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IN RECENT YEARS, a number of solid dosage forms have been produced in the form of coated pellets that can be enclosed in hard gelatin capsules or compressed into tablets. In contrast to other kinds of tablets, which may be coated for reasons of appearance alone, pellets typically are coated to control drug release rates, to provide enteric release, or to mask tastes. Coatings can also be applied to pellets to improve stability of the drug or to separate physically incompatible components of a dosage form. To achieve these ends, the coating should be reproducible, uniform, and free from physical imperfections. Consequently, the coating process used and the evaluation of the coating are critical.

Scanning electron microscopy has improved the general understanding of the physical properties of tablet excipients, of aggregates, and of simple compacts.[1-5] It has also helped to elucidate the effects of lubrication and mixing on the performance of a dosage form.[6-8] Moreover, a few studies have made use of scanning electron microscopy to characterize microcapsules or small particles that have been coated to provide sustained release of drugs.[9,10]

The present article uses scanning electron microscopy to evaluate film coatings applied to pellets. Several different processing methods were used to apply the films, which were of both aqueous and organic-solvent types. Scanning electron micrographs of pellets revealed striking differences in the morphology of pellets that had been coated using the different techniques. In the case of controlled-release dosage forms, drug release rates undoubtedly are affected by the integrity of the film coating. Hence, scanning electron microscopy appears to be a very effective tool for evaluating film coatings that have been applied by different coating processes.

Aqueous Coating Systems

An experimental aqueous coating system was applied to pellets by their suppliers using a range of coating techniques. The processing conditions used by each supplier were typical for each piece of equipment used. The equipment used to apply coatings included a conventional pan (Pellegrini; Nicomac, Milan, Italy), a modified perforated pan (Multi-Cota; Thomas Engineering, Hoffman Estates, Illinois), a laboratory-scale fluidized bed (Uni-Glatt; Glatt Air Techniques, Ramsey, New Jersey), and a pilot-scale fluidized bed (an 18-in. Wurster coater in a Glatt Powder Coater/Granulator 60/100; Glatt Air Techniques). The pellets were examined under a scanning electron microscope (Model T-200; Jeol USA, Peabody, Massachusetts) to determine the morphological differences among the applied films.

Conventional pan coating. Figure 1 shows scanning electron micrographs (SEMs) of pellets coated in the conventional Pellegrini pan. Figure 1A, a single pellet magnified 100X, shows that the coating is not continuous; it is irregular and has many pores. This irregularity is more evident at a higher magnification of 1000X (Figure 1B); here, uncoalesced polymer particles are visible. These observations are expected, given the relative drying inefficiency of coating in a conventional pan. Because aqueous systems require greater drying efficiencies than do organic systems, the problem is exaggerated. Clearly, an incomplete coalescence of polymer particles results in a coat that is not continuous; thus the coating cannot be distinguished from the substrate in the cross section shown in Figure 1C. Penetration of water into the core is another likely cause of the lack of distinction between the coating and the core.

Perforated pan coating. Figure 2 shows pellets that have been coated using a modified perforated pan fitted with a screen insert and a special exhaust duct that drops the pellets in a cascading curtain across the path of the coating as it is sprayed out of the nozzles. These pellets appear to have a better coating than those coated in a conventional pan. Surface imperfections are present, however, and there is no distinct boundary between the film coating and the core, suggesting that some water has penetrated the core. Although the perforated pan offers an improvement over a conventional pan in drying efficiency, it does not appear to produce an optimal coating when aqueous systems are used.

Fluidized-bed coating. The fluidized-bed process is becoming increasingly popular for coating fine or intermediate-size particles. In one arrangement, the coating solution is sprayed downward onto the substrate as it is fluidized by air from below; in other words, the coating is applied in a countercurrent fashion. This method is commonly referred to as the *top-spray* method. Figure 3 shows the morphology of the coating applied using the top-spray method to pellets in a fluidized bed. Both views show an improvement in the smoothness and continuity of the coating surface over pellets coated in a conventional or perforated pan. This improvement is not surprising given the greater drying efficiency of the fluidized bed. The coating is visibly distinct from the

