (1) diffusion and/or dissolution control, (2) ion exchange, (3) repeat action, and (4) osmotic pressure. Each method has advantages and disadvantages. The physicochemical and pharmacokinetic properties of a particular drug, the volume to be administered, and the economic, marketing, and patent situations may dictate which method is to be used. In most instances the dosage forms are presented as either a tablet or a multiparticulate system, the latter usually supplied in capsule form.

Diffusion and/or Dissolution Control Systems. Most oral controlled-release dosage forms are based on diffusion and/or dissolution control. It is generally difficult to separate one mechanism from the other; diffusion and dissolution usually operate simultaneously. Diffusion is the movement of a drug molecule from a region of higher concentration to a region of lower concentration. Fick's law of diffusion may be modified to describe the release of a drug from a particle or a dosage form based on its physical form:

$$Q = \frac{D}{d} A (C_1 - C_2) t$$

where Q = quantity of drug, D = diffusion constant, d = diffusion layer, A = area, C_1 and C_2 = concentration, and t = time. For example, in the case of spherical particles, which may be coated, the following equation may describe the release of a drug from the dosage form.

$$R = \left\{ \frac{2^{2/3} \pi^{1/3}}{\rho^{2/3}} \right\} \left\{ \frac{DC_1}{d} \right\} W^{2/3}$$

where R = rate, ρ = density, W = weight, D = diffusion constant, C_1 = concentration, and d = diffusion layer.[2]

Table I lists some of the currently marketed controlled-release dosage forms that are based on this

Table I: Products based on diffusion and/or dissolution control.

Product	Manufacturer
Ornade Spansules	Smith Kline & French Laboratories
Indocin SR Capsules	Merck Sharp & Dohme
Theo-24 Capsules	G. D. Searle & Co.
Theo-dur Tablets	Key
Theo-dur Sprinkle	Key
Inderal LA Capsules	Ayerst Laboratories
Slowbid Capsules	Rorer Group, Inc.
Micro K Capsules	A. H. Robins Co.
Sudafed SA Capsules	Burroughs Wellcome Co.
Quinaglute Dura-Tabs	Berlex Laboratories, Inc.
Tepanil Tentabs	Riker Laboratories, Inc.
Procan SR Tablets	Parke-Davis
Isordil Tembids	Ives Laboratories, Inc.
Slow-K Tablets	Ciba-Geigy Corp.

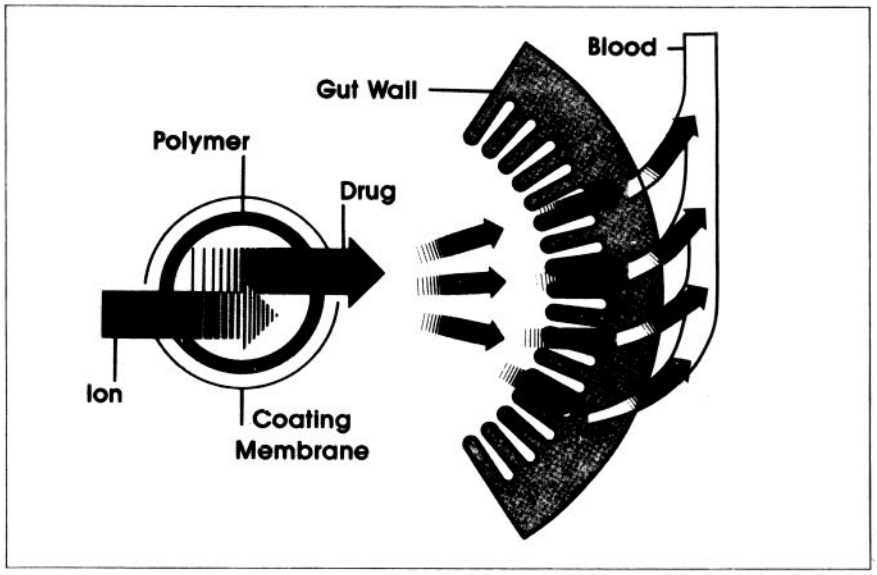

Figure 1: Graphic representation of the Pennkinetic drug-delivery system. Reproduced with permission of Pennwalt Corporation.

