International Journal of Pharmaceutics, 72 (1991) 163–174

ADONIS 037851739100219R

IJP 02419

Factors affecting drug release from drug-coated granules prepared by fluidized-bed coating

Lucy S.C. Wan and W.F. Lai

Department of Pharmacy, National University of Singapore, Singapore (Singapore)

(Received 23 November 1990)
(Modified version received 10 February 1991)
(Accepted 19 February 1991)

Key words: Hydroxypropylmethylcellulose; Methylcellulose; Drug-coated granule; Fluidized-bed coating; Disintegration; Drug release

Summary

The preparation of drug-coated core formulations where the drug is located on the surface of a lactose granule core, using a methylcellulose (MC) or a hydroxypropylmethylcellulose (HPMC) polymeric system with diphenhydramine hydrochloride as a model drug, was studied. The drug and the polymer were applied onto lactose granules using the fluidized-bed coating method. The intermittent spray conditions adopted were able to minimize aggregation of the granules and the spray drying of the coating liquid. A high coating efficiency of over 97% was obtained and the granules were evenly coated. In vitro drug release from the coated granules was shown to be dependent on the drug loading, hydrophilicity, adhesive properties, viscosity and total amount of the polymer in the drug-polymer coat. The effect of the air entrapped in the coated lactose granules on their release profiles is also discussed. These results have important implications for the design of drug-coated granules as a modified-release dosage form employing a water-soluble polymeric system.

Introduction

In the pharmaceutical industry, fluidized-beds are used primarily for drying (Scott et al., 1963; Vanecek et al., 1966; Zoglio et al., 1975), granulation (Rankell et al., 1964; Scott et al., 1964; Davies and Gloor, 1971, 1972) and coating (Wurster, 1959; Singiser and Lowenthal, 1961; Caldwell and Rosen, 1964; Robinson et al., 1968). Often more than one of these applications can be conducted in a single unit.

Correspondence: L.S.C. Wan, Department of Pharmacy, National University of Singapore, 10 Kent Ridge Crescent, Singapore 0511, Singapore.

A multiple-unit type of dosage form such as pellets or granules, compared to single-unit type such as tablets, is less influenced by variations in the gastric emptying rate and overall gastrointestinal transit time and therefore has a more reproducible absorption behaviour. The advantages of multiple-unit dosage form products over single-unit dosage forms have been demonstrated by several workers (Beckett, 1981; Bechgaard, 1982).

The coating of particulates such as powders, granules, pellets and tablets to produce controlled-release dosage forms is becoming increasingly popular, mainly as a result of recent advances in fluidized-bed processes and the development of aqueous polymeric coating systems that avoid the

health hazards and high cost associated with organic solvent-based systems. Commonly, a polymer matrix is formed on the surface of the particles due to solidification of the liquid spray deposited on the particles during the coating process. Depending on the particular method of application, the active drug can be the particle core itself or it can be dispersed in the coating material which is then applied onto an inert core to produce controlled release beads.

Most of the reported methods of producing controlled-release pellets employ aqueous-based polymeric coatings or matrix materials in the form of an emulsion or colloidal suspension of water-insoluble polymers such as ethylcellulose (Goodhart et al., 1984; Lippold et al., 1989; Yang and Ghebre-Sallassie, 1990) and acrylic resin derivatives (Lehmann and Dreher, 1981; Ghebre-Sellassie et al., 1987; Li et al., 1989). The present study has been carried out to examine the feasibility of obtaining drug-coated core formulations where the drug is located on the surface of the core, using a water-soluble polymeric system with diphenhydramine hydrochloride as a model drug.

Materials and Methods

Materials

Lactose granules (Sunward Chemicals, Singapore) in the size range of 600–710 μm were used as the core material for the experiments. MC (Tokyo Kasei, Japan) of different viscosity grades, 13–18, 80–120 and 350–550 cp, and HPMC (Pharmacoat^{R} 615, Shin-Etsu Chemical Co. Ltd, Japan) were selected as the coating polymers. Distilled water was used for the preparation of the polymer solutions and also as the dissolution medium in drug release studies. Diphenhydramine hydrochloride (BP grade) was used as a water-soluble model drug.

Methods

Coating procedure

In this study, the fluidized-bed process was used to apply diphenhydramine HCl onto the surface of lactose granules (600–710 μm). A fluidized-bed Aerocoater^{R} (Model Strea-1, Aeromatic AG, Switzerland) fitted with a bottom-spray insert was used to coat the lactose granules. Batches of 200 g of lactose granules were allowed to fluidize in the coater until the inlet air had reached the required temperature. The coating liquid was then sprayed into the fluidized bed via the binary fluid spray nozzle using a peristaltic pump (Watson-Marlow 502S, U.K.) at preset conditions. Several variations in coating process parameters and drug-polymer coating formulations were evaluated. The formulation and the different process conditions studied are listed in Table 1. In another set of experiments, a selected set of process condi-

TABLE 1

Summary of process conditions used for the application of a standard coating formulation to lactose granules

Formulation	Quantity						
Diphenhydramine HCl	75 g						
Methylcellulose (13–18 cp)	10 g						
Distilled Water to	500 ml						
Process conditions	Expts						
	A	B	C	D	E	F	G
Fluidizing airflow rate (m^3/h)	60–70	90–110	120–130	90–110	90–110	90–110	90–110
Inlet air temperature (°C)	80	80	80	60	95	80	80
Nozzle diameter (mm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Atomizing air pressure (bar)	0.8	0.8	0.8	0.8	0.8	1.6	0.8
Spray rate (ml/min)	6–8	6–8	6–8	6–8	6–8	6–8	6–8
Spray interval [a]	C	C	C	C	C	C	I
Lactose granule load (g)	200 g in all the experiments						

[a] C represents continuous spraying; I, represents intermittent spraying.

tions, described in Table 2, were held constant while various coating formulations were applied to the lactose granules. On completion of coating, the coated granules were fluidized for a further 10 min to ensure complete drying.

