International Journal of Pharmaceutics, 60 (1990) 109–124
Elsevier

IJP 02030

The effect of product bed temperature on the microstructure of Aquacoat-based controlled-release coatings

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(Received 16 June 1989)
(Modified version received 10 October 1989)
(Accepted 1 November 1989)

Key words: Fluid-bed coating; Latex film; Aquacoat; Plasticizer; Coalescence; Seal coat; Energy-dispersive X-ray spectroscopy; Scanning electron microscopy

Summary

Diphenhydramine HCl pellets were coated at various bed temperatures in a laboratory-size fluid-bed equipment. Optimum coalescence of an Aquacoat formulation was achieved when the bed temperature was kept between 30 and 40°C. Coating applied outside this temperature range resulted in the formation of poorly coalesced films and faster release rates. The fast release rates of pellets coated at low bed temperatures were attributed primarily to drug migration into the film layer during the coating process and to incomplete film formation due to hardening of the uncoalesced polymer spheres, which, presumably, had a relatively higher minimum film formation temperature. At high bed temperatures, the rate of evaporation of water is so fast that it does not allow the migration of drug from the substrate into the film layer. The fast release rates observed were, therefore, believed to be due to the development of porous films during the coating process.

Introduction

Synthetic latex technology based on emulsion polymerization was originally developed during World War II to overcome the shortage of natural rubber, but was later expanded to include the development of a number of water-based polymeric dispersions that are suitable for surface coatings (Klein, 1981). As a result, latexes or water-based polymeric dispersions have steadily replaced organic solvent-based systems in all aspects of coating technology. For example, in the early seventies, Rhom Pharma introduced latexes based on acrylic polymers which, until then, were applied from organic solutions. Later, FMC and Colorcon utilized, respectively, emulsion/solvent evaporation and phase inversion techniques to manufacture two pseudolatexes which contain ethyl cellulose as the polymeric component. These dispersions are currently being used to develop controlled-release products (Goodhart et al., 1984; Harris et al., 1986; Chang et al., 1987; Ghebre-Sellassie et al., 1988).

Almost simultaneously, fluid bed machines have evolved to become the most efficient and hence widely used pieces of coating equipment in the pharmaceutical industry, particularly when dealing with water-based coating formulations. During a

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fluid bed coating process, the volume and temperature of the fluidization air determine the rate of evaporation of the water in the coating formulation which, in turn, dictates the nature of the coating deposited on a substrate.

The effect becomes even more critical during the application of polymeric dispersions for controlled release purposes. Depending upon the degree of coalescence of the polymeric spheres during the coating process, further curing of the coating may be required, if reproducible and predictable release profiles are desired. In one study, Aquacoat pseudolatex films applied on drug pellets at 43 °C needed about 4 weeks at room temperature to undergo a complete curing phase (Aquacoat Handbook). However, when the same coating material was dried at 60 °C, the curing time was reduced to 1 h (Aquacoat Handbook). In another study, the curing phase was completed in 30 min when pellets were overcoated with a water-soluble polymer and subsequently fluidized at 60 °C in the same fluid bed coating equipment (Harris et al., 1986).

While the need for a curing step during the development of dispersion-based controlled release coating systems is essentially well-established, to date, no systematic study which focuses on the effect of product bed temperature on the nature of the deposited film has been reported. The objective of the present study was, therefore, to investigate the effect of product bed temperature in a fluid-bed process on the structure and performance of pellets coated using an ethylcellulose pseudolatex coating formulation.

Materials and Methods

Materials

Aquacoat (FMC, Philadelphia, PA), hydroxypropyl cellulose (Hercules, Wilmington, DE), triethyl citrate (Morflex, Greensboro, NC), nonpareil seeds (Ozone Confectioners & Bakers, Elmwood Park, NJ) and talc (Cyprus Minerals, Englewood, CO) were used as received. Diphenhydramine HCl (Warner-Lambert, Holland, MI) was passed through 60-mesh screen prior to use.

TABLE 1

Coating formulations

	Ingredients (% w/w)		
	Sealcoat	Sustaining coat	Overcoat
Aquacoat ECD-30	–	38	–
Hydroxypropyl cellulose NF	6	–	6
Triethyl citrate	–	3.6	–
Mistron talc	1	–	1
Distilled water	93	58.4	93

Preparation of pellets

Diphenhydramine HCl pellets were prepared by powder layering in rotary granulators (CF-Granulator, Freund Industrial, Tokyo, Japan, and Glatt GPCG-5, Glatt Air Techniques, Ramsey, NJ) using nonpareils as starter seeds. The drug-loaded pellets were then screened to generate the 12–18-mesh fraction.

Coating process

About 300-g batches of pellets were coated in a fluid-bed coating machine (Strea I, Aeromatic, Towaco, NJ) using various water-based coating formulations (Table 1). In one set of studies, pellets were coated with the sustaining coat formulation to a 15% weight increase, and were, subsequently, overcoated in the same coating machine to a 1% weight increase. The coating conditions are listed in Table 2. In each experiment, the inlet temperature was adjusted to achieve the desired bed temperatures. In another phase of the study, a

TABLE 2

Coating conditions

Parameters	Sustaining coat	Overcoat
Atomizing pressure (bar)	0.5	0.6
Spray rate (g/ml)	1, 3–4 [a]	2–3
Bed temperature (°C)	22	22
	25	25
	30	30
	35	35
	40	35
	45	35
	50	35

[a] 1 g/ml for the first 10 min, and 3–4 g/ml thereafter.

seal coat was first applied on the core pellets to a 1.3 or 5.2% weight increase prior to the application of the sustaining and the overcoating formulations. The overcoated pellets were cured at 45 °C in a forced-air oven for 14 h.

Pellets were also coated at spray rates of 3, 5 and 9 g/min and a product bed temperature of 35 °C. The process was repeated using the same spray rates and a constant inlet air temperature of 60 °C. The bed temperature was allowed to vary as a function of the inlet temperature. All the batches were subsequently overcoated and cured.

Dissolution studies

The release studies were performed in a USP Dissolution Apparatus II (Hanson Research, Northridge, CA) interfaced with a diode-array spectrophotometer (Hewlett-Packard, Avondale, PA) using water as a dissolution medium.

Energy-dispersive X-ray microprobe analysis

The relative distribution of diphenhydramine HCl across a section of the coated pellets was examined using a scanning electron microscope (Amray, Bedford, MA) that was fitted with an energy-dispersive X-ray spectrometer (Econ 9100/60, EDAX International, Prairieview, IL). The coated pellets were embedded in clear epoxy, sliced horizontally and coated with conductive carbon. The samples were then tilted to an angle of 35° and subjected to an electron beam of 30 kV. The spot size was 2. Because the samples contain a hydrochloride salt of the drug, X-rays characteristic of chlorine were emitted and selectively detected by an energy-dispersive X-ray spectrometer. The emitted X-rays are proportional to the concentration of the drug in the specimen, and are depicted on a photomicrograph as dots.

Results and Discussion

The formation of films from a latex or pseudolatex involves the deposition of droplets of the aqueous polymeric dispersion on a substrate followed by evaporation of water and the coalescence of the polymer particles into a continuous film. Over the years, various theories describing the mechanism of film formation have been presented. Dillon et al. (1951) proposed that the main driving force for the coalescence of the polymeric spheres is the polymer-water interfacial tension. Later, Brown (1956) suggested that the coalescence of the spheres is induced mainly by the capillary forces that are generated by the water-air interfacial tension during the evaporation of water, while Voyutskii (1958) postulated that 'autohesion' or the mutual inter-diffusion of the terminal segments of the polymer chains from adjacent polymeric spheres is the most important factor in the overall mechanism of film formation. Vanderhoff et al. (1966) demonstrated that the surface tension proposed by Dillon et al. and capillary forces enunciated by Brown are actually complementary in nature. In addition, they proposed a phenomenon known as 'Further Gradual Coalescence' (FGC) during which films become more homogeneous upon aging. They attributed FGC to autohesion and the forces that are derived from the polymer-air interfacial tension. Furthermore, Vanderhoff et al. (1973) divided the mechanism of film formation into three stages. An initial stage where the polymer particles are free to move and drying occurs at a constant rate; an intermediate stage in which the particles come into irreversible contact with one another and start coalescing into a continuous film, and a final stage in which the residual water escapes at very slow rate by diffusion either through capillary channels between the deformed spheres or through the polymer itself.