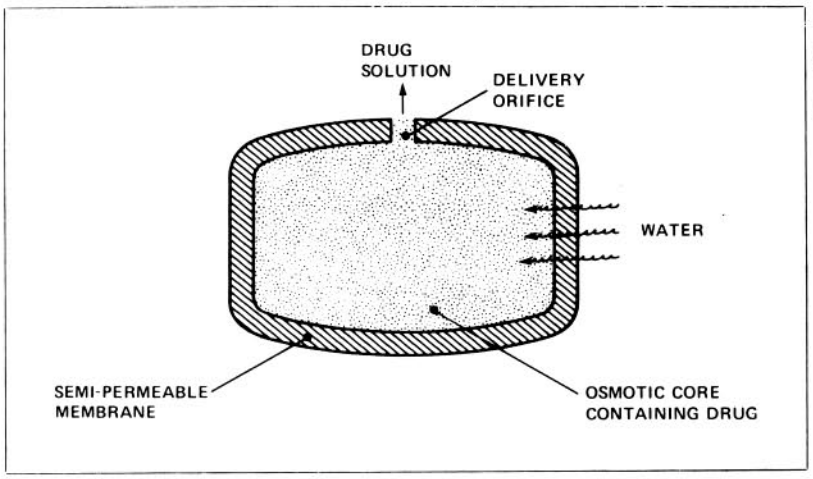

Figure 2: Schematic of the oral osmotic drug-delivery system, OROS. Reproduced with permission of Alza Corporation.

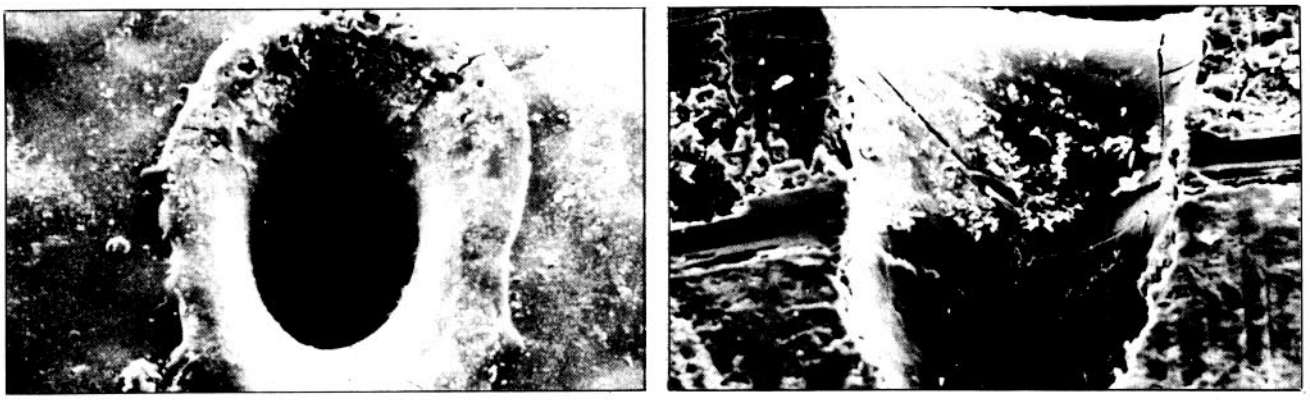

Figure 3: (a) Scanning electron micrograph showing orifice in Acutrim tablet (magnification, 100 ×). (b) Cross section of Acutrim tablet through the orifice (magnification, 150 ×).

principle. Most of these products are multiparticulate systems consisting of coated particles filled into a capsule. These products may be coated with water-insoluble polymer, partially water-soluble membrane, or pH-dependent soluble membrane. The majority of products are coated in either pan, perforated pan, or fluid-bed equipment. Coacervation or phase separation techniques are employed in a small number of pharmaceutical products. In rare cases spray drying or spray congealing is used to microencapsulate drugs.

Uncoated products usually are presented as tablets and are generally known as *matrix systems*. A matrix system is a uniform mixture of drug, excipients, and polymer that is homogeneously fixed in a solid dosage form. The polymers may be hydrophilic, hydrophobic, or water insoluble. Some matrix tablets consist of high-molecular-weight fats and waxes. The matrix may be tableted by direct compression, compression granules, wet granulation, extrusion, or flaking process. The use of Methocel (Dow Chemical, Midland, MI) cellulose ethers in producing matrix-type sustained-release tablets is well documented in the literature.[2–4] Matrix-type diffusion- and/or dissolution-controlled systems do not offer the flexibility of including multiple release rates in a given dosage form, which may be necessary with some drugs to achieve desired plasma levels.