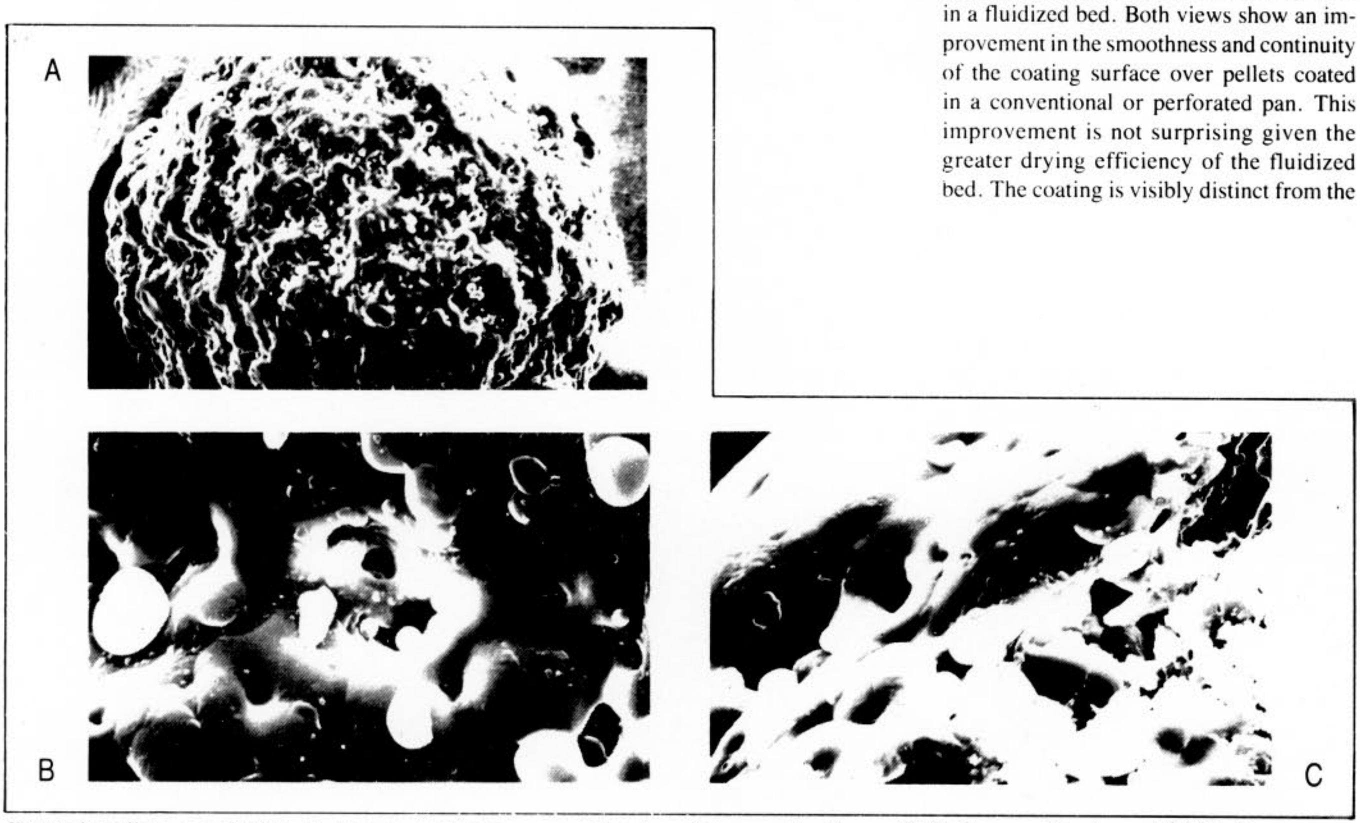

Figure 1: Pellets coated using an aqueous system in a conventional pan (A: magnification = 100X; B: magnification = 1000X; C: cross section, magnification = 1000X).