Assay of drug content

For each batch of coated granules, the diphenhydramine HCl content was determined by dissolving about 1 g of accurately weighed coated granules in distilled water and made up to volume in a 100 ml volumetric flask. Aliquots of the content in the flask were filtered and the absorbance was determined spectrophotometrically (Perkin Elmer Model 550, USA) at 256 nm. All the assays were carried out in triplicate and the mean values reported. The coating process efficiency was determined by expressing the mean drug content as a percentage of the theoretical drug loading.

Sieve analysis

The size distribution of the coated granules were evaluated by mechanical sieving with a series of sieves with aperture sizes, 1.0 mm, 850 μm, 710 μm, 600 μm, 500 μm, 425 μm, 355 μm, and base pan. The sample load was 80 g. The nest of sieves was shaken at 40 Hz continuously for 10 min (Endecotts Sieve Shaker, Model EVS1, U.K.). The weight of the coated granules retained on each

TABLE 2

Summary of formulations applied to lactose granules using standardized process conditions

Process conditions	
(a) Fluidizing airflow rate (m^3/h)	90–110
(b) Inlet air temperature (°C)	80
(c) Outlet air temperature (°C)	50–54
(d) Spray nozzle diameter (mm)	0.5
(e) Atomizing air pressure (bar)	0.8
(f) Spray rate (ml/min)	6–8
(g) Spray interval	Intermittent
(h) Postcoating drying conditions	80 °C, 10 min
(i) Lactose granule load (g)	200

Batch No.	Formulation					
	Diphenhydramine HCl (g)	HPMC15 [b] (g)	MC13–15 [b] (g)	MC80–120 [b] (g)	MC350–550 [b] (g)	Distilled water to (ml)
D30	30	–	10 (2)	–	–	500
D100	100	–	10 (2)	–	–	500
M1510	75	–	10 (2)	–	–	500
M1520	75	–	20 (4)	–	–	500
M1520A	75	–	20 (6)	–	–	334
M1530	75	–	30 (6)	–	–	500
M1530A	75	–	30 (4)	–	–	750
M1545	75	–	45 (6)	–	–	750 [a]
M10010	75	–	–	10 (2)	–	500
M45010	75	–	–	–	10 (2)	500
P1510	75	10 (2)	–	–	–	500
P1520	75	20 (4)	–	–	–	500
P1530	75	30 (6)	–	–	–	500
P1545	75	45 (6)	–	–	–	750 [a]

[a] A larger total volume of coating solution was used to maintain its viscosity to a sprayable level.

[b] The figure in parentheses indicates the % w/v of the polymer in the coating solution.

sieve was recorded. Sieving was repeated for each batch of granules.

Dissolution studies

In vitro dissolution tests were conducted in 900 ml of distilled water at 37 ± 0.5 °C using the USP XXI dissolution Apparatus I (rotary basket method) (Hanson, Easi-Lift, Model QC72R, U.S.A.) at a speed of 50 rpm. The base of the dissolution basket was lined with a plastic disc to retain the granules in the basket during the dissolution test. Accurately weighed samples of coated granules (600–850 μm) containing the equivalent of about 200 mg of diphenhydramine HCl were used. Samples of 5 ml of the filtered dissolution medium were withdrawn periodically and assayed for drug released using a spectrophotometer at 256 nm. A minimum of three replicates were performed for each batch of granules.

Disintegration

The disintegration time of individual coated granules in 900 ml of nonagitated distilled water at 37 ± 0.5 °C was determined. Each granule was placed into the distilled water and the time taken for it to disintegrate was recorded. At least 20 granules were tested and the mean time calculated.

Results and Discussion

Process conditions

The determination of the suitable processing conditions for the use of the fluidized-bed equipment in the coating of lactose granules was carried out.

The results of the variation in process conditions are summarized in Table 3. The quality of the product and the efficiency of the coating process were examined on the basis of the following criteria: (a) proper fluidized particle flow pattern; (b) degree of aggregation of the granules; (c) extent of spray drying; (d) uniformity of the coating in each batch of granules.

The first two factors were studied during the coating process itself. The degree of aggregation of the granules was also assessed by means of sieve analysis of the coated product. The uniformity of the coating in each batch of granules and the extent of spray drying were indicated in the drug content assay results.

The particle flow pattern in a bottom-spray fluidized bed coater is established with the aid of a coating partition and an air distribution plate, which controls the airflow. Most of the warm incoming fluidizing air is diverted through the cylindrical coating partition and together with the

TABLE 3

Summary of results on investigation of process conditions

	Experiments						
	A [b]	B	C	D	E	F	G
Aggregation [a]	X	+	+	+	+	+	–
Spray drying [a]	X	–	–	–	+	+	–
% Weight of granules retained on 1.0 mm sieve (%)	X	25.0	21.4	41.9	18.6	28.3	0.4
Mean drug content per g product (mg)	X	258.8	257.7	259.3	233.1	245.4	257.6
Coefficient of variation (%)	X	0.66	0.81	0.39	0.74	0.49	0.53
% coating efficiency [c]	X	98.4	97.9	98.5	88.6	93.3	97.9

[a] –, indicates little or no aggregation/spray drying; +, occurrence of aggregation/spray drying.
[b] Complete defluidization; process discontinued.
[c] Coating efficiency = mean drug content as percentage of theoretical drug loading.

atomizing air from the spray nozzle, cause the granules to circulate, much like that of a spouting water fountain. The granules are fluidized and carried up the coating partition where they are sprayed concurrently with the coating liquid until they lose their momentum in the expansion zone and fall back onto the top of the bed outside the coating partition. The air in this down bed acts to cushion and dry the partially coated granules as they travel downwards to continue the cycle through the coating partition.