Another sustained-release dosage form is the tablet or capsule that is hydrodynamically balanced to remain buoyant in gastric fluid.[5] The currently marketed product is Valrelease (Hoffmann-La Roche, Nutley, NJ).

Ion Exchange. The principle of ion exchange has been used in analytic and protein chemistry for quite some time. In theory it is an attractive principle because the release of drug is independent of pH, depending rather on the ionic environment of the gastrointestinal tract. The agents used are resinous materials, with their salt-forming groups placed in repeating positions along the resin chain. Appropriate cationic or anionic groups are substituted in order to produce the desired cationic or anionic exchange resins. These resins are nearly all styrene/divinyl benzene copolymers whose ionic groups are included as substituents on the styrene position of the molecule. The strength and hardness of the final resin is regulated by the degree of cross-linking. A concentrated solution of drug is percolated through a bed of resin until equilibrium is established, and excess drug is washed off with deionized water. The drug-resin complex can then be tableted or further coated and tableted, encapsulated, or formulated into a suspension-type dosage form.

Recently, Pennwalt Corporation introduced the Pennkinetic system (Figure 1), in which a drug-resin complex is coated with a polymer and further formulated into a suspension-type dosage form. Water may permeate through the coating, but the drug is not free to migrate out into the suspension base. The ions present in the gastrointestinal tract permeate the coating, releasing the drug from its bound state. The drug, in turn, can migrate through the coating only at a fixed rate that is regulated by the thickness of the coating. The thickness of the coating thereby becomes the rate-limiting step for drug absorption into the body. A prime consideration is that drugs be water-soluble and ionizable. The currently marketed products that make use of this system are Pennwalt's Delsym (dextromethorphan) suspension

and Corsym, which combines antihistamine and nasal decongestant.

Repeat Action. Products that make use of repeat action are only by the broadest definition able to sustain action. Products of this type are usually prepared from soluble drugs. The coating procedures that are used produce complete release once the coat is broached. Drug release is usually controlled by physical factors such as pH and gut action, which because of variations in gastrointestinal transit time, pH, and gastrointestinal motility, create the possibility of imprecisely timed coating breakdown. The currently marketed products include Chlortrimeton Repeatabs (Schering-Plough, Kenilworth, NJ) and Triaminic (Dorsey, Lincoln, NE) tablets.

Osmotic Pressure. An oral osmotic drug-delivery system is shown in Figure 2. Basically, a semipermeable membrane is placed around a core that contains drug. This membrane allows the transport of water or other media into the core, and the resulting drug solution is pumped out through a small orifice in the coating. This orifice is created by a laser beam. An important element in the success of this type of delivery system, aside from the polymer coat and coat formulation, is the size of the delivery orifice. For the system to be effective the orifice must be smaller than the theoretical maximum size to minimize the contribution to the delivery rate made by drug diffusions through the orifice, and the orifice must be sufficiently large to minimize hydrostatic pressure inside the system. Obviously, an orifice that is too small will suppress the release rate, while an orifice that is too large will increase the delivery rate. Figure 3 presents scanning electron micrographs of the currently marketed product Acutrim (Ciba-Geigy, Summit, NJ), showing the orifice present in the coating of the tablet.

COATING FORMULATION VARIABLES

Clearly, most oral controlled-release dosage forms make use of a polymeric coat to control the release of drug from the dosage form. It used to be that coating was applied to pharmaceutical dosage forms primarily for aesthetic purposes, but the coatings applied to controlled-release pharmaceutical drug products have a specific purpose, i.e., to control the release of drug. To assure the reproducible release of a drug from batch to batch, both the coating formulation and the coating process must be optimized. Table II lists the various formulation factors that may affect the release rate of a drug from the dosage form. For example, Figure 4 illustrates the effect of plasticizer type and concentration on the release of drug from the dosage form. In a coating system such as Eudragit E30D (Rohm Pharma, Malden, MA), it is recommended that an antiagglomerating agent such as talc or magnesium stearate be included in order to prevent stickiness during the coating process. The type and concentration of such an agent also affects the drug release rates,[6] as do the ratio of solvents used, type of polymer, and amount of coating applied.