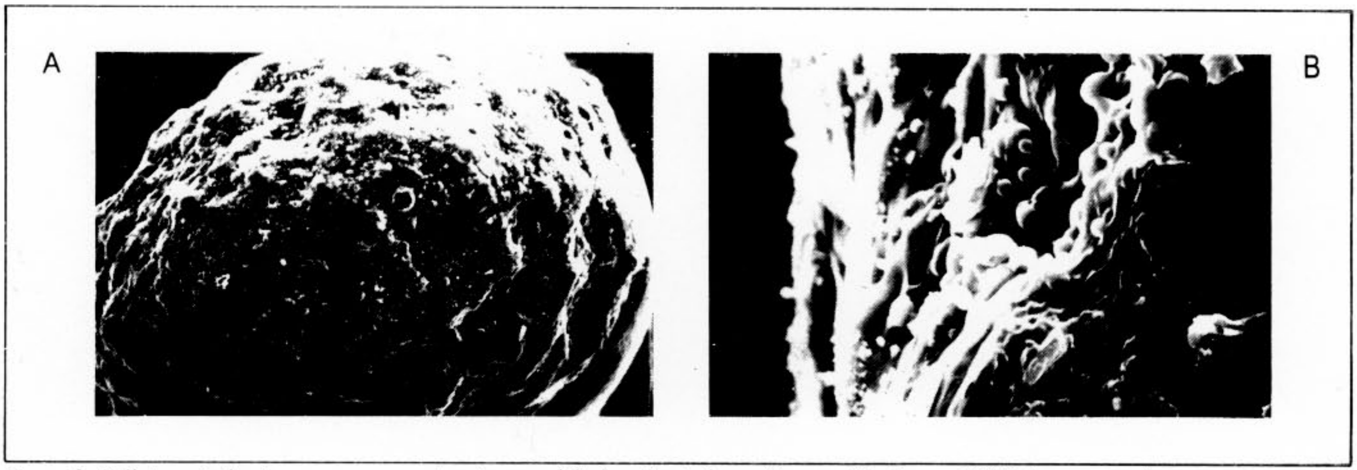

Figure 2: Pellets coated using an aqueous system in a modified perforated pan (A: magnification = 100X; B: cross section, magnification = 1500X).

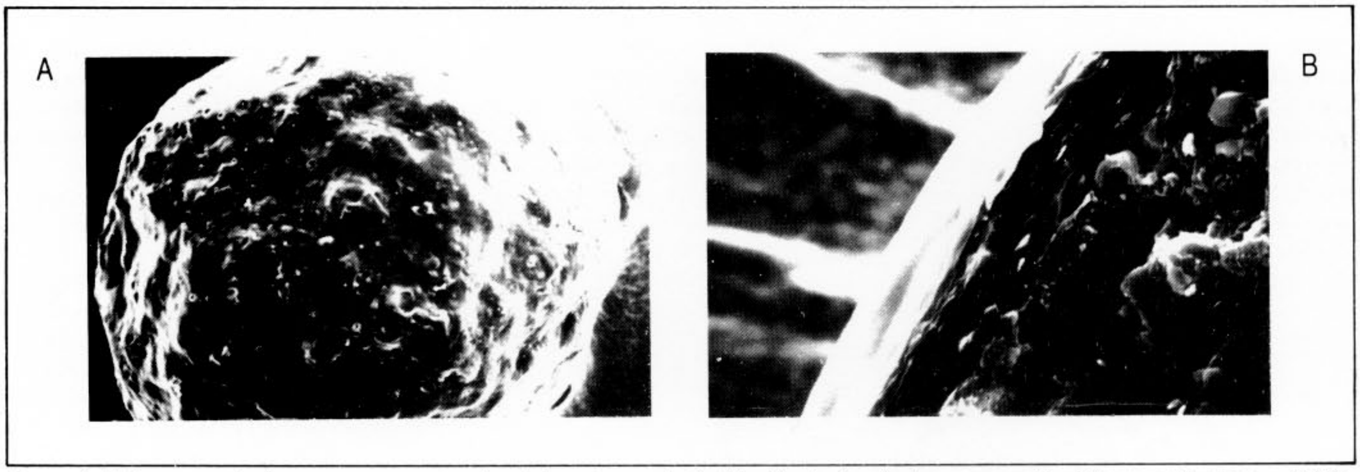

Figure 3: Pellets coated using an aqueous system in a laboratory-scale fluidized bed using the top-spray method (A: magnification = 100X; B: cross section, magnification = 1000X).

core (Figure 3B), probably as a result of decreased penetration of the core by water and improved coalescence of the polymer particles over the surface of the pellet.

Another type of fluidized-bed coating process makes use of the Wurster coater, which was developed nearly twenty years ago. The coating solution is applied from the bottom at the same time and in the same direction as the flow of the pellets through the chamber. The pattern followed by the pellets is much more regular in this method than it is in the top-spray method, resulting in further improvements in the physical characteristics of the coating applied, as is evident from Figure 4.

The cross section (Figure 4B) clearly shows the distinct layer of coating applied to these pellets. In comparison with the coatings applied using any of the three processes previously discussed, the physical quality of this coating appears to be superior. The fluidized-bed process using the Wurster coater appears to provide ideal conditions for the complete coalescence of the polymer particles, with little or no penetration of water into the core of the pellet.