The selection of the proper coating partition height in relation to the air distribution plate used as well as the distance between the lower end of the partition and the air distribution plate is necessary to ensure a smooth circulation of granules in the product container (Hall and Pondell, 1980). Preliminary investigations resulted in the selection of the appropriate coating partition and setup that were adopted in the subsequent experiments: (a) diameter of cylindrical coating partition = 61 mm; (b) height of coating partition = 180 mm; (c) distance of coating partition from air distribution plate = 34 mm.

The primary objective of particle coating is to envelop each particle or granule with sufficient coating material to achieve the desired function. Therefore, product aggregation and spray drying both represent less-than-satisfactory process conditions because they indicate diminished process efficiency. In both cases there is a decrease in the final product yield as aggregated material must be removed by screening while spray drying could lead to unacceptably high loss of coating material as fines entrained in the exhaust air.

To produce discretely coated granules without aggregation, it is desirable for the granules to be sprayed-coated and dried without flocculation. In the coating partition the random and intense contact between the granules and the coating liquid results in aggregration due to liquid bridges, that is, localized wet quenching is inevitable in this spray zone. As the wet flocs of granules (loose aggregates) which are produced begin to move away from the spray zone in the coating partition, drying of the coating solution occurs. If these flocculated granules are not separated into discrete particles or at least reduced to much smaller masses of aggregrated granules before the liquid bridges completely solidify, they will rapidly segregate effectively as large, permanent agglomerates and cause the bed to defluidize prematurely.

A summary of the process conditions employed are shown in Table 1. From the summarized results given in Table 3, it was noted that a fluidizing airflow rate higher than 70 m^3/h was required for the coating process. When a fluidizing airflow rate of 60–70 m^3/h was used (A), the onset of bed quenching was observed within 20 min and complete defluidization of the bed in 30 min, which necessitated the discontinuation of the process. Increasing the airflow rate to 90–110 m^3/h (B) allowed the coating process to proceed to completion although slight defluidization occurred towards the end of the process. The sieve analysis of the coated granules of different batches showed that the product fraction retained on the 1.0 mm sieve consisted almost entirely of aggregated granules. Thus, the percentage of the final coated product that is retained on the 1.0 mm sieve could be used as an indicator of the degree of aggregation of the coated granules.

The particle size distributions of the coated product in Expts B–G are depicted graphically in Fig. 1. In Expt B, a fairly large proportion (25%) of the product was made up of aggregated granules > 1.0 mm in size. However, at maximum airflow rate of 120–130 m^3/h used in Expt C, the extent of aggregation of the coated granules was only slightly reduced to 21.4% from 25%. It is apparent that aggregation occurred more readily at a lower inlet air temperature. The importance of efficient drying of the coated granules in the fluidized-bed is shown in Expt D. A reduction of inlet air temperature from 80 to 60 °C caused a marked increase in the tendency for the aggregation of the granules. About 42% of the coated granules was retained on the 1.0 mm sieve as large aggregates compared to 25% in Expt B. Using a higher temperature of 95 °C in Expt E restricted the formation of large aggregated granules (> 1.0 mm) to 18.6%. However, the coating efficiency decreased to 88.6% (Table 3) indicating significant spray drying of the coating liquid droplets and consequent loss of coating material.

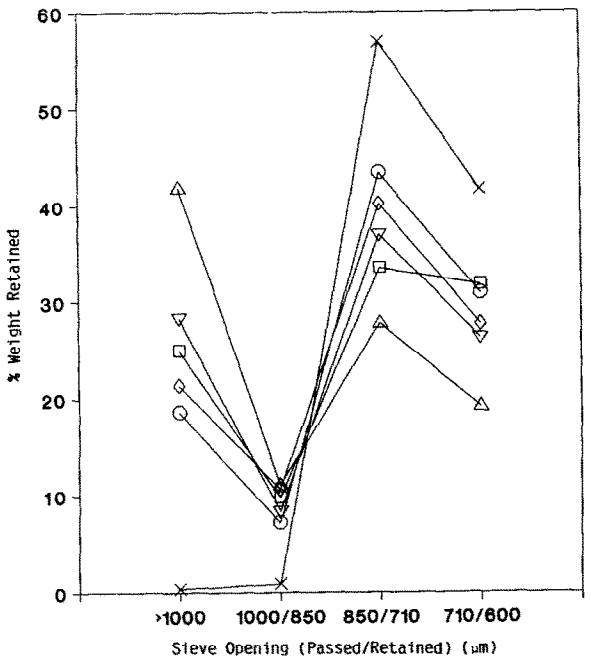

Fig. 1. Size distribution of coated granules produced under different process conditions; (□), B (continuous spray); (◇) C (120–130 m^3/h); (△) D (60 °C); (○) E (95 °C); (▽) F (1.6 bar); (×) G (intermittent spray).