In an attempt to achieve a better understanding of the properties of water-based polymeric coatings, many workers generally resort to the evaluation of free films. While an abundance of information can be derived from the evaluation of free films of various coating formulations, it is actually the functional performance of these films after deposition on substrates that has practical significance. The most logical criterion to assess the nature of coating systems, particularly in controlled release preparations, is, therefore, to monitor the release behavior of the coated product. Depending upon the composition of the coating formulation, the properties of the substrate and the coating conditions, coatings that vary in poros-

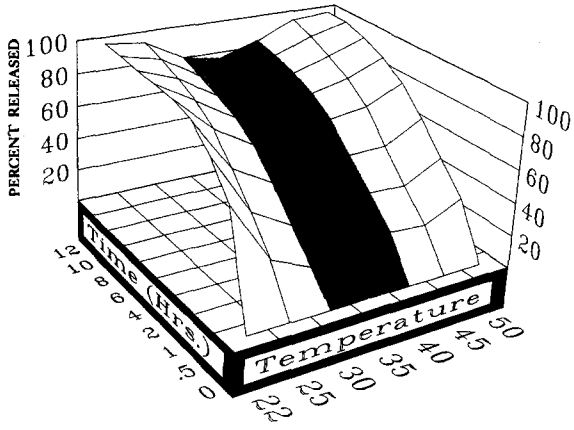


Fig. 1. Three dimensional representation of the release profiles of pellets coated at 22, 25, 30, 35, 40, 45 and 50 °C.

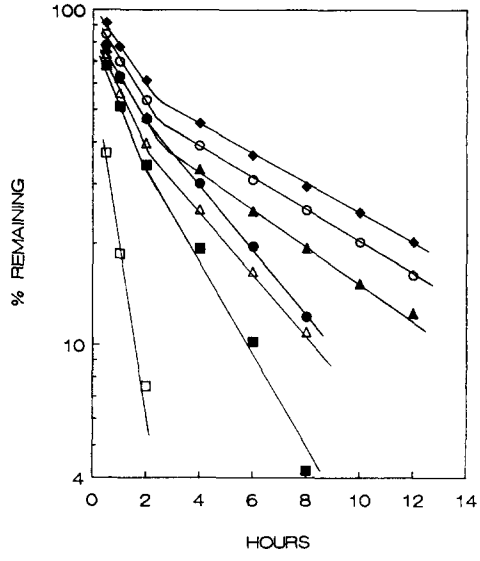


Fig. 2. First-order release profiles of pellets coated at 22 (□), 25 (△), 30 (○), 35 (◆), 40 (▲), 45 (●) and 50 °C (■).

ity and permeability and, consequently, provide different release rates are obtained.

In order to evaluate the effect of coating temperature on the performance of the deposited film, diphenhydramine HCl pellets were coated at different bed temperatures (Table 2) using an Aquacoat formulation. The percent of drug released as a function of bed temperature and time is given in Fig. 1. The rates appear to follow bioexponential first-order kinetics except for those coated at 22 °C (Fig. 2). The first-order rate constants are listed in Table 3. It must be pointed out that the pellets were initially coated very slowly to minimize drug migration into the film coat. After a small portion of the coating formulation was applied, the liquid application rate was increased to complete the process.

Pellets coated at a product bed temperature of 22 °C released more than 90% of the drug after only 2 h (Fig. 1), indicating that the coating did not appreciably retard drug release. The fast release rate could be attributed to the physical properties of the drug and the nature of the film formed under such coating conditions. Because of the high water solubility of diphenhydramine HCl, drug molecules dissolved during the early stages of the coating process are expected to migrate from the drug layer into the film layer in spite of the initial low spray rate (Fig. 3A), and seriously interfere with the film formation mechanism of the dispersion. That is, a significant amount of drug may dissolve in the coating formulation and reduce the surface tension of the liquid which is essential for the development of the capillary pressure needed for the deformation of the polymeric spheres. As a result, the film deposited on the substrate may become less continuous, and eventually lead to relatively fast release rates. Drug molecules may also interpose themselves between adjacent polymer spheres and dissolve during dissolution to generate a porous and more permeable coating material that subsequently releases the drug at fast rates. In addition, the low product bed

TABLE 3

Release rate constant for pellets coated with Aquacoat at different bed temperatures

Bed temperatures (°C)	k_1 (h^{-1}) [a]	k_2 (h^{-1}) [b]
22	1.045	–
25	0.402	0.201
30	0.300	0.109
35	0.262	0.101
40	0.312	0.123
45	0.335	0.264
50	0.450	0.381

[a] First-order rate constant for the initial phase (up to 2 h).
[b] First-order rate constant for the final phase (after 2 h).

