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IN RECENT YEARS, fluid-bed techniques have gained considerable popularity in the application of controlled-release coatings. At the same time, an ambitious shift has been made from the use of organic solvents to the use of aqueous films because of their environmental and economic advantages. A variety of both water-soluble and insoluble products, from small crystals to tablets, are now being coated with aqueous films. Newly developed films are being used to provide for enteric release, taste masking, sustained and controlled release, stability, and improved appearance. Although films applied using organic solvents offer processing advantages because of the low heat of vaporization characteristic of these solvents, safety precautions, environmental constraints, and the cost of equipment have made the use of water as a solvent more attractive.

Initially, aqueous systems were viewed with skepticism because of their lengthy processing times and because the appearance of products coated with aqueous films was inferior to that of products coated using organic systems. The recent development of latex and pseudolatex materials has broadened the spectrum of aqueous coatings available, however, and has eliminated some of the earlier objections to aqueous systems. When the appropriate equipment has been selected and correct conditions are maintained, it is now possible to apply both aqueous and organic films to small particles without causing agglomeration. Both types of films may also be applied to tablets or small particles that contain water-soluble or moisture-sensitive drugs.

The effects of various types of coating equipment on both the morphology of the applied films and the drug release rates has been reported in the literature.[1,2] Other researchers have investigated the coating of tablets and small particles with acrylic resins by means of fluid-bed technology.[3] The present article describes the results of a study of the effect of three techniques of fluid-bed coating and two types of solvents on the morphology of applied films, and consequently of the effect of the films morphology on drug release rates.

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Materials and Methods

Two types of enteric coatings — one aqueous and the other organic — were applied to aspirin granules and caffeine pellets. Because water has a high heat of vaporization, fluid-bed equipment offering a good drying efficiency was selected for the application of films. The following three techniques for spray-coating in fluid-bed equipment (Glatt GPCG 5/9; Glatt Air Techniques, Ramsey, New Jersey) were examined:

- top-spraying using a conventional fluid-bed granulator
- bottom-spraying using a Wurster column
- tangential-spraying using a rotor granulator.

These three processes are illustrated in Figures 1, 2, and 3, respectively.

Typical coating application conditions using a binary nozzle were applied for all three methods. Films were applied to 18/20 mesh caffeine pellets of 81.5% potency (Sidmak Laboratories, East Hanover, New Jersey) using either an organic system (Eudragit S100; Röhm Pharma, Weiterstadt, West Germany) or an aqueous system (Eudragit L30D, Röhm Pharma). Aspirin granules of 99.4% potency (Dow Chemical, Midland, Michigan) were coated with either an organic system (cellulose acetate phthalate or CAP; Eastman Chemical Products, Kingsport, Tennessee) or an aqueous system (Eudragit L30D). Caffeine pellets and aspirin granules were coated to theoretical weight gains of either 5% w/w or 15% w/w with both coating materials using each of the three application methods.

After coating was completed, the efficacy of each processing technique was evaluated in terms of the morphology of the coatings as observed under a scanning electron microscope (model SX-40, ISI, Milpitas, California). Each technique also was evaluated in terms of in vitro release rates, which were determined using USP method A for enteric-coated articles, in which the dissolution basket (Distek, Somerset, New Jersey) was rotated at 100 rpm. Absorbances were read by an automated spectrophotometer (model 8450A; Hewlett-Packard, Paramus, New Jersey) at 273

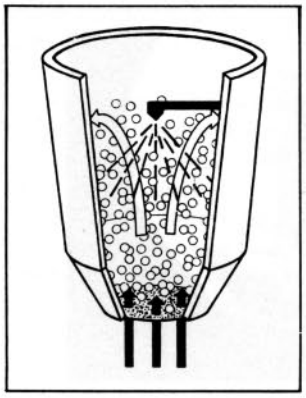


Figure 1: A top-spray coating process in a conventional fluid-bed granulator (Glatt Air Techniques).

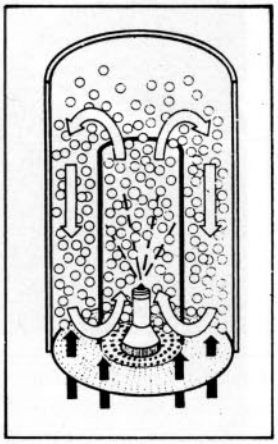


Figure 2: A bottom-spray coating process in a Wurster column (Glatt Air Techniques).

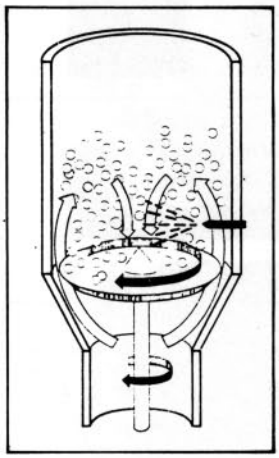


Figure 3: A tangential-spray coating process in a rotor granulator (Glatt Air Techniques).