The process of film coating small particles is very similar to the processes of granulation or agglomeration. Indeed, both processes can be conducted in the same piece of equipment. The key to applying a film so that it performs as designed, however, is somewhat more complex. On the one hand, droplets of coating solution must have as low a viscosity as possible when they come into contact with the substrate so that they will spread uniformly and form a continuous film. On the other hand, perpetual agglomeration and deagglomeration can occur under these conditions, resulting in surface craters, or, more severely, in irreversible agglomeration.

To avoid the formation of liquid bridges between two or more pellets, liquid must be evaporated quickly from the surface of the core. In addition, high surface evaporation, which is characteristic of the fluidized bed, is also necessary to avoid penetration of the core by the solvent.

Organic Coating Systems

For purposes of comparison with the results obtained with aqueous coating systems, further experiments were conducted to evaluate coating techniques using organic solvents. Accordingly, pellets were coated in

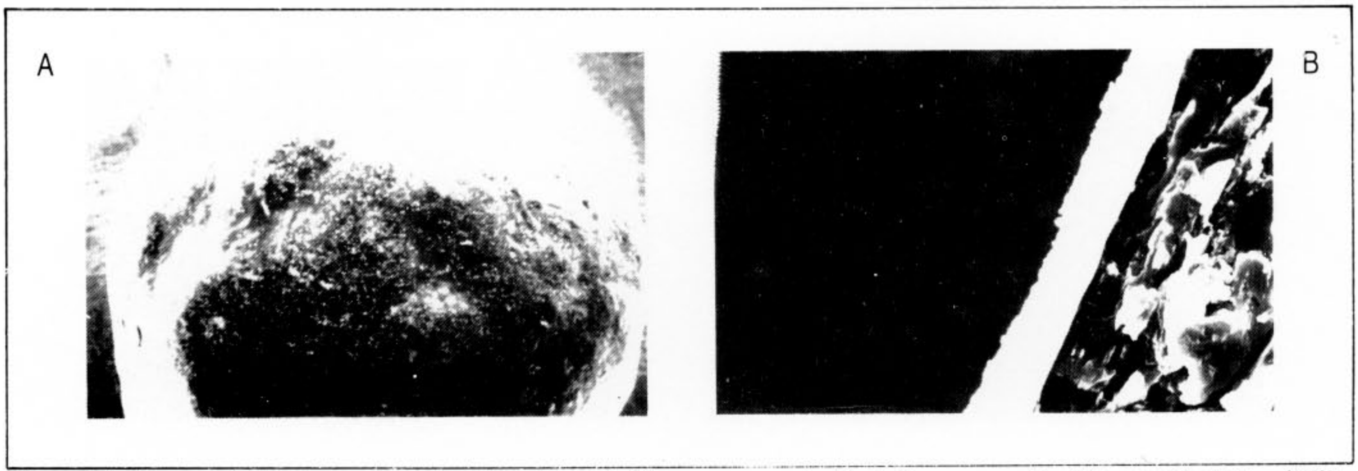

Figure 4: Pellets coated using an aqueous system in a pilot-scale Wurster coater using the bottom-spray method (A: magnification = 100X; B: cross section, magnification = 1000X)

a fluidized-bed unit (Glatt Powder Coater/ Granulator 5/9; Glatt Air Techniques) using three different coating methods: top-spray, bottom-spray, and tangential-spray.

Nonpareil seeds were first coated with a red-colored aqueous solution of hydroxypropyl methylcellulose (HPMC) (Opadry; Colorcon, West Point, Pennsylvania) that served as a control for visual demonstration of coating efficiency. The color solution was applied onto a spiraling helix of fluidized pellets in a rotary fluidized bed. Figures 5A and 5B depict the surface characteristics of these colored nonpareil seeds. The red layer is readily seen in the cross sections in Figures 5C and 5D. When these pellets are placed in water, the color releases immediately.

These seeds were further coated with ethyl cellulose using ethanol as a solvent. Two-percent coatings (based on substrate weight) were applied using the three spraying methods mentioned earlier.