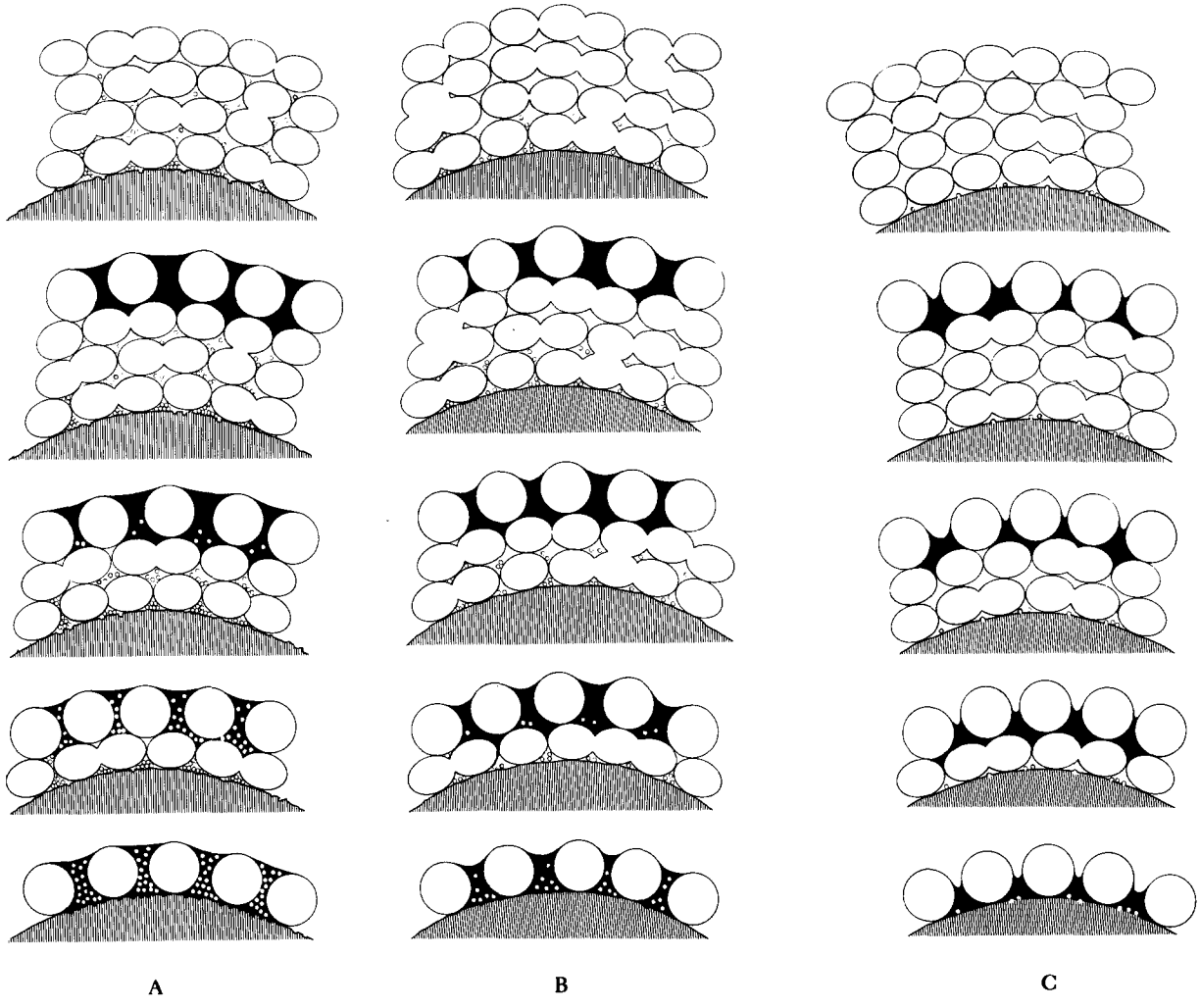


Fig. 3. Schematic representation of the successive layering of the polymeric beads during coating at (A) 22, (B) 35, (C) 50 °C. The vertically hatched segments indicate substrate, large open circles/ellipses denote polymeric spheres, fully shaded regions represent water and small open circles designate drug molecules.

temperatures may not be conducive to optimum film formation. This is because the temperatures employed may be less than the minimum film formation temperature of the plasticized polymer and, consequently, lead to hardening of the polymeric spheres. The capillary forces developed during water evaporation, therefore, may not be high enough to cause significant polymer deformation and fusion. As a result, the coating material may become discontinuous or porous. Viewed under a scanning electron microscope (SEM), the film layer of a cross-section of a pellet coated at 22 °C appears spongy (Fig. 4A), and does not contain well defined and discrete polymeric beads (Fig. 4C), probably due to significant drug migration into the film (Fig. 3A). Because the coating is porous in structure, the coating thickness (23 μm) on these pellets is almost twice that applied at higher bed temperatures (13 μm), even though the coating levels are the same. Additional curing of the pellets for 14 h at 55 °C or for 2 days at 60 °C did not produce a significant change in release

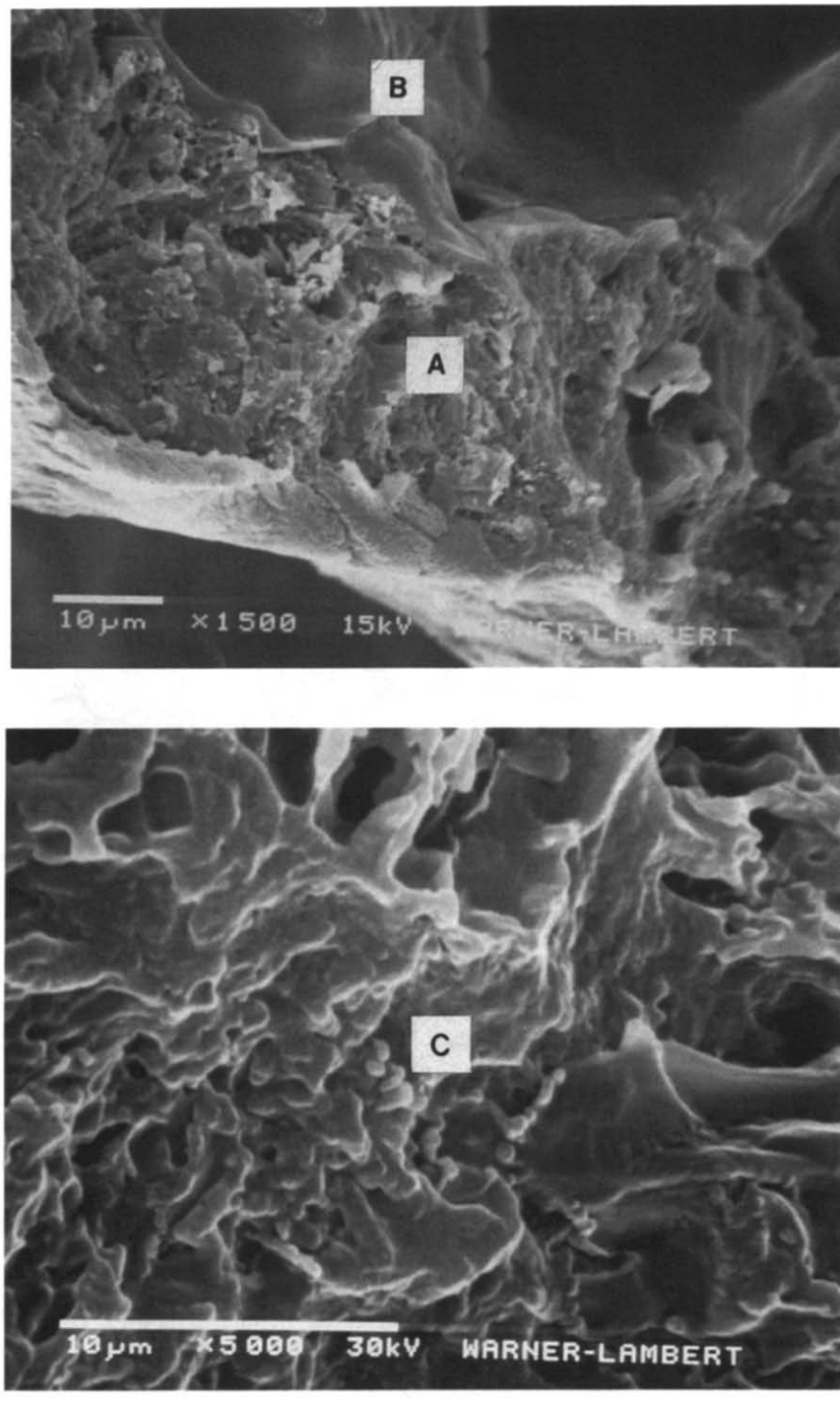


Fig. 4. SEM photomicrographs of the cross-section of a pellet coated at 22°C. (A) Film layer, (B) drug layer, (C) film layer at high magnification.

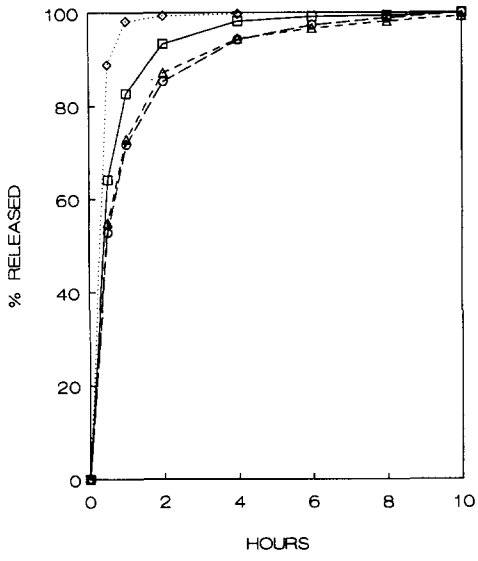


Fig. 5. Release profiles of pellets coated at 22 °C: no curing (◇), initial curing at 45 °C for 14 h (□), followed by an additional curing at 55 °C for 14 h (△), and further curing at 60 °C for 2 days (○).

rates (Fig. 5). This implies that a minimum degree of fusion should occur during the coating process if the curing phase is to proceed to completion. If the conditions of the coating process are such that the polymeric spheres are not, at least, partially fused, further coalescence does not appear to take place even if the coated pellets are subsequently subjected to high temperatures. The slight reduction in release rates that was observed in Fig. 5 could be attributed to additional fusion of the polymeric spheres brought about by the residual moisture in the film, or the interdiffusion of the terminal segments of the polymer chains as suggested by Voyutskii.