The effect of increasing the atomizing air pressure was studied in Expt F. The higher atomizing pressure (1.6 bar) resulted in the production of finer atomized coating solution droplets, thus increasing the tendency for the spray drying of the coating droplets. This is reflected in the lower coating efficiency of 93.3%. The aggregation problem did not seem to improve with an increase in the atomizing air pressure. A similar extent of aggregation of the product (28.3%) occurred as in Expt B. In addition, the granules were blown up by the strong atomizing air and trapped by the exhaust air grid, thus decreasing the final product yield.

The overall process efficiency with respect to the application of the drug-polymer coating solution could be assessed in terms of the drug content uniformity and coating efficiency. The results are shown in Table 3. The small drug content variation from the mean value with a coefficient of variation of less than 1% indicated that the drug distribution is relatively uniform. The bottom-spray process employed evidently was quite efficient in applying the drug to the surface of the granules and resulted in little loss of material (high percentage coating efficiency of over 97% in most cases).

In order to decrease further the extent of aggregation and at the same time minimize spray drying, Expt G was performed in which the process conditions used were the same as those in Expt B except that an intermittent spray method was adopted instead of continuous spraying. The spraying of the coating solution was stopped at occasional intervals and the contents of the product container were partially dried in the warm fluidizing air to facilitate the separation of loose aggregates into discrete granules in between applications. This considerably decreased the formation of aggregrated product. Only 0.4% of the coated granules existed as aggregrated units larger than 1.0 mm in size (Fig. 1). The coating efficiency and uniformity of coating distribution were high and comparable to that obtained in Expt B. This intermittent spray method also has the advantage of minimizing adjustment of other process parameters when investigating different coating formulation variables, for example, coating compositions of varying viscosity, whereby a higher viscosity would tend to cause increased granule aggregation tendency (Chopra and Tawashi, 1982). Therefore, the process conditions in Expt G were adopted for the subsequent study of the formulation variables. It is important to emphasize that the optimal conditions for a particular application will differ in fluidized-bed spray coaters of other dimensions and designs.

Drug loading

The intermittent spray process in Expt G was used as the standardized process conditions for studying the effect of formulation variables which are outlined in Table 2. A high coating efficiency of at least 97% and uniform drug distribution with a coefficient of variation of less than 1% were achieved in all the different batches.

The release curves for the coated granules with varying drug loading are shown in Fig. 2. When the drug loading was increased to 100 g, as in batch D100, the release rate of the drug was

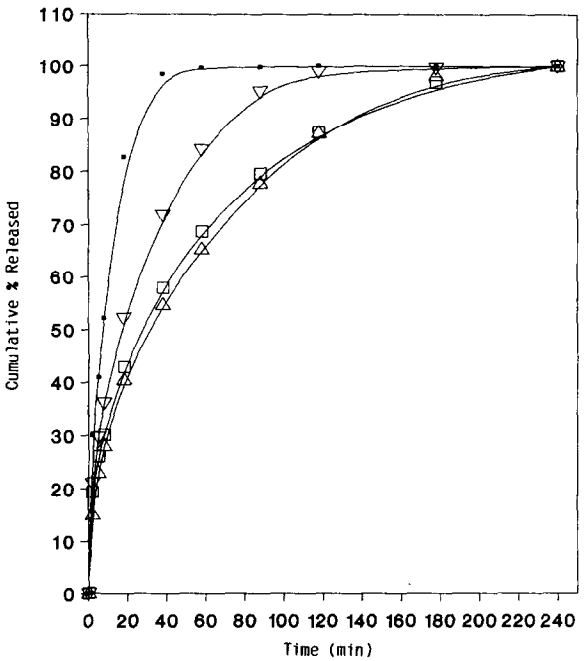

Fig. 2. Effect of diphenhydramine HCl loading on its release from the coated granules; (□) D30 (30 g); (△) M1510 (75 g) ; (▽) D100 (100 g); (■) drug powder.

higher compared to a drug loading of 75 g (batch M1510). On the other hand, the release profile of batch D30 with a drug loading of 30 g was almost identical to that of batch M1510. On spraying, a portion of the dissolved drug would be recrystallized from the coating solution as fine crystals. These are deposited onto the surface of the lactose granules and held there by a combination of the adhesive effect of the polymeric binder and the liquid bridges of the application medium. The MC polymer would have a maximum binding capacity or ability to immobilize drug particles on the granule surface. At a high drug loading, the MC in the drug coat might not be evenly distributed. In addition, the drug particles might not be fully coated by the relatively small amount of methylcellulose polymer compared to a coating formulation that has a lower drug : polymer ratio. Hence, the non-uniform binding effect of the MC in the dry coat could have led to a faster drug release rate in batch D100.

Polymer content and viscosity grade

The drug : polymer ratio was varied keeping the amount of drug constant and changing the amount of polymer used (Table 2). As shown in Fig. 3, the release rate of diphenhydramine HCl from the coated granules was lowered when the amount of MC used in the formulation was increased from 10 g (batch M1510) to 20 g (batch M1520). This is reflected in the increase in $T_{50\%}$ from 31.8 to 72.7 min and $T_{90\%}$ from 133.0 to 193.6 min. However, when the MC content in the formulation was increased further to 30 g (batch M1530), the overall drug release rate of the coated granules was higher than that of batch M1510 and batch M1520. Shorter $T_{50\%}$ (34.5 min) and $T_{90\%}$ (74.5 min) were observed. A drug release profile similar to that of M1530 was obtained for batch M1545 suggesting that any further increase in the amount of MC deposited onto the lactose granules has little effect on the drug release.