Top-spray coating. Figures 6A and 6B show the surface of pellets coated using the top-spray method. Imperfections, seen at both low and high magnifications, can be attributed to the manner in which the liquid is applied. Although the spray nozzle is positioned so that it is immersed in the fluidized pellets, the fluidizing pattern is disorganized. As a result, droplets travel random distances before impinging on the substrate. The capacity of a droplet to spread to form a continuous film depends on its viscosity, which changes as the solids content of the droplet increases with evaporation. Because in this method the coating solution is sprayed against the heated air stream, the evaporation of the ethanol solvent (which has a low heat of vaporization) is quite rapid. As a result, the surface of the coating is rough.

The cross section shown in Figures 6C and 6D reveals, however, that the film coating is distinguishable from the precoat and from the core. When placed in water, the pellets release color quickly because of imperfections in the film.

Although this method may be unacceptable for producing a reproducible sustained-release coating, it is appropriate for other applications. Taste-masking with water-insoluble polymers such as ethyl cellulose, which has a bland taste, is one example. Other desired release characteristics may require the use of water as a solvent because it is much more forgiving — a result of its much higher heat of vaporization.

Bottom-spray coating. The bottom-spray method, which makes use of the Wurster coater, appears to provide a smooth, continuous film of polymer, as shown in Figures 7A and 7B. Figures 7C and 7D, which are SEMs of these pellets in cross section, show distinct layers of film coating (ethyl cellulose) and undercoat (HPMC). This layering demonstrates that very little (if any) solvent has penetrated to the core. The thickness of the coating in such cases is easy to control as well as to reproduce. Consequently, drug release rates can also be controlled from batch to batch.

The design of the Wurster coater organizes the pellets to be close to the spray nozzle, an arrangement that prevents any appreciable change in the ratio of solids to liquids in the coating solution. Furthermore, this technique allows each layer of coating to dry more completely before pellets are recycled to receive further coating. Pellets coated by this method release color very slowly when placed in water, although the quantity of coating is the same as and the