Coating at elevated product bed temperatures also produces less than optimum films characterized by fast release rates as indicated by the release profile of pellets coated at 50 °C (Fig. 1). Migration of the dissolved drug into the film layer during the coating process is less likely to occur due to the rapid evaporation of water at elevated temperatures (Fig. 3C). However, at such high bed temperatures, the rate of evaporation of water may overcome the diffusion of water from between the polymeric spheres to the surface, and prevent the development of the necessary capillary pressure required for the deformation of the polymeric spheres. The result would be the formation of porous films which contain poorly coalesced spheres in spite of the processing temperatures being higher than the softening temperature of the plasticized polymer. The existence of uncoalesced polymeric spheres in such coatings is confirmed by SEM (Fig. 6).

In contrast, a product bed temperature of 35 °C appeared to be high enough to prevent appreciable drug migration into the film layer and sufficiently low to allow, during water evaporation, the development of the capillary forces needed for polymer deformation and fusion (Fig. 3B). Utilization of such an optimum bed temperature during the initial stage of film formation and throughout the coating process apparently provides, upon completion of FGC, a more continuous coating material as indicated by the slow release rates (Figs 1 and 2) and the SEM photomicrographs (Fig. 7) which show appreciable coalescence of the polymeric spheres.

Effect of sealcoat on drug migration

It is apparent from the preceding discussion that, aside from the film formation properties of the plasticized polymer, the most important factor that plays a significant role in the effect of product bed temperatures on the structure and performance of the coating material from aqueous polymeric dispersions is the degree of migration of the soluble component of the substrate into the film layer. In an attempt to elucidate the migration phenomenon, pellet cores from the same batch were initially sealcoated with a solution of HPC prior to the application of the sustaining coat at different product bed temperatures. The first-order rate constants obtained from the pellets coated at different bed temperatures are listed in Table 4. The slowest release rates were observed with pellets coated at the optimum product bed temperatures of 30–40 °C, and are not significantly different from those obtained with pellets that do not contain seal coat (Table 3). This implies that, at these product bed temperatures, little, if any, drug migration occurs during the application of the sustaining coat. Similarly, sealcoated pellets that

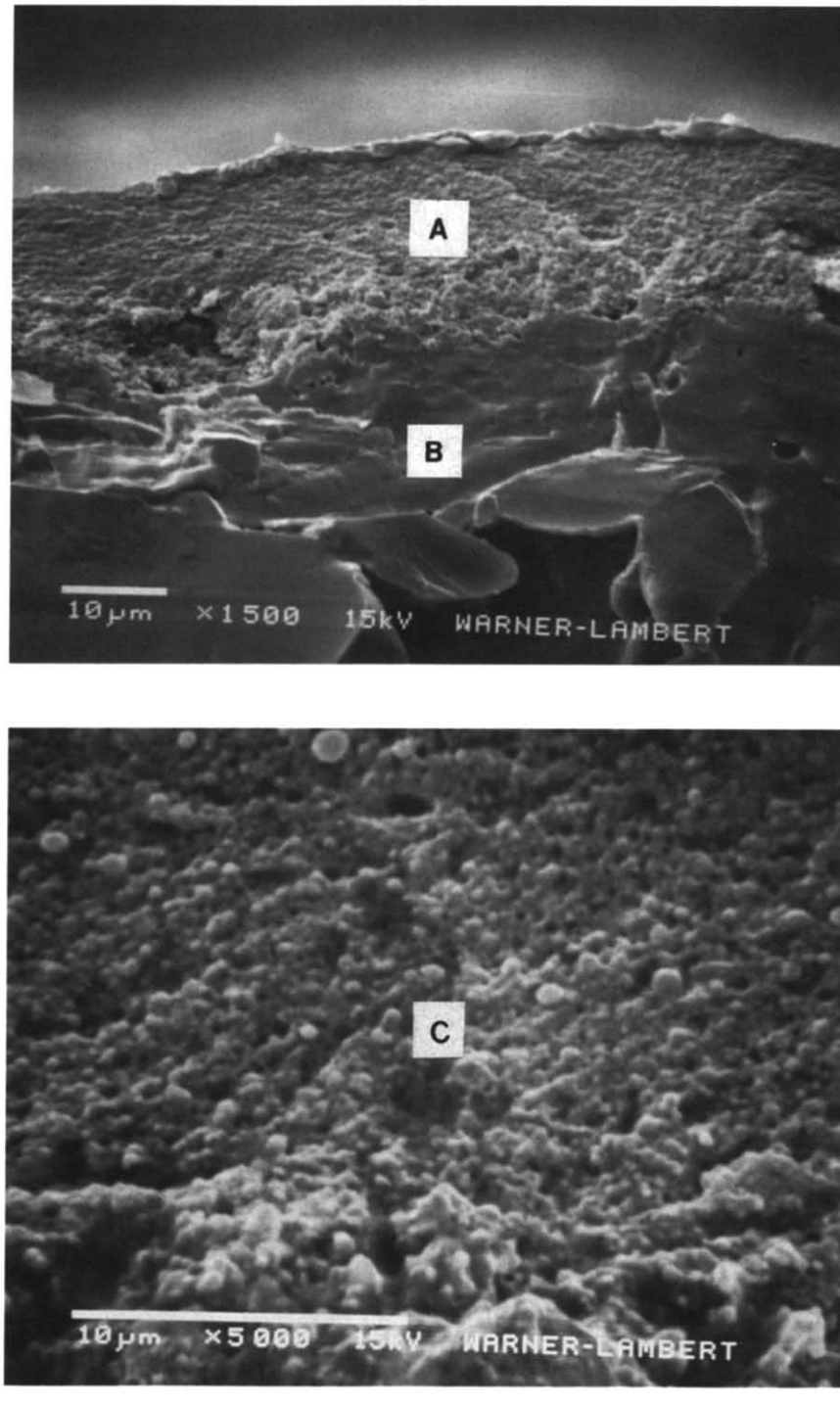


Fig. 6. SEM photomicrographs of the cross-section of a pellet coated at 50 °C. (A) Film layer, (B) drug layer, (C) film layer at high magnification.