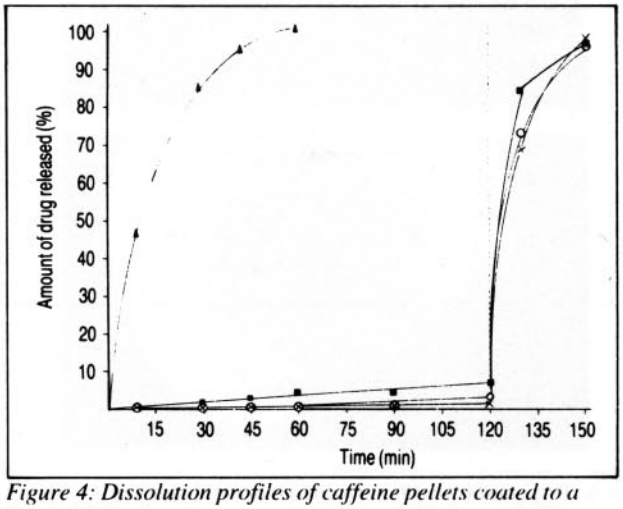


Figure 4: Dissolution profiles of caffeine pellets coated to a level of 5% w/w using an aqueous system (Eudragit L30D). For 0 min to 120 min, pH = 1.2; for 120 min to 150 min, pH = 6.8 (▲ = uncoated; ○ = top-spray method; ■ = bottom- spray method; × = tangential-spray method).

nm for caffeine and, for aspirin, at the wavelength of the isosbestic point of aspirin and salicylic acid (280 nm in the acid stage and 265 nm in the buffer stage).

Results and Discussion

Caffeine pellets. Dissolution profiles of caffeine pellets that were coated to 5% w/w with the aqueous system are shown in Figure 4. These profiles indicate that all three methods of spraying produced effective enteric coatings. The similar profiles for all three processing techniques are consistent with the similar morphological characteristics observed under a scanning electron microscope (Figures 5–7).

In contrast to pellets coated with the aqueous system, the dissolution profiles of pellets that were coated with the organic system at a level of 5% w/w were significantly different for each of the three processing methods (Figure 8). At a coating level of 15%, the differences between the bottom-spray technique and the tangential-spray technique were greatly reduced; both methods produced acceptable in vitro dissolution rates (Figure 9). The top-spray technique, however, was not successful in terms of in vitro dissolution rates, even at a coating level of 15% w/w.

An explanation for these differences can be found in the mechanics of each processing technique. In the top-spray method (Figure 1), the substrate is fluidized up to the level of the liquid nozzle, which sprays coating solution countercurrently onto the material in the bed. This arrangement allows the solvent to evaporate before it contacts the substrate, causing a change in the ratio of solids to liquid in the coating droplet. In other words, spray-drying inevitably occurs when the top-spray technique is used to apply films based on organic solvents.

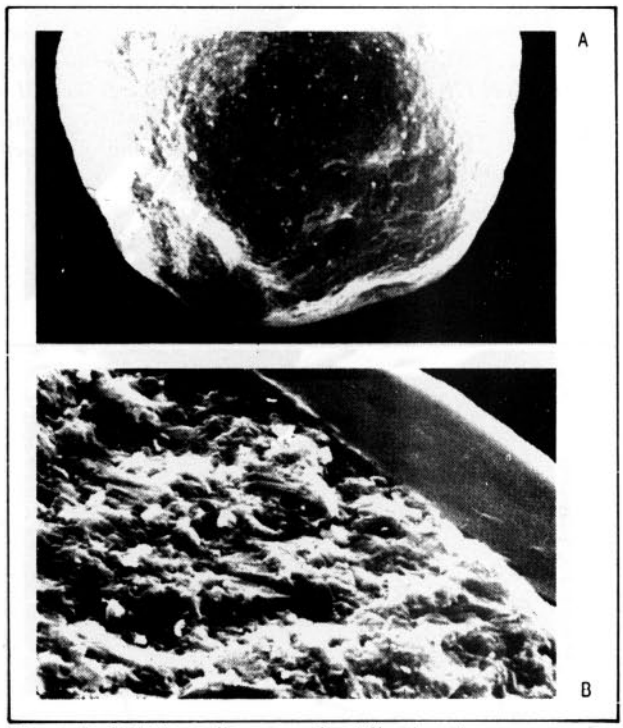


Figure 5: Caffeine pellets coated to 5% w/w using an aqueous system (Eudragit L30D) and the top-spray method (A: magnification = 70X; B: cross section, magnification = 1000X).

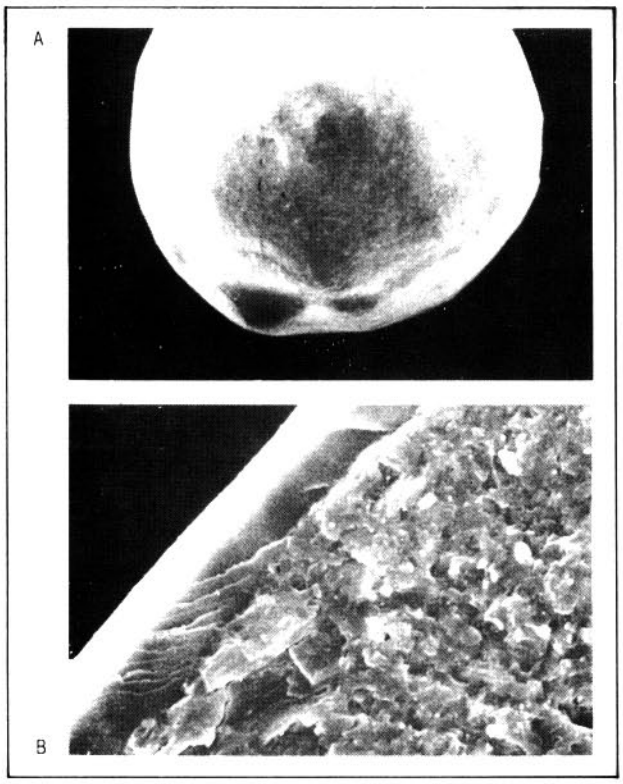


Figure 6: Caffeine pellets coated to 5% w/w using an aqueous system (Eudragit L30D) and the bottom-spray method (A: magnification = 70X; B: cross section, magnification = 1000X).