Factor	Variables
Aqueous	Aquacoat, Eudragit L30D, Eudragit E30D, and Surelease
Organic	Eudragits L, S, RL, RS Celluloses—HPMC, ethyl cellulose, etc. Enteric—shellac, PVAP, CAP, etc.
Plasticizers	Type and concentration
Additives	Talc, magnesium stearate, etc.
Solvents	Ethanol, methanol, methylene chloride, ratio of mixed solvents
Polymer	Type, viscosity, source
Coating	Amount

Table II: Coating formulation variables.

COATING PROCESS VARIABLES

The optimization of formulation variables may not have any significance if one ignores the optimization of processing variables (see Box). The morphologic differences in applied coatings created by variations in the

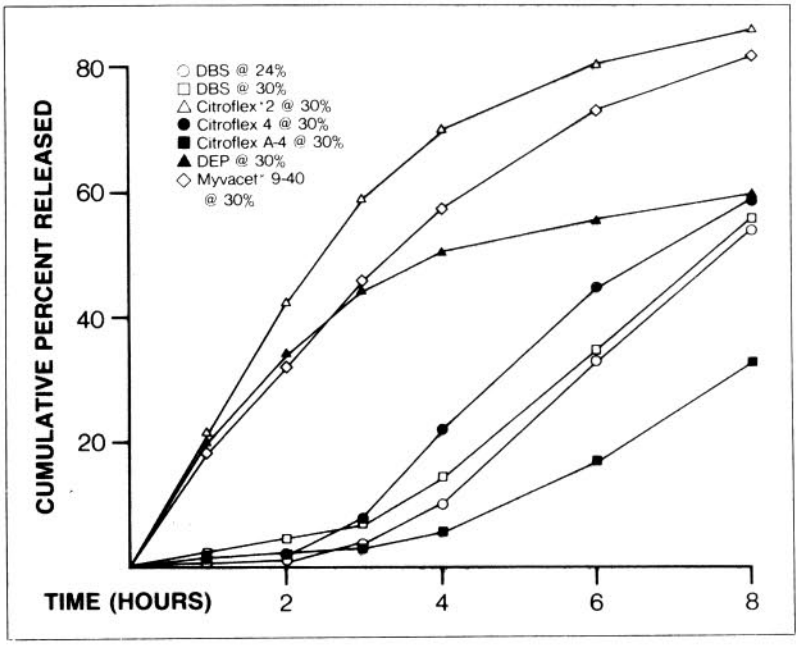

Figure 4: Effect of plasticizer type and concentration on the release rate of phenylpropanolamine seeds coated with Aquacoat dispersion. Reproduced with permission of FMC Corporation.

COATING PROCESS VARIABLES

- Type of equipment
- Mode of spraying
- Spray rate
- Inlet temperature
- Air volume
- Nozzle port size
- Atomizing air pressure
- Nozzle height
- Drying time
- Effect of moisture

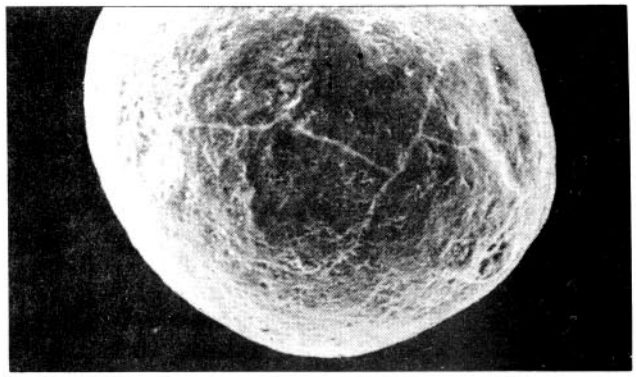

Figure 5: Nonpareil seed layered with indomethacin and binder (magnification, 75×).