The MC in the granule coating hydrates and gels when in contact with water, thereby influenc-

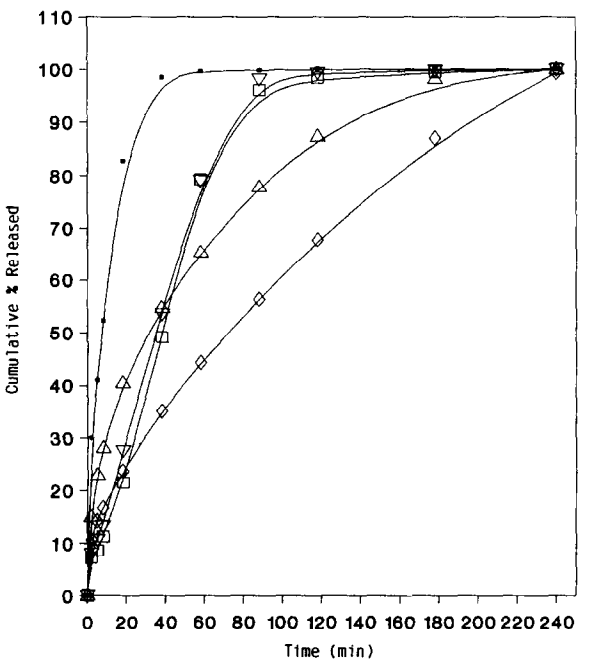

Fig. 3. Release of drug from granules coated with drug-MC solutions of varying MC content; (△) M1510 (10 g); (◇) M1520 (20 g); (▽) M1530 (30 g); (□) M1545 (45 g); (■) drug powder.

TABLE 4

Disintegration of granules coated with varying amounts and viscosity grades of MC and HPMC

Batch No. [a]	Drug : polymer ratio	% w/w of polymer in coated product [b]	Disintegration time [c] (s)
M1510	7.5 : 1	3.5	17.8 ± 3.0
M1520	3.75 : 1	6.8	46.8 ± 9.2
M1530	2.5 : 1	9.8	ND
M1545	1.7 : 1	14.1	ND
M10010	7.5 : 1	3.5	ND
M45010	7.5 : 1	3.5	ND
P1510	7.5 : 1	3.5	16.1 ± 4.9
P1520	3.75 : 1	6.8	44.2 ± 9.8
P1530	2.5 : 1	9.8	70.3 ± 12.4
P1545	1.7 : 1	14.1	126.4 ± 25.1

[a] Codes refer to formulations outlined in Table 2.
[b] Amount of polymer applied as a percentage of total weight of coated product.
[c] ND: coated granules did not disintegrate but remained as intact particles.

ing the release of the drug from the coated granules. As the MC content in the dry drug-polymer coat is increased, the resulting gelatinous diffusion layer would be thicker and more resistant to water penetration and erosion. Therefore, the dissolution and diffusion of the drug out of the gelled coat will be delayed. This is in aggreement with the disintegration data given in Table 4. The coated granules from batch M1510 disintegrated very fast, in 18 s, while batch M1520 required a longer time of 47 s to disintegrate. The granules floated in the water prior to their disintegration. However on disintegration, the fragments sank to the bottom of the disintegration apparatus and formed into a gelled mass. The relatively thin MC coat in batches M1510 and M1520 allowed rapid water penetration and swelling, culminating in the disintegration of the coated granules. On the other hand, the coated granules in batches M1530 and M1545 did not disintegrate but remained afloat in water. The lactose core was slowly dissolved and diffused out of the gelled coat. This is indicated by the white core becoming translucent with time. Although water penetrated into the granules, the disintegrating forces caused by the swelling of the MC in the drug-polymer coat and the increase in the internal hydrostatic pressure were not able to overcome the binding forces due to the adhesive action of the thicker coat. The coated granule is hydrodynamically balanced upon hydration, the buoyancy resulting from an increase in the bulk volume due to the swelling of the polymer and the air entrapped in the lactose core of the gelled particle during the fluidized-bed coating process. The disintegration of the coated granules from batches M1510 and M1520 enabled the entrapped air in the lactose cores to escape. Consequently, the disintegrated fragments sank into the water.

The disintegration characteristics of the coated granules could in fact be used to account for the release profiles obtained in Fig. 3. It was observed that the samples from M1510 and M1520 which have a low level of MC in the formulation, 10 and 20 g, respectively, swelled, disintegrated and formed into a gelled mass that was stuck to the base of the dissolution baskets almost immediately on contact with water. But when the content of MC in the coating formulation was increased beyond 20 g to 30 g (M1530) and 45 g (M1545), the coated granules did not gel up as a single mass at the bottom of the dissolution baskets. Instead, they were dispersed inside the dissolution baskets as small aggregates of intact gelled granules. The buoyancy of the coated granules and the swirling action of the rotating dissolution baskets contributed to the dispersion of the aggregates. The existence of the wetted granules as small aggregates during the dissolution test effectively increased the surface area available for drug release which negated the retarding effect with increasing MC content in the granule coat. As a result, M1530 and M1545 had unexpectedly faster drug release than M1510 and M1520.