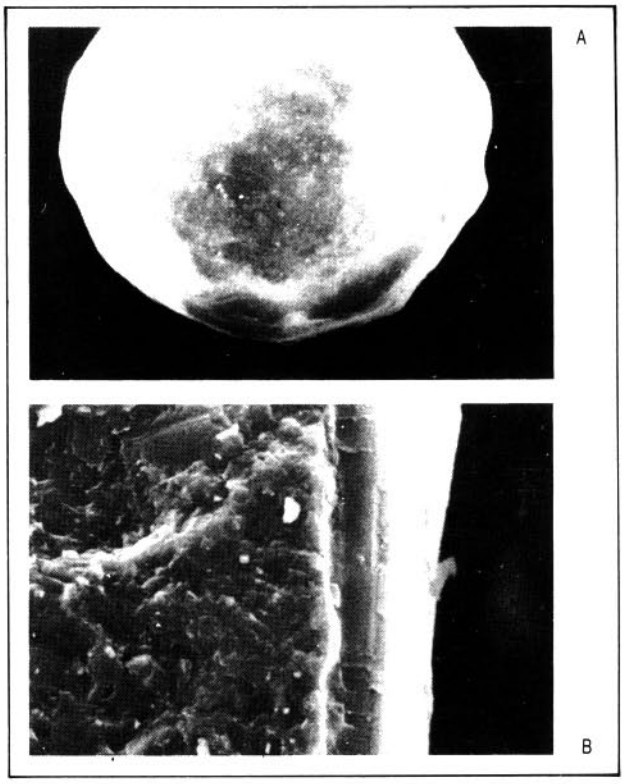
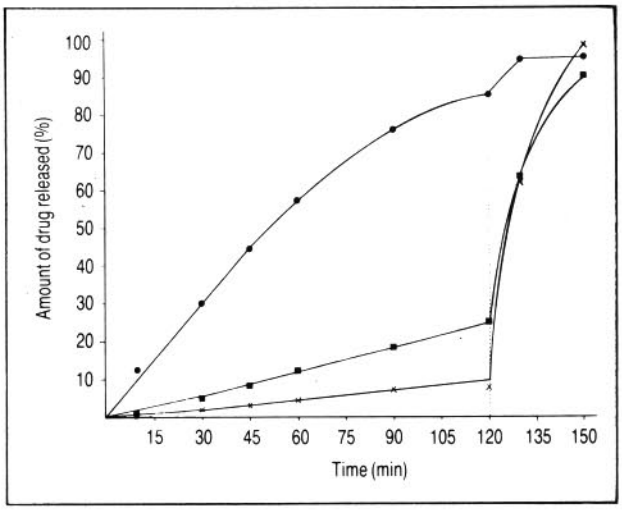


Figure 7: Caffeine pellets coated to 5% w/w using an aqueous system (Eudragit L30D) and the tangential-spray method (A: magnification = 70X; B: cross section, magnification = 1000X).

Figure 8: Dissolution profiles of caffeine pellets coated to a level of 5% w/w using an organic system (Eudragit S100). For 0 min to 120 min, pH = 1.2; for 120 min to 150 min, pH = 6.8 (● = top-spray method; ■ = bottom-spray method; × = tangential-spray method).



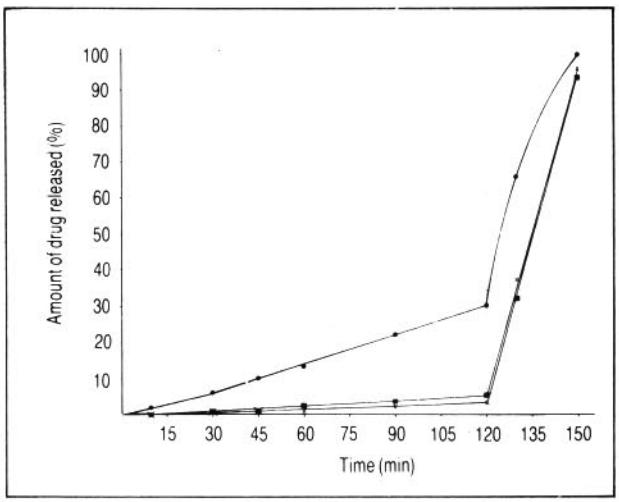


Figure 9: Dissolution profiles of caffeine pellets coated to a level of 15% w/w using an organic system (Eudragit S100). For 0 min to 120 min, pH = 1.2; for 120 min to 150 min; pH = 6.8 (● = top-spray method; ■ = bottom-spray method; × = tangential-spray method).

This outcome is quite apparent when the morphology of the applied coating is examined under a scanning electron microscope (Figures 10 and 11). As can be seen in Figure 11, the effective coating thickness produced by the top-spray method is significantly less than that produced by either the bottom-spray or the tangential-spray method. This reduction in the thickness of the coating can be attributed to spray-drying as well as to the random motion of fluidized particles past the spray nozzle when the top-spray method is used.

When the Wurster bottom-spray method is used (Figure 2), it is possible to apply droplets to the substrate before much evaporation of solvent occurs, and the subsequent evaporation of solvent from the surface of the pellets is complete before the solvent can penetrate the pellets' cores. Suspending the pellets in air keeps them discrete from one another and allows films to be applied to pellets with little or no agglomeration. In this system, the close proximity of the liquid nozzle to the fluidized particles and the rapid cycle times yield a more uniform distribution of the film.

When the tangential-spray method is used (Figure 3), it also is possible to apply droplets to the substrate before much evaporation occurs, because the nozzle is immersed in the fluid bed. The morphological characteristics of films applied using the tangential-spray method were found to be similar to those obtained when the Wurster column was used (Figures 10B, 10C, 11B, and 11C). Tables I, II, and III demonstrate the reproducibility of in vitro release rates obtained using each of the three fluid-bed processing methods.