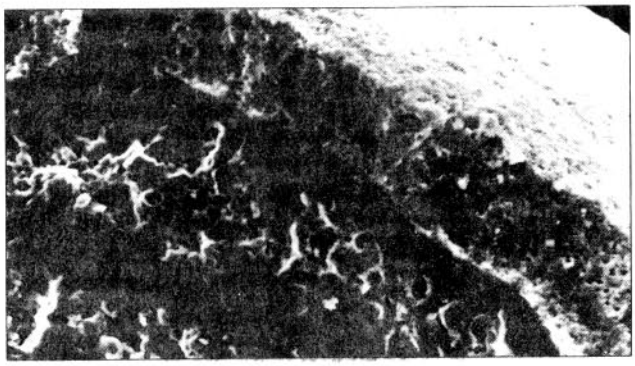

Figure 6: Cross section of nonpareil seed layered with indomethacin and binder (magnification, 300×).

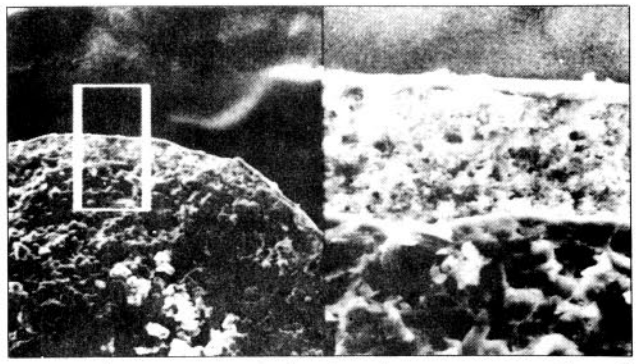

Figure 7: Cross section of pellet showing nonpareil seed, indomethacin-binder layer, and sustained-release coating layer (magnification, 100× and 500×).

coating processes have been characterized in the past.[7-9] These morphologic differences appear to determine the different rates at which the drug is released from the dosage form.[10,11]

The effect of spray rate and the size of equipment also are important variables to be considered during the optimization process. The inlet air temperature, along with the amount of air introduced in the equipment, may be important to control for polymeric systems such as Eudragit E30D. These parameters also must be considered in aqueous-based latex systems such as Aquacoat (FMC Corporation, Philadelphia, PA), Eudragit L30D, Eudragit E30D, and Surelease (Colorcon, West Point, PA). The nozzle port size, together with the atomizing air pressure, determines the size of the coating droplet, and as a general rule, the finer the droplet size, the better the film characteristics.

The effect of different spray rates on the in vitro release rates of granules coated with the aqueous polymeric dispersion has been documented.[12] Granules coated under slower spraying conditions release drug more slowly. The most probable explanation is that slower spray rates allow warmer bed temperatures, which in turn allow more extensive coat curing and less coat permeability.

SUBSTRATE MANUFACTURE

Optimizing the manufacture of the core substrate in terms of formulation and process is as important as optimizing the coating formulation and coating process. Ideally, one should strive to achieve a smooth substrate surface so that the coating adheres to it efficiently. Because the thickness of the coat dictates the rate at which drug is released from the coated particles, the smooth surface of the substrate allows uniform coating thickness not only for each particle but also from batch to batch. With the properly selected formulation and processing conditions it is possible to obtain a very smooth substrate surface, as Figures 5, 6, and 7 illustrate.

There are a number of ways to produce the substrate material, including conventional granulation, extrusion and spheronization, and drug layering. The extrusion-spheronizer process is of particular advantage when a high dose of drug is to be incorporated into the substrate material. This is, however, a multistep batch process involving wet mixing, extrusion, spheronization, and drying. If the dose of a drug is not too high, the drug layering process is much more convenient. It involves adding drug in a dry form while spraying the binder solution onto the nonpareil particles, dissolving the drug in binder solution, or suspending the drug in binder solution. Conventional pan, perforated pan, and fluid-bed processors are the equipment of choice for this process.