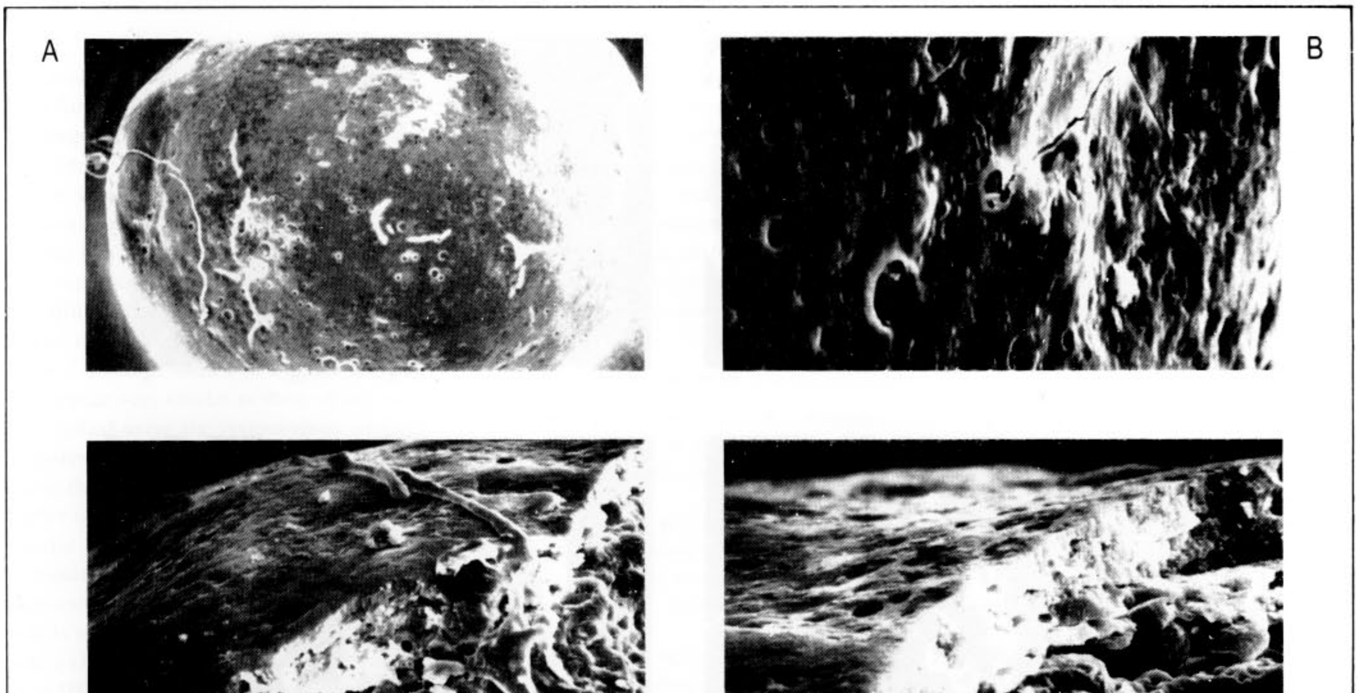

Figure 5: Pellets coated with HPMC in a rotary fluidized bed using the tangential-spray method (A: magnification = 100X; B: magnification = 1000X; C: cross section, magnification = 350X; D: cross section, magnification = 1000X).

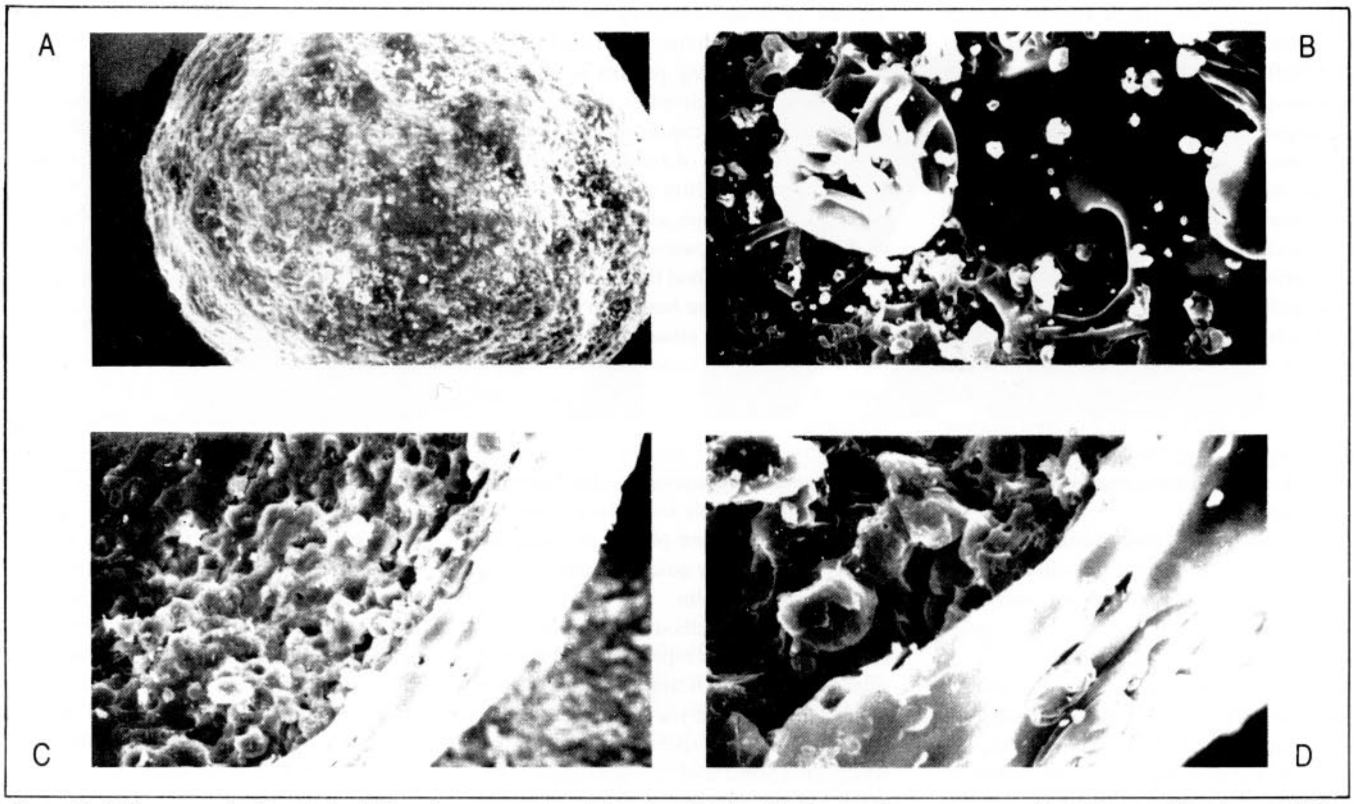

Figure 6: Pellets coated with ethyl cellulose in an organic solution in a fluidized bed using the top-spray method (A: magnification = 100X; B: magnification = 1000X; C: cross section, magnification = 350X; D: cross section; magnification = 1000X).