Aspirin granules. At least two new enteric-coated aspirin products recently have been marketed in the form of hard gelatin capsules filled with coated particles. More such products are likely to be introduced into the market soon because of recently renewed interest in such enteric-coated products.[9]

Figure 12 shows the morphological characteristics of uncoat-

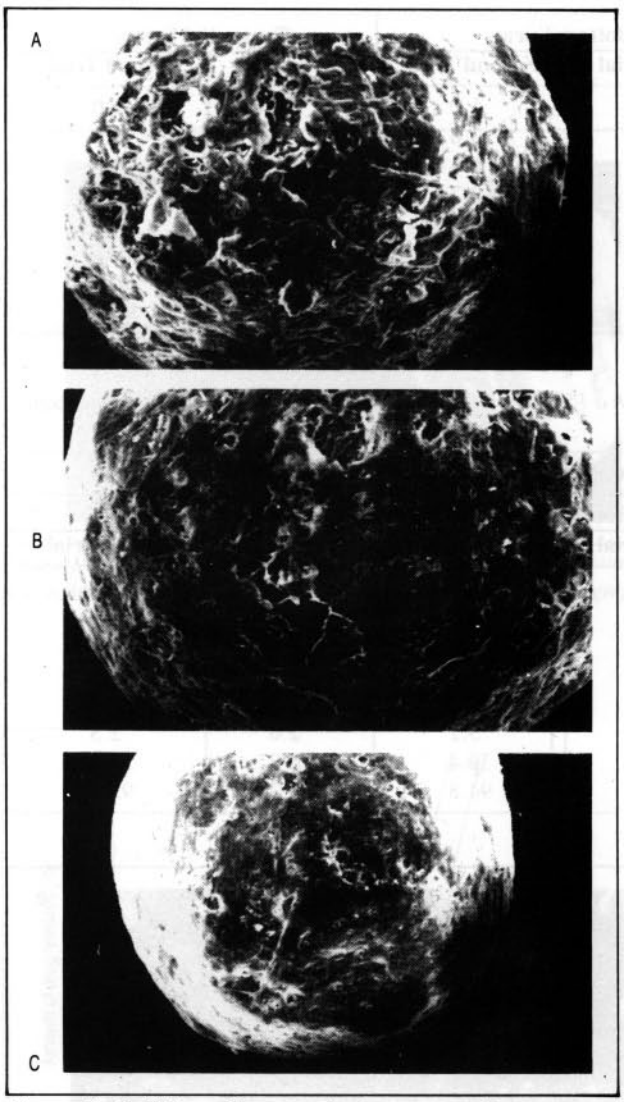


Figure 10: Caffeine pellets coated using an organic system (Eudragit S100) to a level of 5% w/w (A = top-spray method, magnification = 70X; B = bottom-spray method, magnification = 70X; C = tangential-spray method, magnification = 50X).

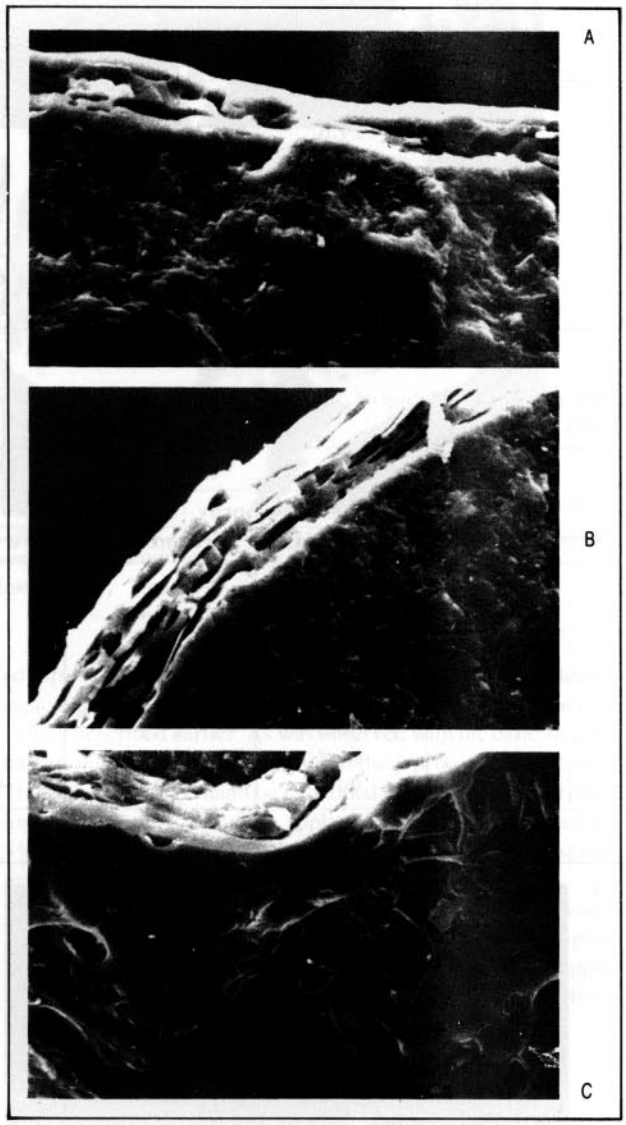


Figure 11: Cross-sectional views of caffeine pellets coated to a level of 15% w/w using an organic system (Eudragit S100; A = top-spray method; B = bottom-spray method; C = tangential-spray method; magnification = 340X).

Table I: The dissolution of caffeine pellets that have been coated with a 15% coat of an aqueous coating material (Eudragit L30D).