Increasing the viscosity grade of the MC polymer in the granule coat may increase the gel layer viscosity and thus slows drug diffusion. However, the release profiles (Fig. 4) did not appear to fit into such a trend. A higher release rate was observed for the higher viscosity grades of MC 80–120 cp and 350–550 cp used in batches M10010 ($T_{50\%}$ = 32.0 min, $T_{90\%}$ = 76.0 min) and M45010 ($T_{50\%}$ a 35.0 min, $T_{90\%}$ = 57.5 min), compared to MC 13–18 cp in M1510 ($T_{50\%}$ = 31.8 min, $T_{90\%}$ = 133.0 min). The results from the disintegration test

(Table 4) showed that a similar situation to M1530 and M1545 was obtained; the granule samples from M10010 and M45010 did not disintegrate when they were hydrated in water. It has been shown that MC films undergo rapid swelling when hydrated whereby the swelling rate decreases with increase in the viscosity grade of the MC (Wan and Prasad, 1990). The swelling of the film is the net effect of the balance between the adhesive forces that retard swelling and the stretching of the individual MC polymer strands in the film on hydration. The adhesive and thickening properties of MC are dependent on the polymer chain length and the degree of substitution (Greminger et al., 1980). These factors are reflected in the viscosity of the MC whereby a higher viscosity grade MC has greater adhesive action. In M10010 and M45010, the strong adhesive effect of the high viscosity MC maintained the integrity of the granules and prevented their disintegration caused by swelling. Accordingly, the granule samples of M10010 and M45010 were also observed to be

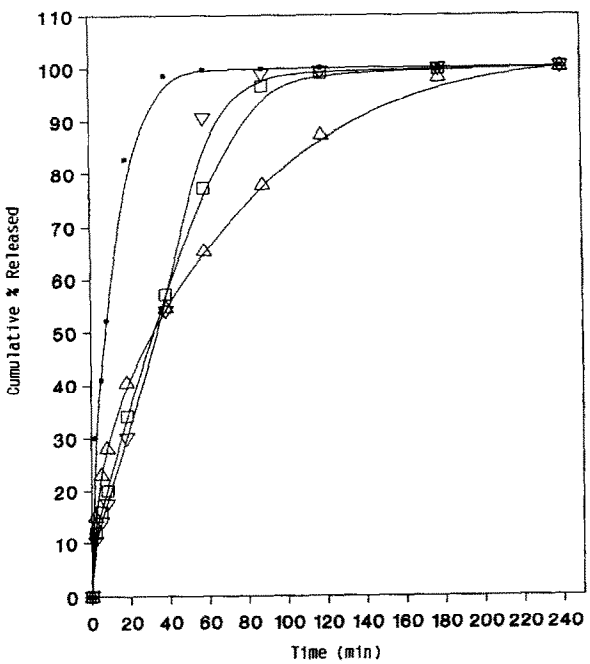

Fig. 4. Release profiles of drug-coated granules prepared with different MC viscosity grades; (△) M1510 (13–18 cp); (□) M10010 (80–120 cp); (△) M45010 (350–550 cp); (■) drug powder.

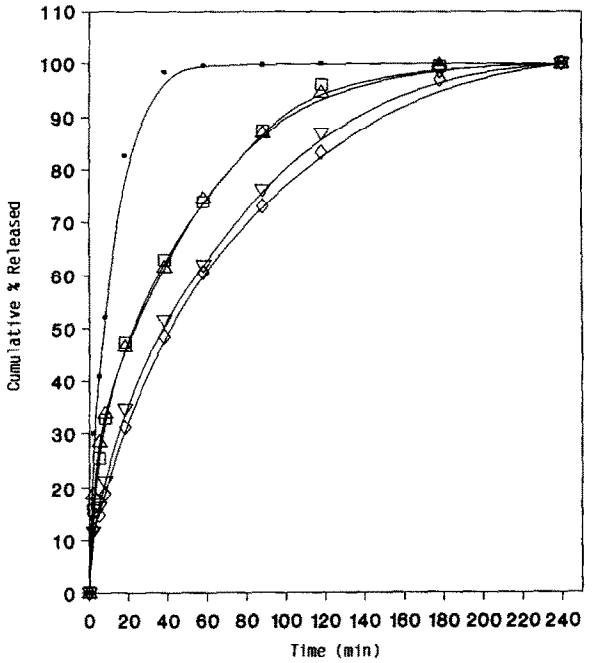

Fig. 5. Influence of HPMC content in coating formulation on the drug release from the coated granules; (△) P1510 (10 g); (□) P1520 (20 g); (▽) P1530 (30 g); (◇) P1545 (45 g); (■) drug powder.

dispersed in the dissolution baskets during the dissolution test and no gelled mass was formed at the base of the rotating baskets. Hence, a similar explanation to that discussed earlier for batches M1510, M1520, M1530 and M1545 is also applicable to the results observed here. The increase in the surface area for release due to dispersion of the coated granules during the dissolution test apparently more than offset the expected drop in drug release rate for higher viscosity MC.

Coated granules produced from formulations with HPMC as the film-forming polymer demonstrated a different drug release behaviour. The release profiles of the coated product are depicted in Fig. 5. In this case, there exists a correlation between the disintegration pattern and the corresponding release rate of the coated granules. The release rate decreases with increase in the HPMC content in the granule coat. The prolongation in the $T_{50\%}$ from 23.2 to 40.0 min and $T_{90\%}$ from 96.8 to 147.4 min corresponded to the increase in the HPMC content in the formulation from 10 to 45

g. The disintegration time varied directly with the amount of HPMC applied onto the granules. The rank order of the disintegration time of the coated granules is as follows (Table 4): P1510 < P1520 < P1530 < P1545. All the drug-HPMC coated granules disintegrated as opposed to the drug-MC coated ones although the same amount of polymer was used in either formulation. As already mentioned, the net effect on the disintegration behaviour of the coated granules depends on the magnitude of the swelling phenomenon and the opposing adhesive action of the polymeric coat. The higher hydrophilicity and hydration rate of the HPMC relative to MC (Doelker, 1987) allowed rapid hydration and swelling, leading to the disintegration of the granules coated with HPMC before the adhesive action of the HPMC could be effected. Besides, the lactose core, being highly water-soluble, will further enhance the rate of water penetration and hydration of the drug-HPMC coat on the granules. This is caused by the osmotic effect exerted when the lactose core dissolves.