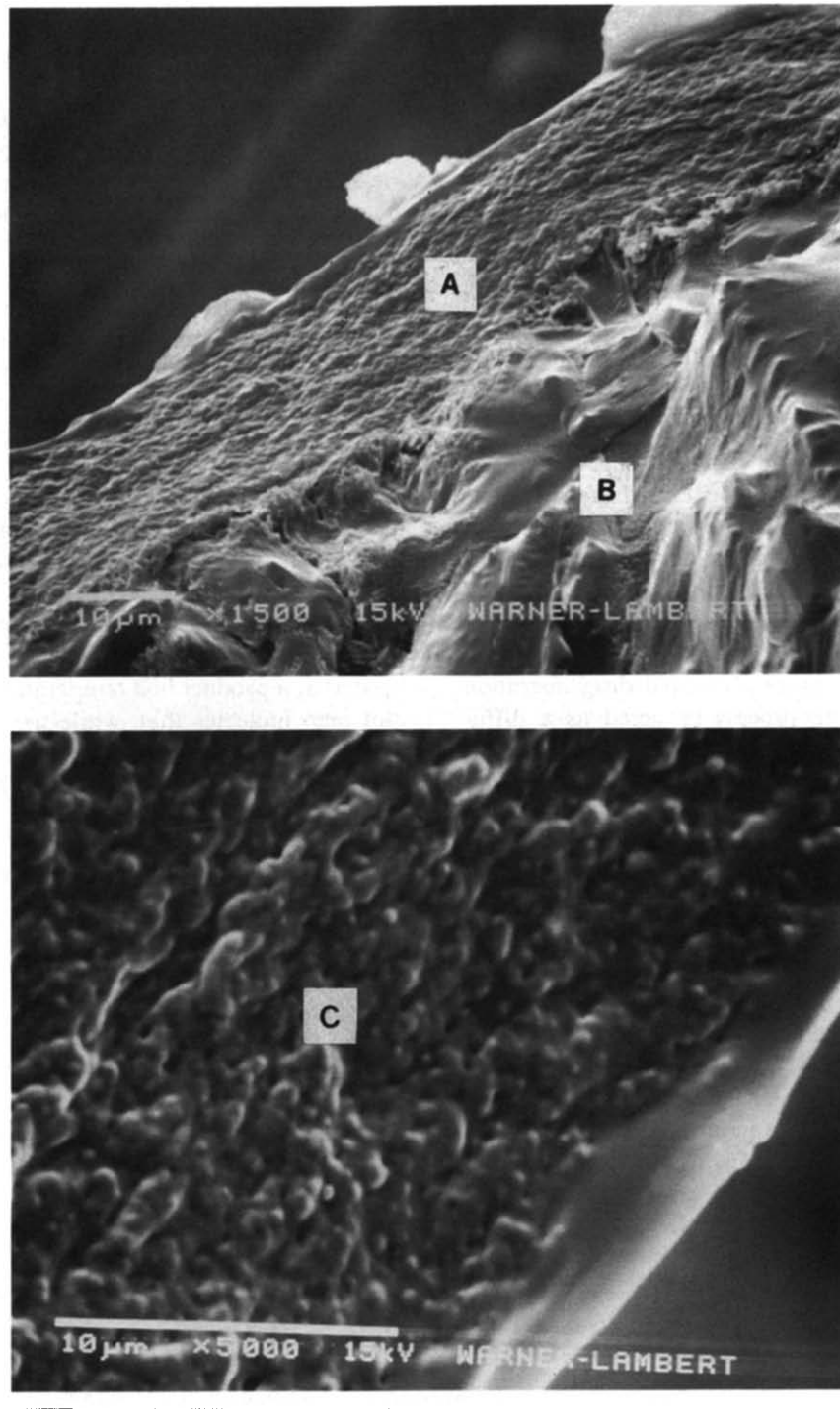


Fig. 7. SEM photomicrographs of the cross-section of a pellet coated at 35 °C. (A) Film layer, (B) drug layer, (C) film layer at high magnification.

TABLE 4

Release rate constants for sealcoated pellets subsequently coated with Aquacoat

Bed temperature (°C)	k_1 (h^{-1}) [a]	k_2 (h^{-1}) [b]
22	0.536	–
25	0.308	0.185
30	0.295	0.104
35	0.261	0.136
40	0.267	0.103
45	0.290	0.217
50	0.418	0.301

[a] First-order rate constant for the initial phase (up to 2 h).
[b] First-order rate constant for the final phase (after 2 h).

were further coated with a sustaining coat at bed temperatures of 45 and 50 °C also generated release profiles almost identical to those of pellets without seal coat, once again confirming the absence of drug migration during the coating operation. In contrast, pellets that had a sealcoat and further coated at 22 °C released the drug at slower rates than those without sealcoat. This indicates that the sealcoat either prevented drug migration during the coating process or acted as a diffusional barrier during the dissolution course. Since an increase in the levels of the sealcoat was not accompanied by a reduction in release rates (Fig. 8), it can be inferred that the sealcoat totally eliminated or minimized drug migration into the sustaining coat during the coating operation.

X-ray microprobe analysis

The migration of drug molecules during coating was also investigated using energy-dispersive X-ray microprobe analysis. Since diphenhydramine exists in the pellets as a HCl salt, the chlorine atom was used as a probe to monitor drug distribution across a cross-section of a pellet as reported elsewhere (Ghebre-Sellassie et al., 1986, 1988). When the sample was bombarded with an electron beam, X-rays which were specific to chlorine were emitted and detected by an X-ray spectrometer. These were then projected as dot maps on the photomicrographs. The intensity of these dots represents the relative distribution of chlorine across the pellets. Fig. 9 shows a photomicrograph and the corresponding dot map of a cross-section of a pellet coated at 50 °C. It is evident from Fig. 9 that the intensity of the dots corresponding to the drug layer is very high. The high intensity of dots almost abruptly ends at the drug-film interface. The few dots located on the film layer represent the background. The sharply defined boundary between the film and drug layers confirms the negligible migration of drug that occurred during coating at a product bed temperature of 50 °C. On the other hand, the boundary between the drug and the film layers of the pellets coated at 22 °C is diffuse and much less defined, with numerous dots residing in the film (Fig. 10). This suggests that significant drug migration occurred during the coating process, as was substantiated by the fast release rates. That excessive migration of drug occurred during coating at 22 °C is further supported by the existence of a more defined boundary between the drug layer and the film layer in those pellets containing sealcoat relative to those without (Fig. 11).

Fig. 12 shows a photomicrograph and the corresponding dot map of a cross-section of a pellet coated at a product bed temperature of 35 °C. The dot map indicates that, while the interface is not as distinct as that which was observed with the pellets coated at 50 °C, it is much more defined

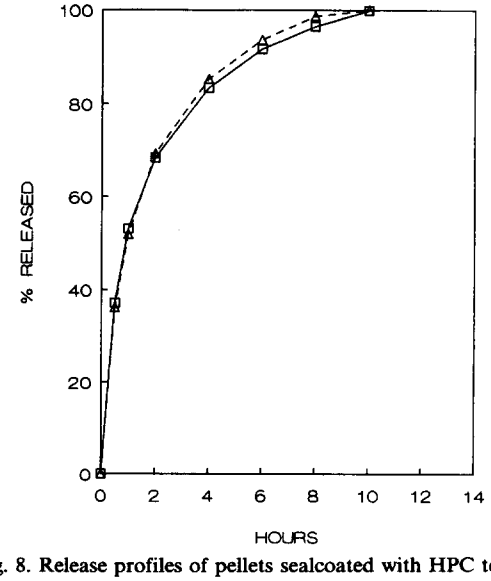
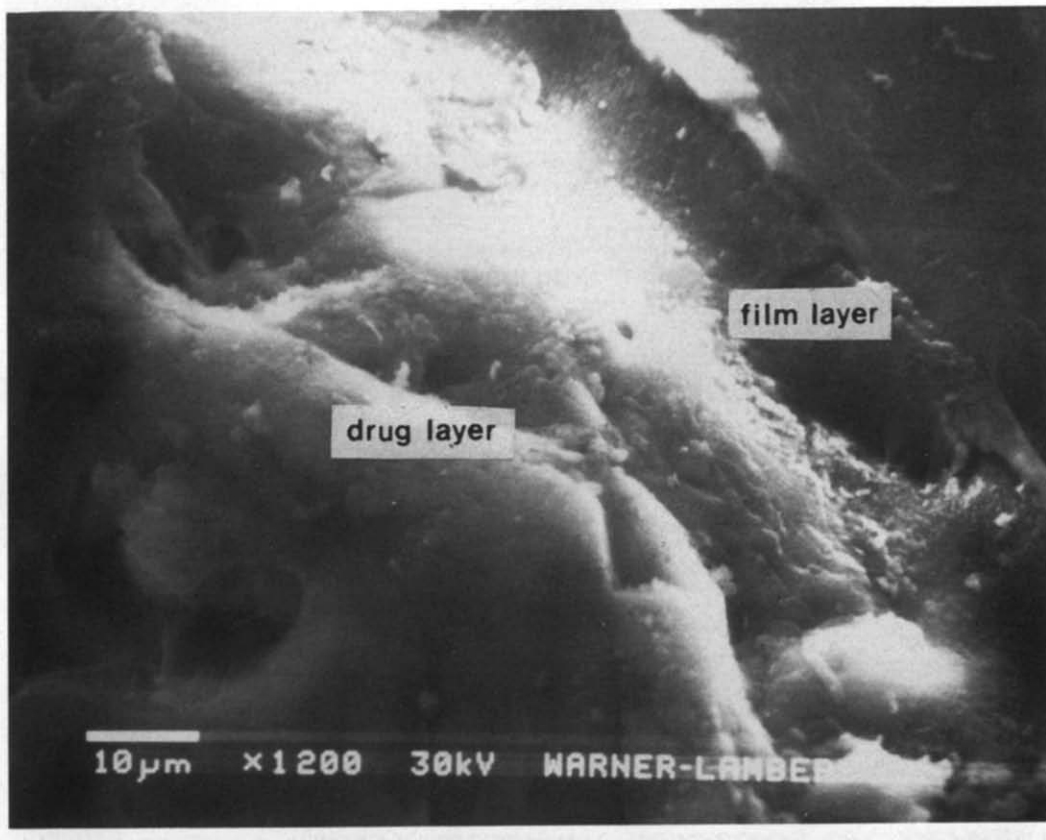