Time (min)	Amount Dissolved (%)					
	Top Spray		Bottom Spray		Tangential Spray	
	First Trial	Second Trial	First Trial	Second Trial	First Trial	Second Trial
10	0	0	0.1	0.3	0	0
30	0	0	0.3	0.6	0	0
45	0	0	—	—	0	0
60	0	0	0.4	0.6	0	0
90	0	1.0	0.5	1.2	0	0
120	1.0	1.0	1.0	2.8	0	1.0
130	61.8	58.9	41.2	43.0	51.3	57.1
165	100.3	99.2	89.9	87.2	95.2	96.8

Table II: The dissolution of caffeine pellets that have been coated with a 5% coat of an organic enteric coating material (Eudragit S100).

Time (min)	Amount Dissolved (%)					
	Top Spray		Bottom Spray		Tangential Spray	
	First Trial	Second Trial	First Trial	Second Trial	First Trial	Second Trial
10	12.5	8.6	1.4	1.0	1.0	2.0
30	29.6	26.2	5.1	3.6	2.0	3.0
45	43.6	39.3	8.1	6.1	3.1	4.3
60	57.2	52.1	11.6	8.7	4.4	5.6
90	75.6	72.6	18.4	13.7	7.0	8.0
120	84.5	83.1	25.4	18.9	9.6	10.6
130	93.7	93.8	63.1	68.2	61.8	60.8
150	94.9	94.8	89.9	95.7	97.8	94.9

Table III: The dissolution of caffeine pellets that have been coated with a 15% coat of an organic enteric coating material (Eudragit S100).

Time (min)	Amount Dissolved (%)					
	Top Spray		Bottom Spray		Tangential Spray	
	First Trial	Second Trial	First Trial	Second Trial	First Trial	Second Trial
10	1.9	1.4	0	0	0	0
30	6.1	4.4	1.0	0	0	1.0
45	9.7	7.0	1.2	1.0	1.0	1.0
60	13.4	9.8	1.7	1.0	1.0	1.0
90	21.5	15.7	3.1	2.0	2.0	2.0
120	30.0	21.9	4.8	3.2	2.0	2.3
130	65.4	49.9	31.5	30.4	36.8	28.1
150	99.0	97.5	92.7	94.8	95.7	93.5

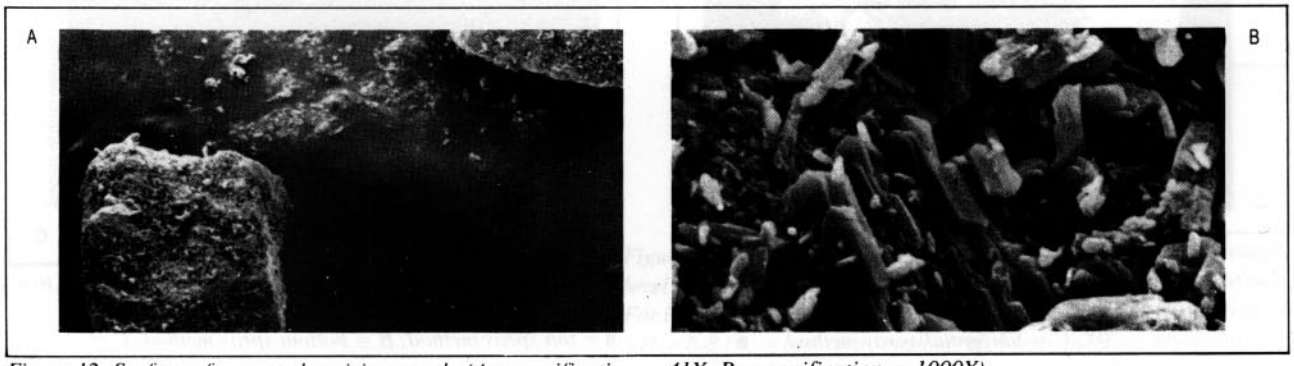


Figure 12: Surface of uncoated aspirin granule (A: magnification = 41X; B: magnification = 1000X).

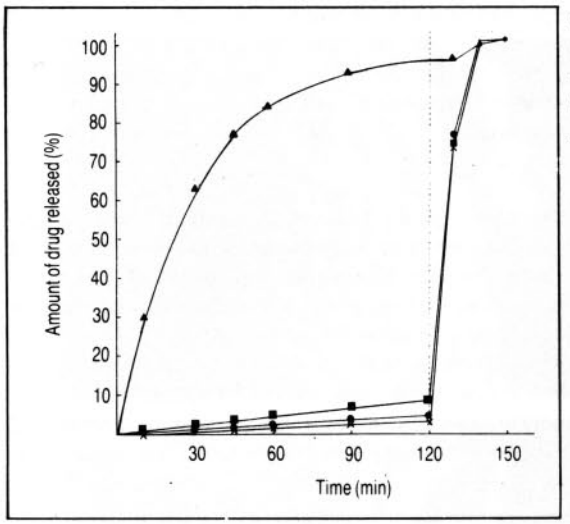


Figure 13: Dissolution profiles of aspirin pellets coated to a level of 5% w/w using an aqueous system (Eudragit L30D). For 0 min to 120 min: pH = 1.2; for 120 min to 150 min, pH = 6.8 (▲ = uncoated; ● = top-spray method; ■ = bottom-spray method; × = tangential-spray method).