The reproducibility of particle size distribution, surface area, and density of substrate material, in addition to reproducibility of morphologic properties, should become the criteria by which a process is selected. The importance of optimizing the substrate manufacture process, especially in terms of its morphologic characteristics, cannot be overstated. Consider, for example, the scanning electron micrographs of two batches (lot A and lot B) of coated pellets containing an experimental new drug (Figures 8a and 8b). The applied coating appears to be very smooth, uniform, and free from imperfections (a desirable characteristic of the controlled-release film). However, no sustained release of the drug was observed in vitro for lot A. When the substrate lots used to manufacture these two batches were examined, lot A was

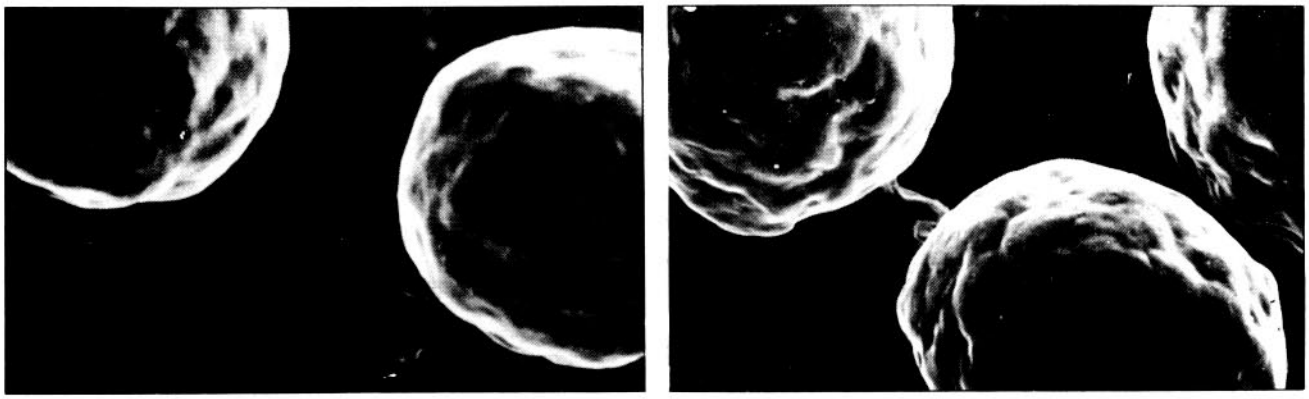

Figure 8: Coated pellets of a new experimental drug. (a) Lot A (magnification, 50×). (b) Lot B (magnification, 75×).

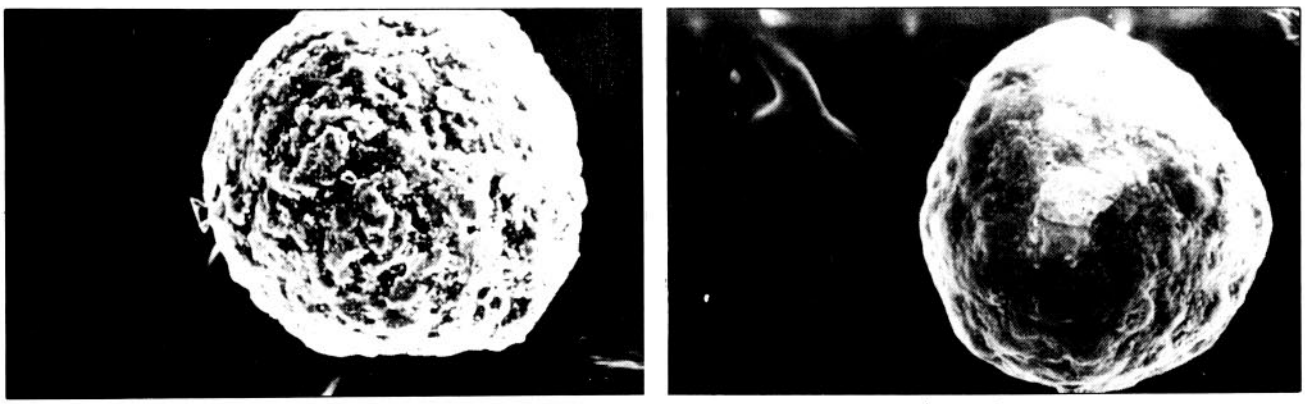

Figure 9: Uncoated pellets of a new experimental drug (magnification, 75×). (a) Lot A. (b) Lot B.