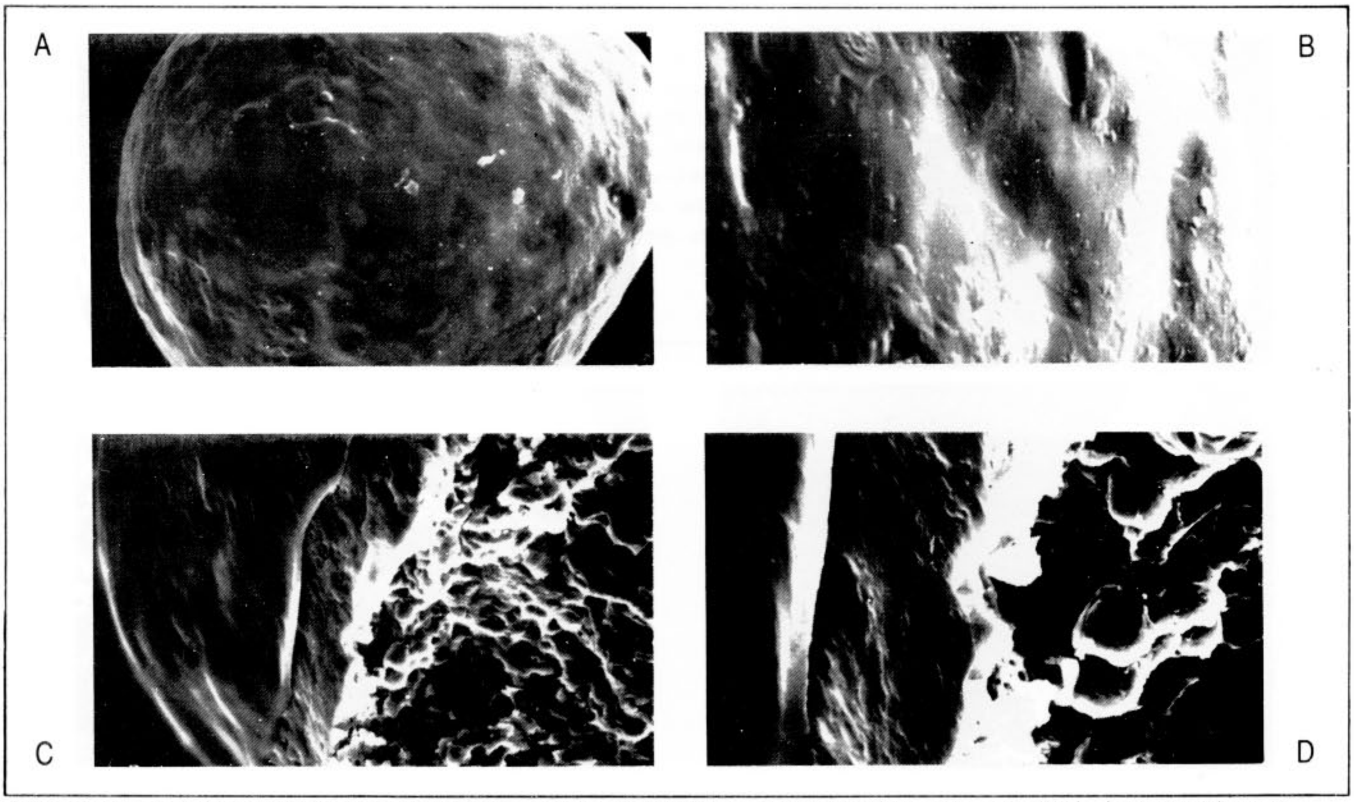

Figure 7: Pellets coated with ethyl cellulose in an organic solution in a fluidized bed using the bottom-spray method (A: magnification = 100X; B: magnification = 1000X; C: cross section, magnification = 350X; D: cross section, magnification = 1000X).