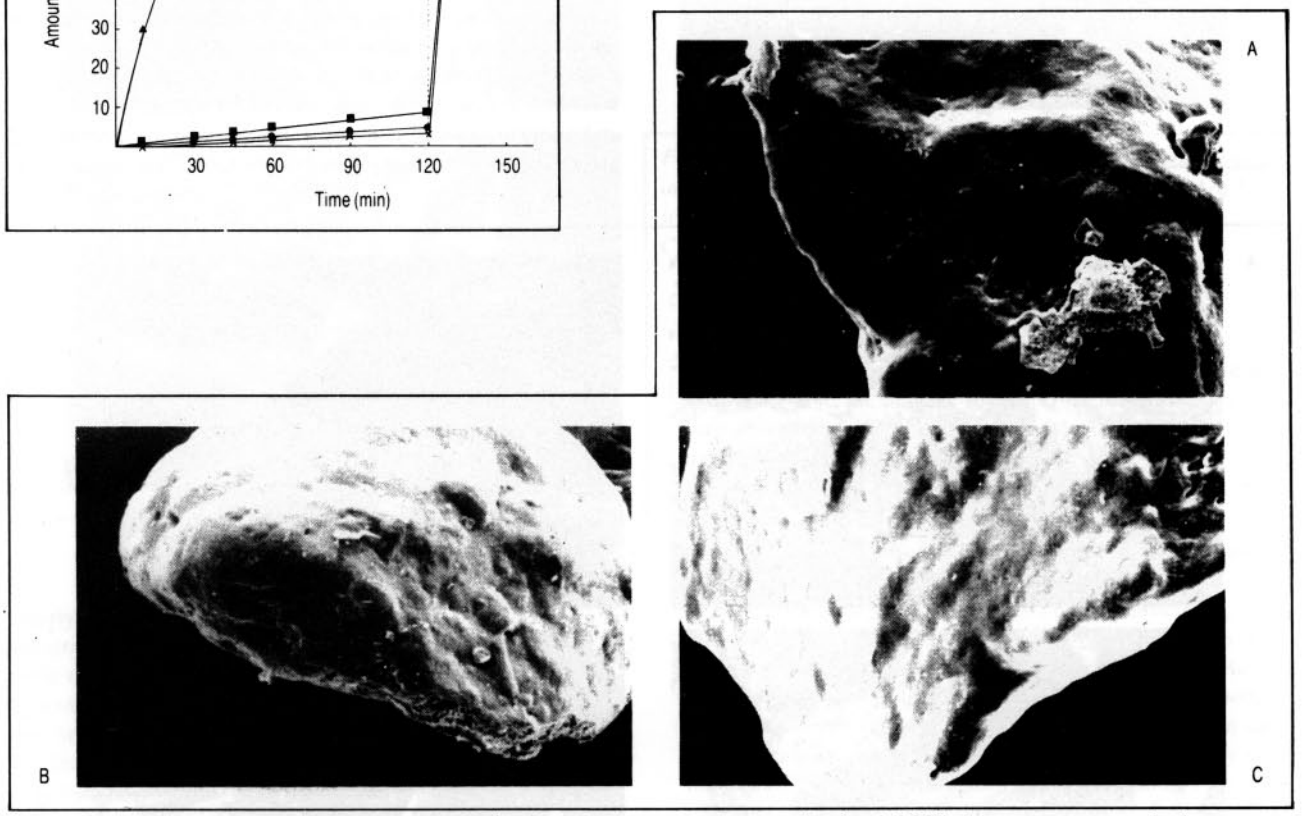


Figure 14: Aspirin granules coated to a level of 5% w/w using an aqueous system (Eudragit L30D) (A = top-spray method; B = bottom-spray method; C = tangential-spray method; magnification = 90X).

ed aspirin granules; Figure 13 shows the dissolution profiles of aspirin granules that were coated to 5% w/w with the aqueous system described earlier. As was observed with the caffeine pellets, these profiles are similar for all three processing methods. This similarity may again be explained in terms of the morphological characteristics of the applied films. Granules coated to 5% w/w using the top-spray, bottom-spray, and tangential-spray methods are shown in Figure 14.

In contrast, when the organic coating system (CAP) was applied to aspirin granules at a level of 5% w/w, the dissolution profiles depended on the processing method that was used to apply the coating (Figure 15). At a level of 15% w/w, however, these

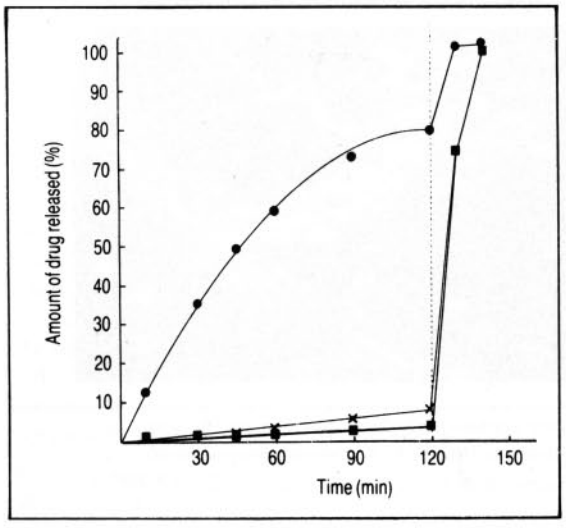


Figure 15: Dissolution profiles of aspirin granules coated with an organic system (cellulose acetate phthalate) to a level of 5% w/w. For 0 min to 120 min, pH = 1.2; for 120 min to 150 min, pH = 6.8 (● = top-spray method; ■ = bottom-spray method; × = tangential-spray method).