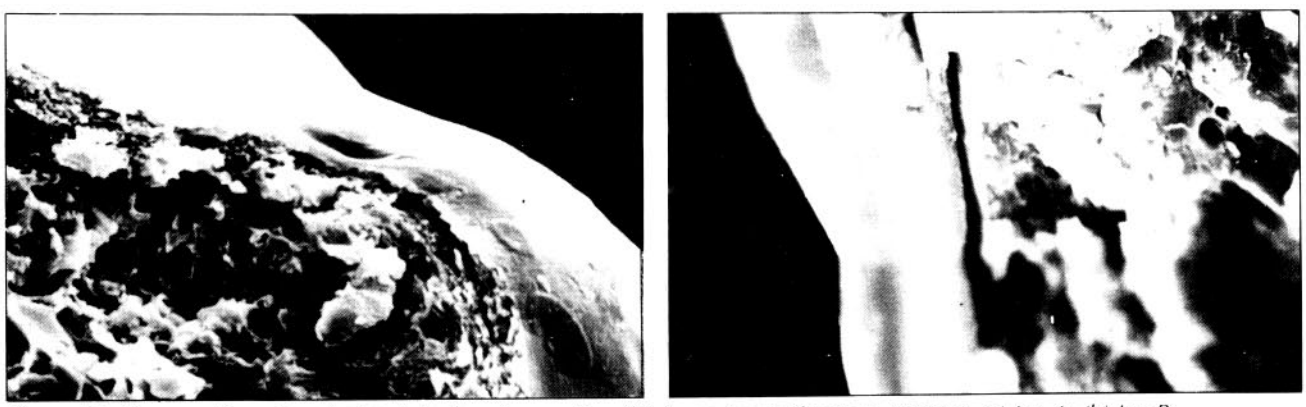

Figure 10: Cross section of coated pellets showing coating thickness (magnification, 4000×). (a) Lot A. (b) Lot B.

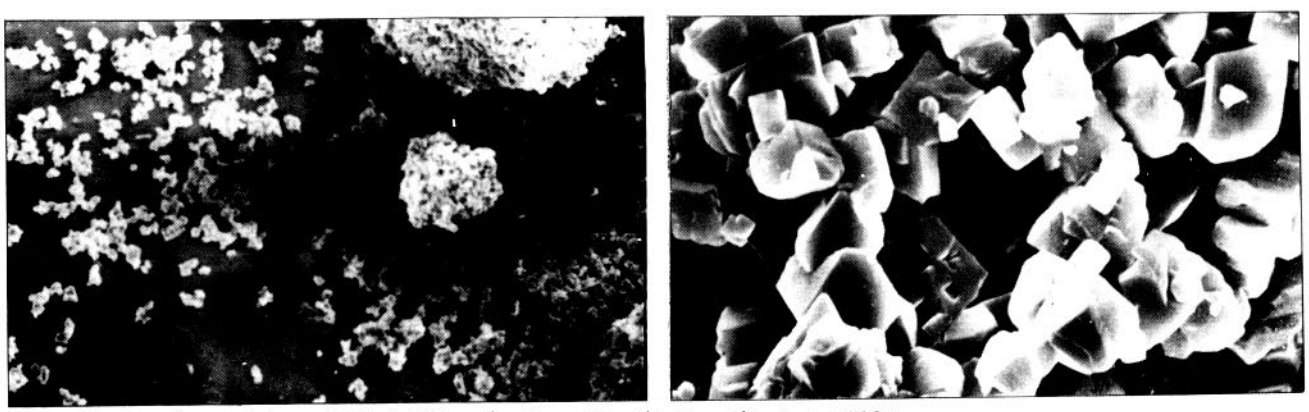

Figure 11: Experimental drug, lot A. (a) Magnification, 50×. (b) Magnification, 1000×.