The surface morphology of the drug-coated beads plays an important role in their release of the drug (Mehta and Jones, 1985). Mehta (1986) has also discussed the effect of the quality of the surface of the drug layer on the ultimate drug release characteristics. A recent report by Rekhi et al. (1989) demonstrated that drug release rate from drug-layered nonpareil seeds may be affected by the imperfections on the surface of the drug-polymer coat. An attempt was therefore made to determine whether the more rapid drug release from M1530 compared to M1520 was due to the concentration of MC in the coating solution. Batches of coated granules were prepared by spraying with 6% w/v MC (M1520A and M1530) and with 4% w/v MC (M1520 and M1530A) coating formulations but keeping the total amount of MC deposited constant. The coating formulations are shown in Table 2. The drug release profiles from the resultant coated granules were compared in Fig. 6. The overall release rates of M1520A and M1530 which were coated at a higher MC concentration (6% w/v) showed an increase in comparison to M1520 and M1530A which were sprayed with 4% w/v MC. This may be attributed

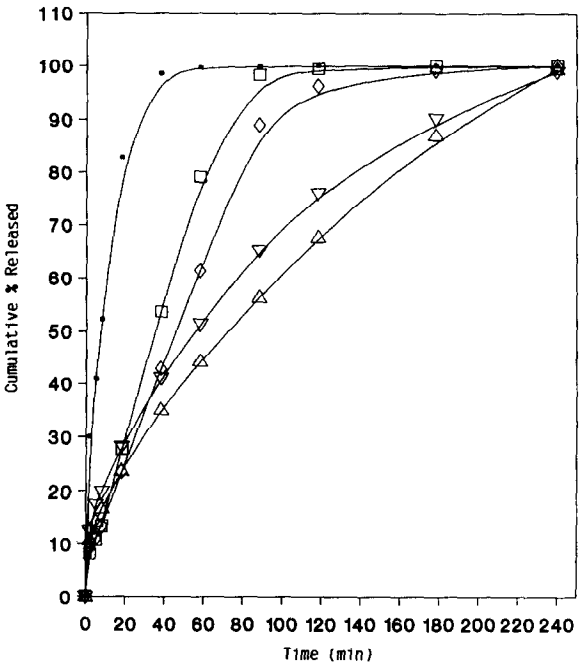

Fig. 6. Release of drug from coated granules as a function of the MC concentration in the coating solution at the same MC content; (△) M1520 (4% w/v); (▽) M1520A (6% w/v); (□) M1530 (6% w/v); (◇) M1530A (4% w/v); (■) drug powder.

to the presumably different morphological characteristics of the resultant drug-MC coat obtained from coating formulations of varying viscosity. Notwithstanding, the effect of viscosity of the coating solution on the release rate of the coated product, the release profiles in Fig. 6 did not deviate from the earlier observation that a generally higher release rate is exhibited in granules coated with 30 g of MC (M1530) vis-à-vis 20 g of MC (M1520).

Conclusion

In fluidized-bed coating, simultaneous drying and particle enlargement are carried out by spraying coating liquid onto a fluidized layer of dry particles. Particle growth occurs either by particle coalescence or by the more desirable mechanism of layering of solids from the feed liquid onto the surface of the bed particles.

In order to achieve reliable operational conditions, the fluidized-bed coater must operate in such a manner that no large aggregates are formed which may segregate in the bed and cause a demixed or defluidized bed to be initiated. Decrease in mixing behaviour in the bed will eventually cause complete defluidization resulting in a deterioration in product physical form. In the study, the intermittent spray conditions adopted were effective in minimizing aggregation of the coated granules and spray drying of the coating liquid, and therefore resulted in high process efficiency.

The dosage form described in this work consists of a lactose granule core which is coated with a water-soluble polymeric film containing the drug. The drug-polymer film on the granules in effect, functions essentially as a hydrophilic matrix system. Drug release it seemed, is controlled by a combination of diffusion of the drug from and erosion of the polymeric coat.

The in-vitro drug release profiles of the drug-coated lactose granules depend to a large extent, on the drug loading as well as the nature, viscosity grade and the total content of the polymer present in the coat of the final product. An increase in the amount or the viscosity grade of the polymer applied is not necessarily accompanied by a decrease in the drug release rate of the coated granules. Another important factor to consider is the rupture or disintegration of the coated granules when they are hydrated. This would depend on the nature of the polymer forming the coat, such as its hydration rate and adhesive properties. The disintegration behaviour together with the air entrapped in the lactose core during the coating process which imparts buoyancy to the final coated granules, can have a significant effect on the overall release kinetics of the drug from such coated granules. Recent studies by Korsmeyer et al. (1983) and Hashim and Li (1987) have in fact suggested that entrapped air seemed to result in zero-order release of potassium chloride from compressed HPMC matrices. The results obtained in this study are therefore important considerations in the design of drug-coated granules as modified-release dosage form employing a water-soluble polymeric system.

References

Bechgaard, H., Critical factors influencing gastrointestinal absorption. What is the role of pellets? *Acta Pharm. Technol.*, 28 (1982) 149–157.

Beckett, A. H., Important formulation factors influencing drug absorption. In Prescott, L.F. and Nimmo, W.S. (Eds), *Drug Absorption*, ADIS, New York, 1981, pp. 133–143.