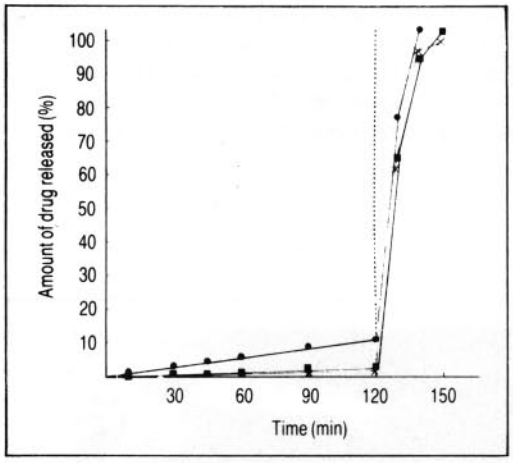


Figure 16: Dissolution profiles of aspirin granules coated with an organic system (cellulose acetate phthalate) to a level of 15% w/w. For 0 min to 120 min, pH = 1.2; for 120 min to 150 min, pH = 6.8 (● = top-spray method; ■ = bottom-spray method; × = tangential-spray method).

differences were greatly reduced, as Figure 16 shows. These results are consistent with those observed with caffeine pellets and shown in Figures 8 and 9. As before, differences in the in vitro release rates among the three processing methods may be related to the morphological properties of the applied films.

When the top-spray technique was used to apply coating to a level of 5% w/w, the applied film did not appear to be smooth and uniform, a result that probably is caused by spray-drying and/or random fluidizing patterns (Figure 17A). Figure 17B

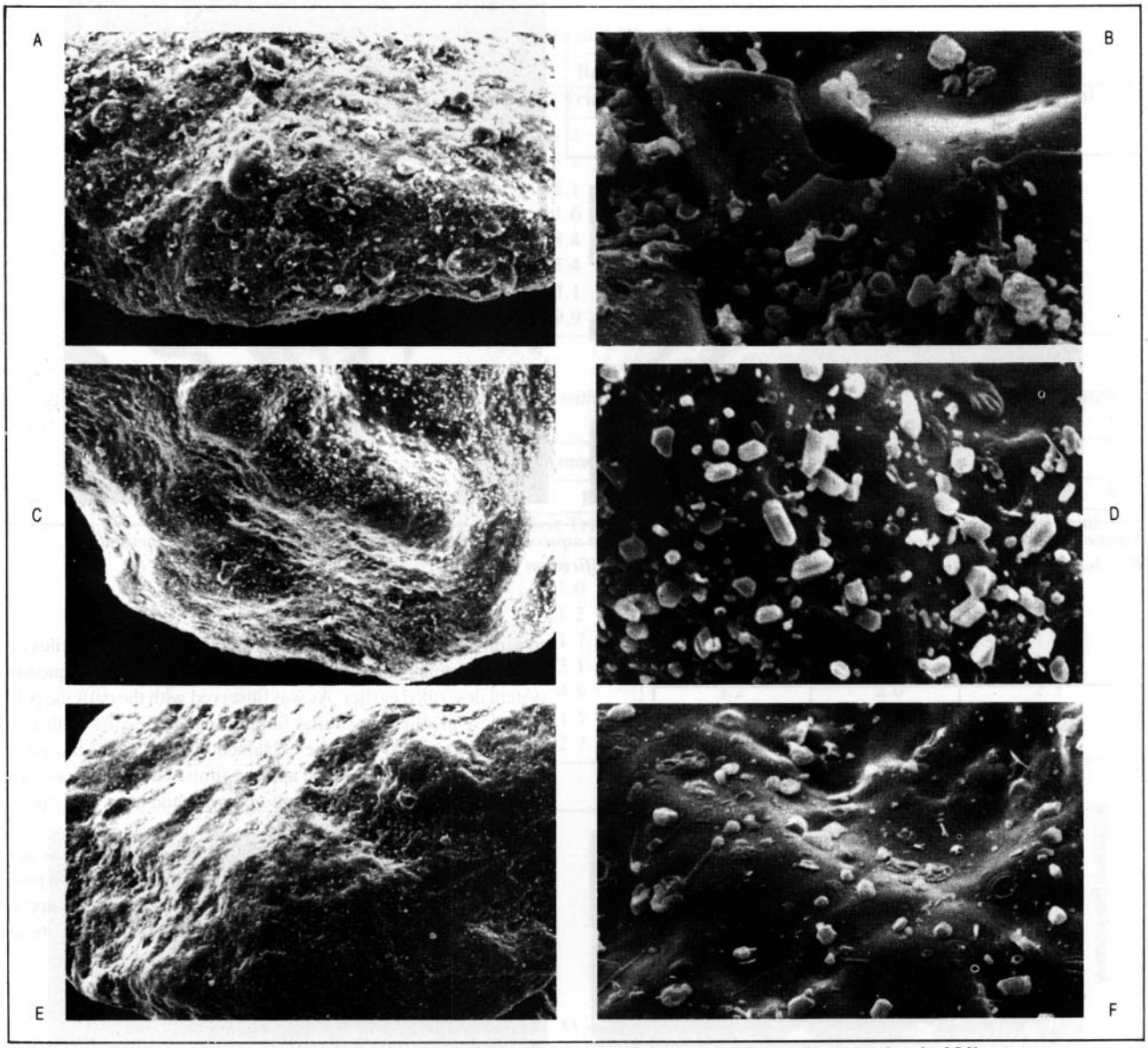


Figure 17: Surface of aspirin granules coated with an organic system (cellulose acetate phthalate) to a level of 5% w/w (A = top-spray method, magnification 100X; B = top-spray method, magnification 1000X; C = bottom-spray method, magnification 100X; D = bottom-spray method, magnification 1000X; E = tangential-spray method, magnification 100X; F = tangential-spray method, magnification 1000X).