Fig. 8. Release profiles of pellets sealcoated with HPC to 1.3% (□) and 5.2% (△) followed by Aquacoat at 22 °C.



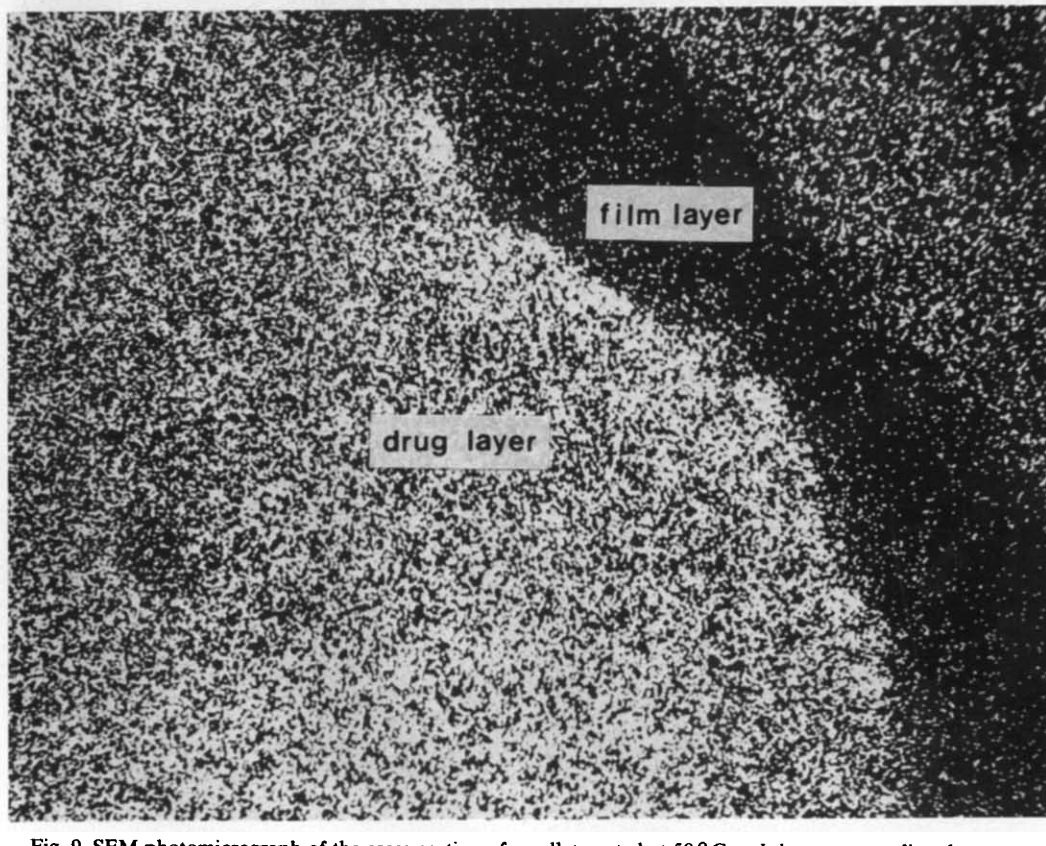
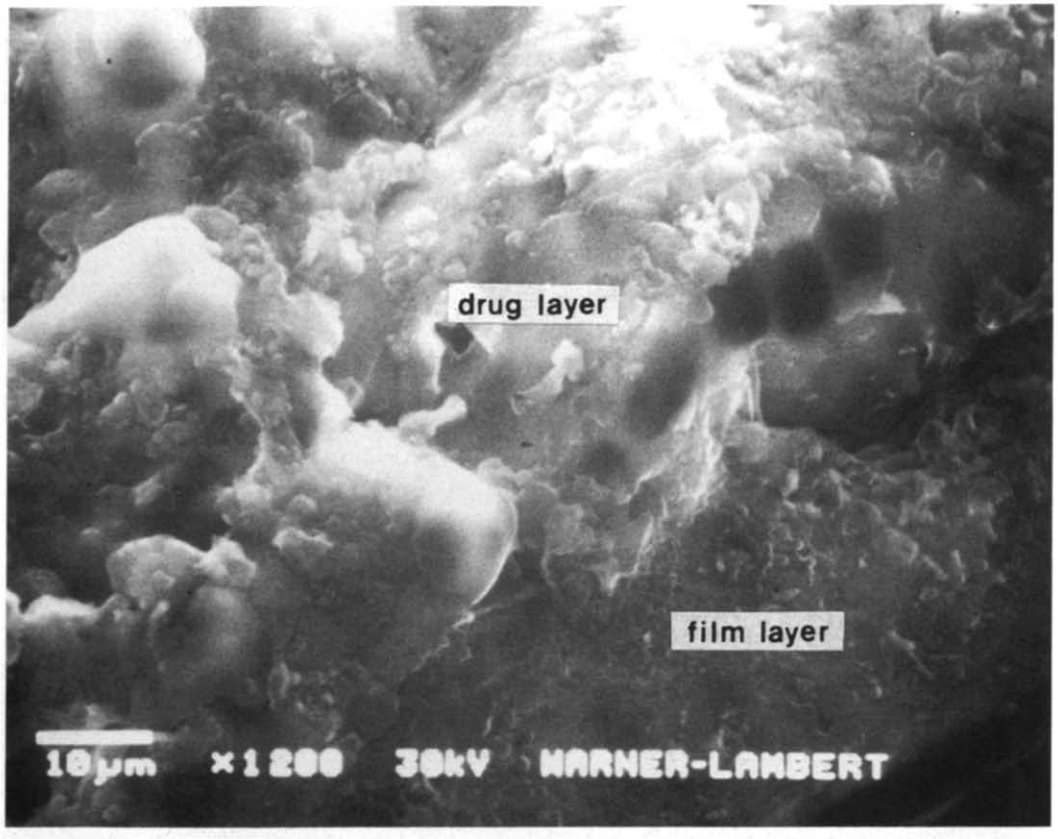


Fig. 9. SEM photomicrograph of the cross-section of a pellet coated at 50 °C and the corresponding dot map.