Caldwell, H.C. and Rosen, E., New air suspension apparatus for coating discrete solids. *J. Pharm. Sci.*, 53 (1964) 1387–1391.

Chopra, S.K. and Tawashi, R., Tack behaviour of coating solution I. *J. Pharm. Sci.*, 71 (1982) 907–911.

Davies, W.L. and Gloor, Jr., W.T., Batch production of pharmaceutical granulations in a fluidized bed I: Effects of process variables on physical properties of final granulation. *J. Pharm. Sci.*, 60 (1971) 1869–1874.

Davies, W.L. and Gloor, Jr., W.T., Batch production of pharmaceutical granulations in a fluidized bed II: Effects of various binders and their concentrations on granulations and compressed tablets. *J. Pharm. Sci.*, 61 (1972) 618–622.

Doelker, E., Water swollen cellulose derivatives in pharmacy. In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy, Vol. II, Polymers*, CRC Press, Boca Raton, FL, 1987, pp. 115–160.

Ghebre-Sellassie, I., Gordon, R.H., Nesbitt, R.U. and Fawzi, M.B., Evaluation of acrylic-based modified-release film coatings. *Int. J. Pharm.*, 37 (1987) 211–218.

Goodhart, F.W., Harris, M.R., Murthy, K.S. and Nesbitt, R.U., Evaluation of aqueous film-forming dispersions for controlled release. *Pharm. Technol.*, 8 (1984) 64–71.

Greminger, Jr., G.K. and Krumel, K.L., Alkyl and hydroxyalkyl cellulose. In Davidson, R.L. (Ed.), *Handbook of Water-soluble Gums and Resins*, McGraw-Hill, New York, 1980, pp. 1–25.

Hall, J.S. and Pondell, R.E., The Wurster process. In Kydonieus, A.F. (Ed.), *Controlled Release Technologies: Methods, Theory and Applications*, Vol. II, CRC Press, Boca Raton, FL, 1980, pp. 133–154.

Hashim, H. and Li, A.W.P., Improving the release characteristics of water-soluble drugs from hydrophilic sustained release matrices by in-situ gas generation. *Int. J. Pharm.*, 35 (1987) 201–209.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanisms of potassium chloride release from compressed, hydrophilic polymeric matrices: Effect of entrapped air. *J. Pharm. Sci.*, 72 (1983) 1189–1191.

Lehmann, K., and Dreher, D., Coating of small particles with acrylic resins by fluid-bed technology. *Int. J. Pharm. Technol. Prod. Manuf.*, 2 (1981) 31–34.

Li, S.P., Jhawar, R., Mehta, G.N., Harwood, R.J. and Grim, W.M., Preparation and in-vitro evaluation of a controlled release drug delivery system of theophylline using an aqueous acrylic resin dispersion. *Drug Dev. Ind. Pharm.*, 15 (1989) 1231–1242.

Lippold, B.H., Sutter, B.K. and Lippold, B.C., Parameters

controlling drug release from pellets coated with aqueous ethylcellulose dispersions. *Int. J. Pharm.*, 54 (1989) 15–25.

Mehta, A.M., Factors in the development of oral controlled release dosage forms. *Pharm. Manuf.*, 3 (1986) 23–29.

Mehta, A.M. and Jones, D.M., Coated pellets under the microscope. *Pharm. Technol.*, 9 (1985) 52–60.

Rankell, A.S., Scott, M.W., Lieberman, H.A., Chow, F.S. and Battista, J.V., Continuous production of tablet granulations in a fluidized bed II. Operation and performance of equipment. *J. Pharm. Sci.*, 53 (1964) 320–324.

Rekhi, G.S., Mendes, R.W., Porter, S.C. and Jambhekar, S.S., Aqueous polymeric dispersions for controlled drug delivery – Wurster process. *Pharm. Technol.*, 13 (1989) 112–125.

Robinson, M.J., Grass, G.M. and Lantz, R.J., An apparatus and method for the coating of solid particles. *J. Pharm. Sci.*, 57 (1968) 1983–1988.

Scott, M.W., Lieberman, H.A., Rankell, A.S. and Battista, J.V., Continuous production of tablet granulations in a fluidized bed I. Theory and design considerations. *J. Pharm. Sci.*, 53 (1964) 314–320.

Scott, M.W., Lieberman, H.A., Rankell, A.S., Chow, F.S. and Johnston, G.W., Drying as a unit operation in the pharmaceutical industry I. Drying of tablet granulations in fluidized beds. *J. Pharm. Sci.*, 52 (1963) 284–291.

Singiser, R.E. and Lowenthal, W., Enteric filmcoats by the air-suspension coating technique. *J. Pharm. Sci.*, 50 (1961) 168–170.

Vanecek, V., Markvart, M. and Drbohlav, R., *Fluidized Bed Drying*, CRC Press, Cleveland, OH, 1966.

Wan, L.S.C. and Prasad, P.P.K., Studies on the swelling of the composite disintegrant-methycellulose films. *Drug Dev. Ind. Pharm.*, 16 (1990) 191–200.

Wurster, D.E., Air-suspension technique of coating drug particles: a preliminary report. *J. Am. Pharm. Assoc. Sci. Ed.*, 48 (1959) 451–454.

Yang, S.T. and Ghebre-Sellassie, I., The effect of product bed temperature on the microstructure of aquacoat-based controlled-release coatings. *Int. J. Pharm.*, 60 (1990) 109–124.

Zoglio, M.A., Streng, W.H. and Carstensen, J.T., Diffussion model for fluidized bed drying. *J. Pharm. Sci.*, 64 (1975) 1869–1873.