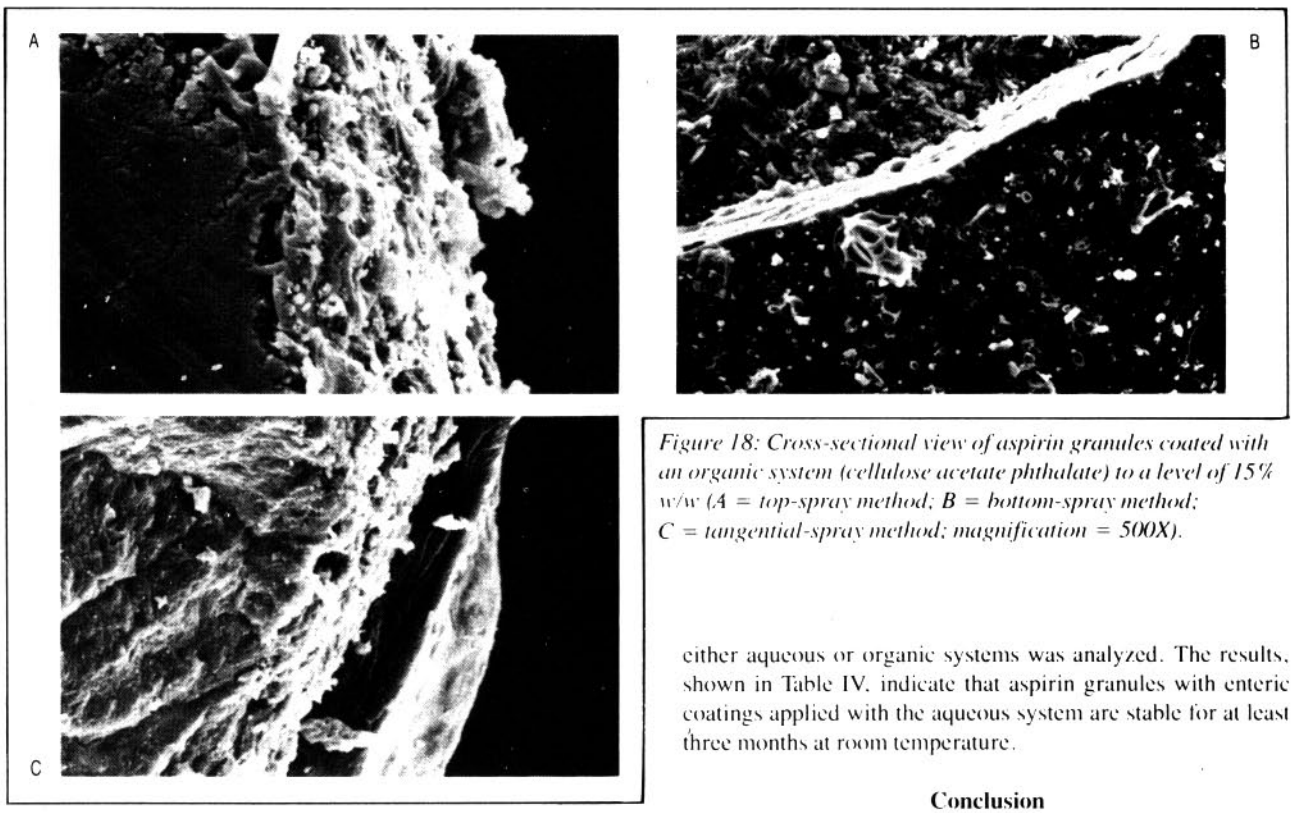


Figure 18: Cross-sectional view of aspirin granules coated with an organic system (cellulose acetate phthalate) to a level of 15% w/w (A = top-spray method; B = bottom-spray method; C = tangential-spray method; magnification = 500X).

clearly shows a spray-dried coating droplet deposited on the substrate. Furthermore, the cross-sectional examination of these coated aspirin granules showed differences in the thickness of coatings (Figure 18). Although the thicknesses of coatings applied by bottom-spraying and tangential-spraying were similar, a significantly reduced coating thickness was observed in aspirin granules that were coated using the top-spray method. Again, these observations are consistent with the observed characteristics of caffeine pellets.

Finally, the stability of aspirin granules that were coated using either aqueous or organic systems was analyzed. The results, shown in Table IV, indicate that aspirin granules with enteric coatings applied with the aqueous system are stable for at least three months at room temperature.

Table IV: Stability data for various coating systems.

System Description	Amount of Aspirin (%)	Time (months at room temperature)
Uncoated	99.4	3
Aqueous TS* 5% coat	98.7	3
Aqueous TS 15% coat	94.3	3
Aqueous W* 5% coat	97.6	3
Aqueous W 15% coat	97.5	3
Aqueous R* 5% coat	97.6	3
Aqueous R 15% coat	98.6	3
Organic TS 5% coat	99.3	<1
Organic TS 15% coat	100.0	<1
Organic W 5% coat	97.4	<1
Organic W 15% coat	94.5	<1

*TS = top-spray method; W = Wurster (bottom-spray method); R = rotor (tangential-spray method).

Conclusion

This study indicates that both caffeine pellets and aspirin granules can be successfully coated with an aqueous enteric coating system using any of the three fluid-bed processing methods described in this article. When an organic system is used, however, the success of the process will depend on the selection of an appropriate fluid-bed processing technique. The bottom-spray and tangential-spray techniques appear to perform satisfactorily when organic systems are used. The top-spray technique, however, does not appear to be the optimal choice for organic systems because of the distance and direction the coating solution must travel before impinging on the substrate and because the heat of vaporization tends to be lower for an organic solvent than it is for water. The high particle velocity and efficient heat transfer in the top-spray mode, however, allow aqueous coating of small particles to be performed with little or no spray-drying.

The use of the fluid bed in applying controlled-release coatings has increased greatly as experience with it has enabled the development of highly reproducible processes. The work presented here is intended to aid the pharmaceutical scientist in matching an enteric coating system — be it based on an aqueous solvent or on an organic one — to the most appropriate fluid-bed coating technique.

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