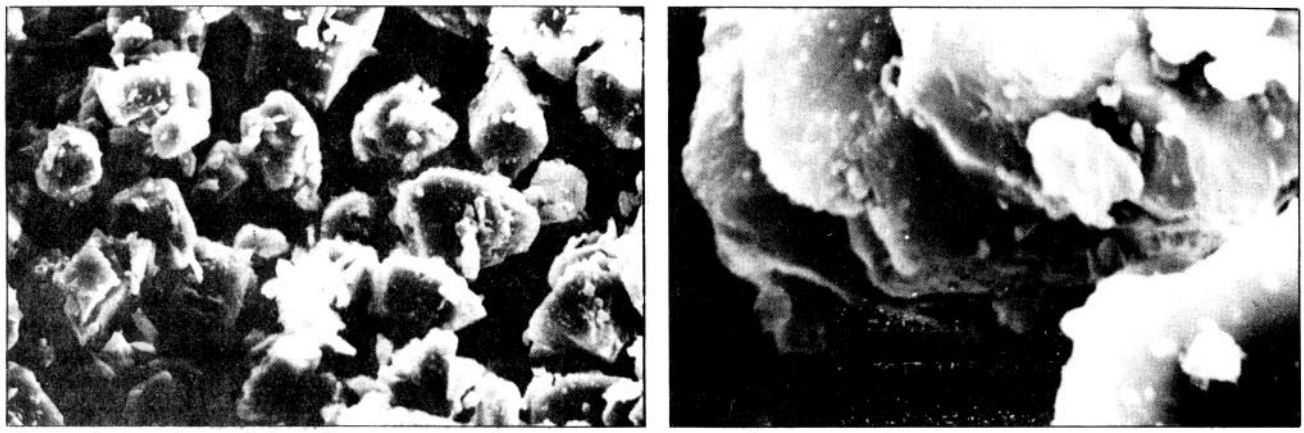

Figure 12: Experimental drug, lot B. (a) Magnification, 500×. (b) Magnification, 3500×.

Evaluation	Critical Factors
In vitro	Type of media Type of agitation Speed of agitation Medium change
In vivo	Animal model Sampling time Loading dose Gastrointestinal transit time Absorption window Therapeutic levels Protocol Interpretation of results

Table III: Dosage form evaluation.

found to have used a substrate whose surface was significantly rougher than that used in lot B (Figure 9). As a result, when the same amount of coating was applied to these two different lots of substrate, lot B's coating was significantly thicker than lot A's (Figure 10), which may explain the faster release rates of lot A.

RAW MATERIALS

The batch-to-batch variation in the physicochemical properties of the raw materials used to produce various controlled-release dosage forms may contribute to the variations in the drug release rates from batch to batch. The batch-to-batch variations in the physicochemical properties of the drug itself may contribute to variations in release rates. Figures 11 and 12 show the morphologic properties of two lots of the same drug used to produce two lots of a controlled-release dosage form of this drug. In lot A the particle size was on the average 10 μm with crystalline structure and some agglomerates present in the batch. In lot B, however, particle size ranged from 20 to 40 μm with no agglomeration present in the batch. The intrinsic dissolution rates of these two lots of drugs differed significantly, and as a result the finished product showed differences in the dissolution rates.

DOSAGE FORM EVALUATION

Table III lists some of the factors that must be considered in evaluating both the in vitro and in vivo performance of controlled-release dosage forms. It is imperative that a dissolution method be developed by optimizing various factors that can then allow the prediction of in vivo performance. Once the method is developed, formulations can be screened according to the in vitro dissolution profile. (It is helpful to use an animal model for further screening.) The protocol selected for the in vivo study is of prime importance because the performance of a dosage form in vivo depends on it. The therapeutic levels and the in vivo release rates have to be predetermined in order to formulate a controlled-release dosage form. The interpretation of the in vivo data is critical in terms of determining the bioequivalency of a controlled-release dosage form to a conventional dosage form. In general the C_{max}, C_{min}, and area under the curve of a controlled-release dosage form should not differ significantly from those of a conventional dosage form. Unfortunately, a number of controversies and issues still remain to be resolved in assessing the performance of a controlled-release dosage form.[13]

CONCLUSION

Controlled-release dosage forms are becoming increasingly popular for many reasons, and it is anticipated that a large number of drug products will be introduced in controlled-release systems. A number of approaches to the development of controlled-release dosage forms are available, but the one based on diffusion and/or dissolution control remains the most common. An in-depth pharmacokinetic and pharmacodynamic characterization of a drug followed by formulation and processing

optimization is necessary to ensure the successful and reproducible performance of a controlled-release form. Many scientists are continuing research in the area of controlled-release dosage forms in order to conquer some of the problems posed by gastrointestinal physiologic and anatomic factors. Nevertheless, commercial production of advanced, sophisticated systems may still be at least a decade away.

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