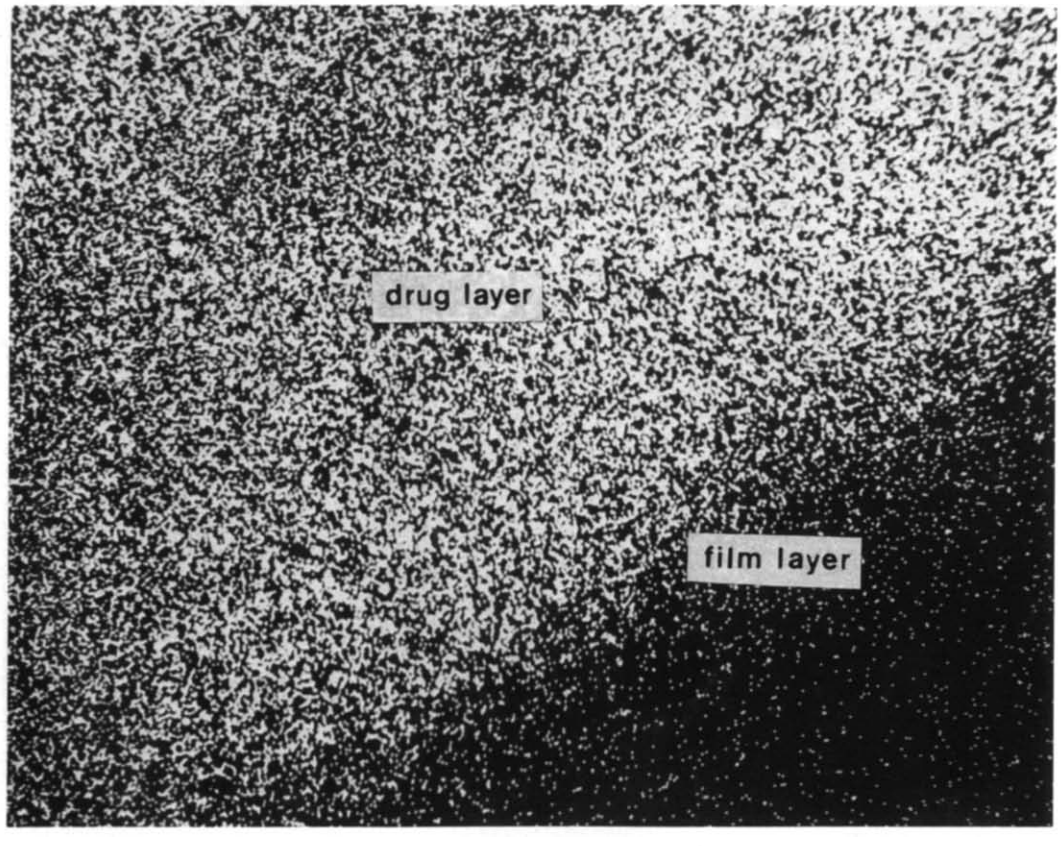


Fig. 10. SEM photomicrograph of a cross-section of a pellet coated at 22° C and the corresponding dot map.

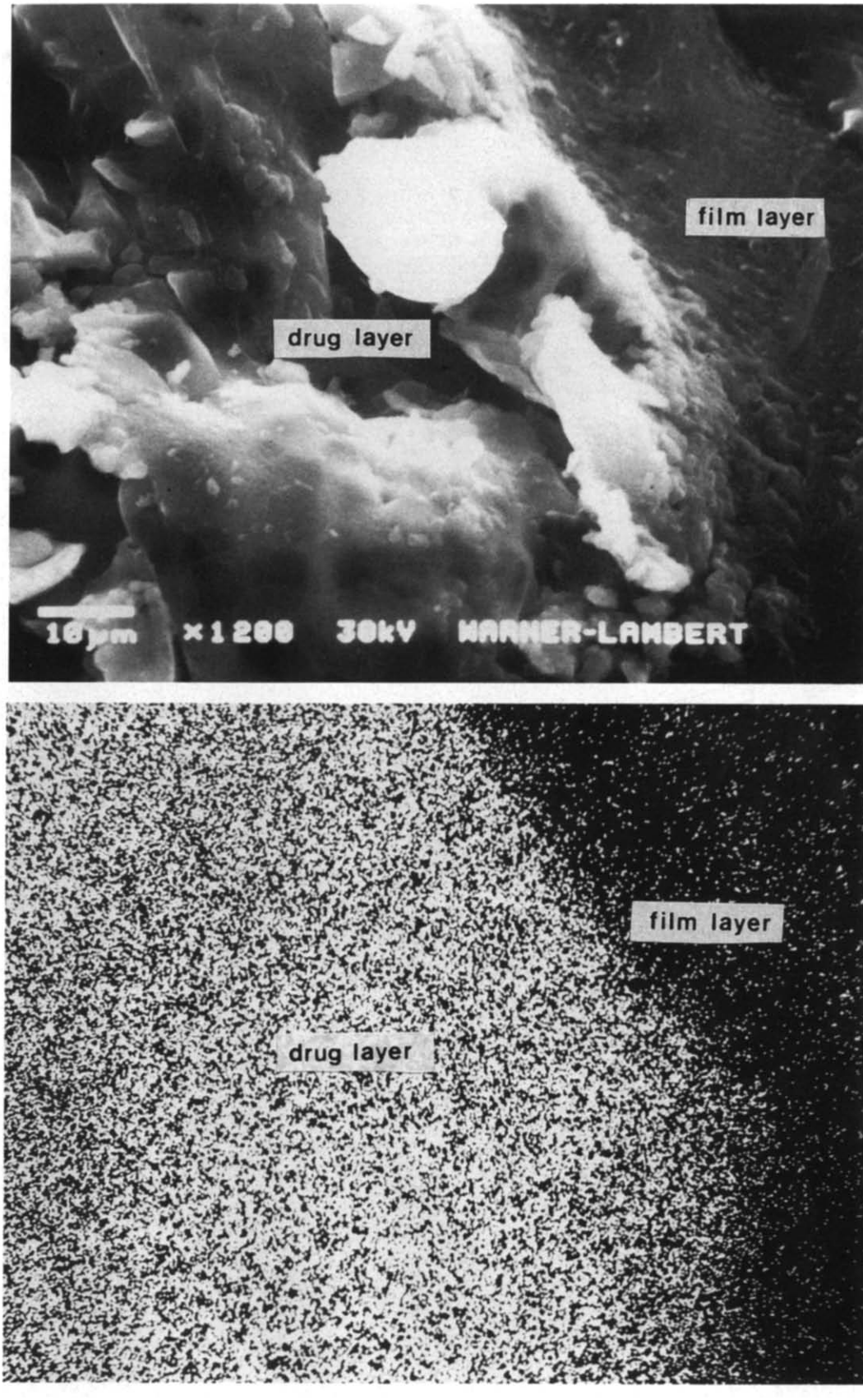


Fig. 11. SEM photomicrograph of a cross-section of a pellet seal-coated with HPC and subsequently coated with Aquacoat at 22°C and the corresponding dot map.