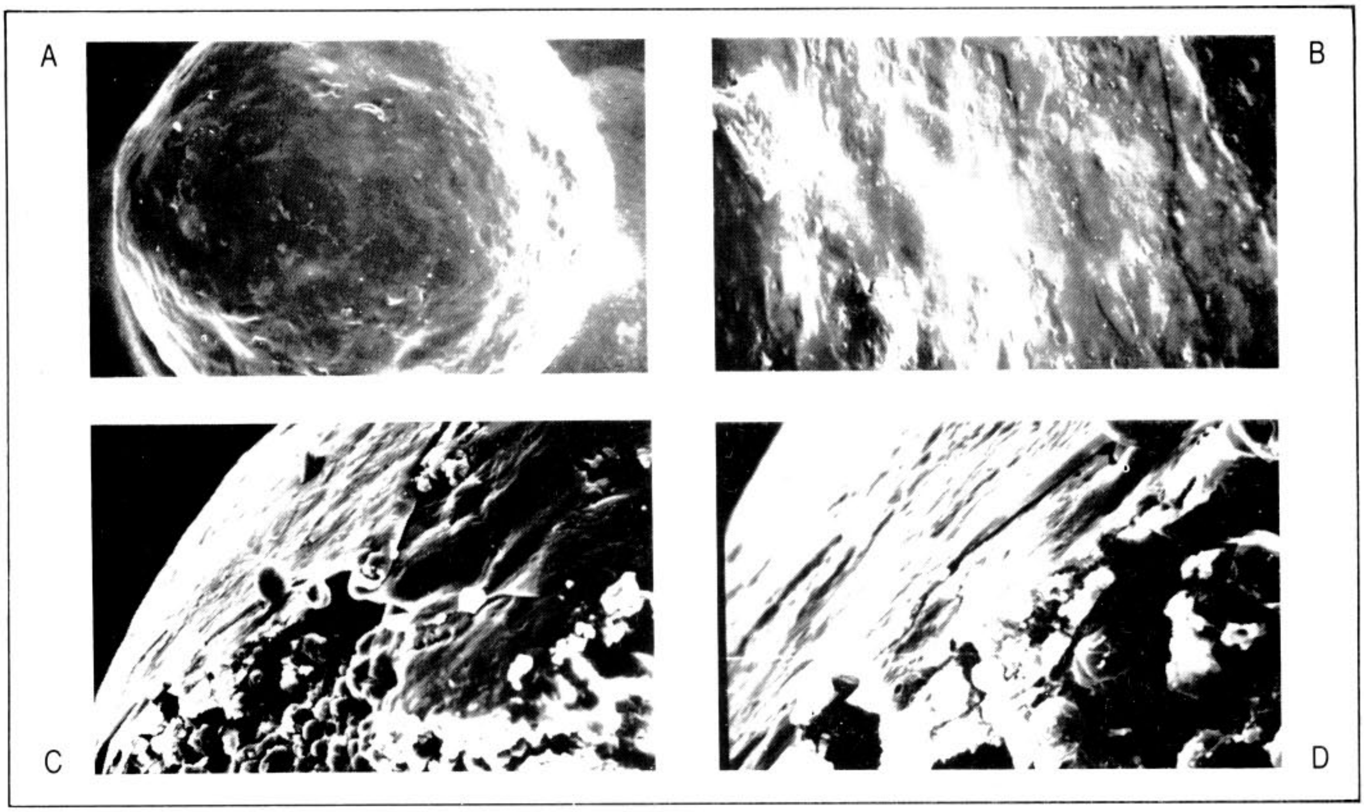

Figure 8: Pellets coated with ethyl cellulose in an organic solution in a fluidized bed using the tangential-spray method (A: magnification = 100X; B: magnification = 1000X; C: cross section, magnification = 350X; D: cross section, magnification = 1000X).

processing conditions are similar to those used for top-spray coating.

Tangential-spray coating. Using the tangential-spray method, the coating solution is sprayed tangentially in the same direction as the pellets in the bed, which are rotated in a homogeneous, spiral motion by the combined action of the fluidizing air, centrifugal force, and gravity.

The morphological characteristics of the applied coating, shown in Figures 8A and 8B, appear very similar to those of the coating applied using the bottom-spray method (Figures 7A and 7B). This is encouraging because the spray application rate is typically higher using the tangential-spray method. A shorter processing time is a benefit when it requires no sacrifice of the desired film characteristics. The cross sections of these pellets shown in Figures 8C and 8D also reveal a clear demarcation between the undercoat (HPMC) and the film coating (ethyl cellulose).

Conclusion

It is evident from the SEMs presented in this article that the physicomechanical properties of films are highly dependent on the processing techniques used to apply them. Because the morphology of a film coating plays a significant role in the release of drug from pellets, examination under the scanning electron microscope can provide scientists involved in formulation, processing, and quality control with an effective tool for product development.

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