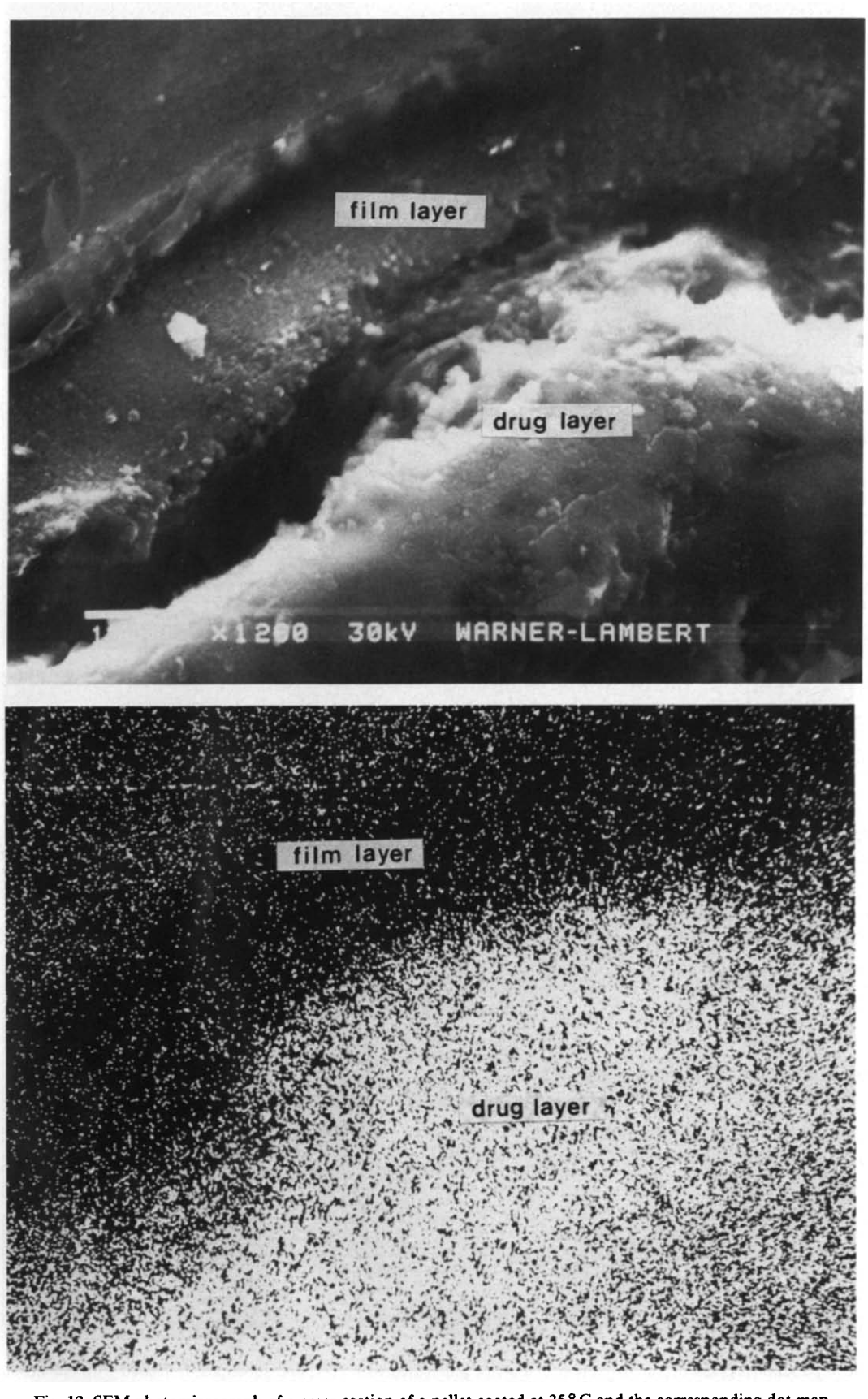


Fig. 12. SEM photomicrograph of a cross-section of a pellet coated at 35 °C and the corresponding dot map.

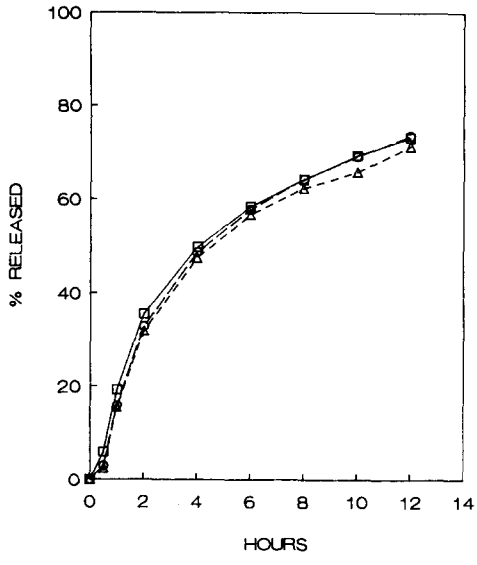


Fig. 13. Release profiles of pellets coated at 3 (□), 5 (△) and 9 ml/min (○), and a constant bed temperature of 35 °C.

than that which was seen with the pellets coated at 22 °C. The extent of drug migration is not appreciable, and does not appear to make a significant contribution to the release rates.

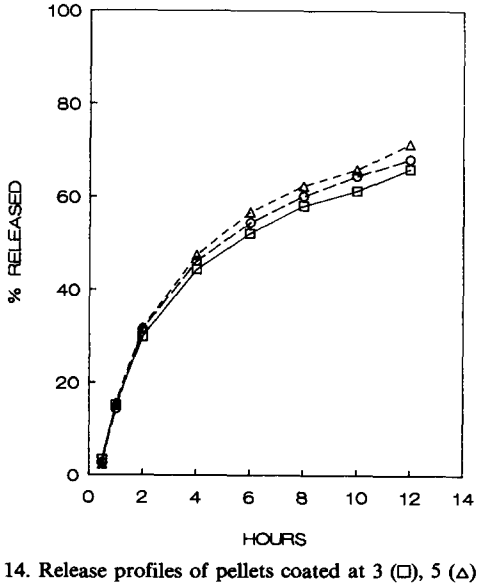


Fig. 14. Release profiles of pellets coated at 3 (□), 5 (△) and 9 ml/min (○), and a constant inlet temperature of 60 °C.

Processing under optimum conditions

Once the optimum bed temperature (i.e. 35 °C) for the formulation had been identified, it was used to coat pellets at different spray rates in order to determine the effect of liquid application rate on film properties. The release profiles of the pellets are shown in Fig. 13. As long as the coating process is carried out at the optimum bed temperature, changing the spray rate over a wide range does not appear to result in significant alterations in the release behavior of the coated pellets.

In another study, pellets were coated at different spray rates and a constant inlet temperature of 60 °C, thereby allowing the product bed temperatures to vary. The release profiles of these pellets are given in Fig. 14, and indicate that, for the particular formulation studied, the product bed temperature range that provides optimum film characteristics lies between 30 and 38 °C. These results are consistent with what was observed earlier in Fig. 1. The slowest release rates and hence the most continuous films were obtained when the product bed temperature was maintained between 30 and 40 °C (shaded area in Fig. 1).

The results of the preceding experiments suggest that processing times could be reduced appreciably without adversely affecting film characteristics, provided that optimum bed temperatures are maintained. This has a very important practical significance in that it results, particularly in a production setting, in tremendous savings both in terms of turnover times and resources.

Conclusions

Application of insufficient thermal energy during film deposition not only prevents deformation and fusion of the polymeric spheres, but also allows migration of water-soluble substrates into the film layer. Further curing of these films appears to have little effect in promoting FGC. Excessive heat also results in the formation of poorly coalesced spheres due to a high evaporation rate of water. Because of the differences in the physicochemical properties of the substrates, the glass transition temperatures of polymers and

solubility parameters of plasticizers, the effect of bed temperature on the properties of films formed from various formulations is expected to be different. Consequently, the optimum bed temperature range for a given polymeric dispersion-based formulation should be determined prior to the development of controlled-release products.

Acknowledgements

The authors are very grateful to Mr. Ingi Choo, Mr. Jeremy Salter and Ms. Nancy Testa for their assistance during the development of the SEM photomicrographs.

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