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REGULATING DRUG RELEASE VIA NON-UNIFORM DISTRIBUTION OF COATING COMPOSITION IN MULTILAYER DRUG-COATED GRANULES

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ABSTRACT

Multilayer drug-coated granules with a non-uniform distribution of the coating composition specifically the drug loading and the polymer viscosity, across the thickness of the film matrix were prepared by the fluidized bed coating process. The rate and duration of diphenhydramine hydrochloride release from the coated granules can be modified through control of the gradient change in the coating composition across the thickness of the methylcellulose (MC) film matrix. A steeper gradient change across the film matrix resulted in a slower overall release rate. Formulations with gradient drug loading distribution exhibited an extended release time that can be twice as long as that for the control formulation. Gradient layered matrices obtained by sequentially depositing different viscosity grades of MC produced release profiles that differed from film matrices prepared using MC blends.

INTRODUCTION

The principle of film coating offers great flexibility in regulating the delivery of drug from the formulation and is therefore suitable for many types of systems (1). A previous study by Wan and Lai (2) has demonstrated that incorporation of drug in water-soluble methylcellulose films deposited onto inert lactose granules afforded a feasible means of achieving controlled release for multiparticulate dosage forms. Although a drug-containing matrix is a simple and economical method to achieve controlled release of drugs for oral dosage forms, constant-rate release cannot be easily attained in such matrices because of rapid changes in diffusional distance, unfavourable geometrical factors and the balance between dissolution and diffusion may not yield the proper control.

The concept of non-uniform drug distribution in insoluble polymer matrices has been examined recently as a mechanism to achieve constant drug release (3-6). The objective of the present paper was to study the influence of the change in distribution of the coating composition specifically the drug loading and the polymer viscosity, across a water-soluble polymer film matrix on the release of the active ingredient from the resultant coated granules. This work is an extension of the idea proposed in an earlier report on multilayer drug-coated cores (2).

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MATERIALS AND METHODS

Materials

Lactose granules (Sunward Chemicals, Singapore) of 600-710 μm were used as an inert core substrate to which the film matrix was applied. Methylcellulose (MC, Tokyo Kasei, Japan) of various viscosity grades (13-18, 20-30, 80-120 and 350-550 cP) was selected as the water-soluble film-forming polymer. Diphenhydramine hydrochloride (B.P. grade) was employed as a model drug. All materials were used as supplied.

Coating Procedure

Batches of about 200 g of lactose granules were coated in a bottom-spray fluidized bed Aerocoater® (Model Strea-1, Aeromatic AG, Switzerland). The process conditions given in Table 1 were similar to those adopted previously (2).

The lactose granules were sprayed consecutively with three solutions of the drug and polymer of varying composition, thus building up the film matrix. The composition of the various coating formulations is listed in Table 2. Finally, the multilayer coat consisted of three discrete component layers each with a step-wise change in composition to approximate a continuous gradient distribution of the drug or polymer viscosity. The total amount of drug and polymer forming the gradient film matrix was kept constant at 75 g and 30 g respectively, for each of the formulations. After coating and drying, coated granules in the sieve fraction of 600-850 μm (Endecotts Sieve Shaker, Model EVS1, UK) were taken for further evaluation. GLM (gradient layered matrix) 1 series in Table 2 refers to the effect of gradient drug loading, GLM 2 series refers to the effect of gradient polymer viscosity distribution obtained from different viscosity grades of MC while GLM 3 series refers to the effect of gradient polymer viscosity distribution obtained from MC blends.

Release Studies

The details of the in-vitro dissolution tests in distilled water were given in a previous report (2). Accurately weighed samples of drug-coated granules (600-850 μm) containing the equivalent of about 200 mg of diphenhydramine hydrochloride were used. Each formulation was analyzed at least in triplicate.

Viscosity Determination

The apparent viscosity of the various solutions of drug-MC blend was determined with a Brookfield Synchro-lectric viscometer (model LVT, Brookfield Engineering Laboratories, Inc., USA) using spindle #1 at 30 rpm. The temperature was held constant at 37 ± 0.5 °C.

RESULTS AND DISCUSSION

Effect of the Variation in Drug Loading Across the Multilayer Film Matrix

Figure 1 shows the variation in the in-vitro release profile with the drug diphenhydramine hydrochloride loading profile in the multilayer drug-coated granules.

It is evident that formulations in the GLM 1 series, i.e., GLM 1C, 1D and 1E in which the drug loading across the thickness of the film matrix of the coated granules was distributed in a gradient manner such that the drug loading was lowest in the outer component layer, followed by an increasing amount in the middle component layer and ending with the highest drug loading in the inner component layer of the multilayer coat, showed a longer release time compared to the control batch GLM 1B which had a uniform drug loading. The inner, middle and outer component layers refer to the order of application of different coating solutions (Table 2), with the inner layer being nearest to and the outer layer furthest away from the core of the lactose granule. Total drug release was completed in 7 h for GLM 1D and GLM 1E. This was about twice as long as that of the control batch GLM 1B (uniform drug loading) with the same polymer content. Gradient distribution of the drug loading in the film matrix with increasingly more drug towards the inner

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TABLE 1

Summary of Process Conditions

Parameter	Setting
Fluidizing air flow rate (m^3/h)	90-110
Inlet air temperature (°C)	80
Outlet air temperature (°C)	50-54
Spray nozzle diameter (mm)	0.5
Atomizing air pressure (bar)	0.8
Spray rate (mL/min)	5-7
Intermittent spray cycle	1-5 min spraying/30 s drying
Postcoating drying	80 °C, 10 min

TABLE 2

Specifications for the Coating Formulations. The gradient layered matrix was prepared as a three-step gradient system by spraying a different solution (500 mL) for each of the component layers

Batch	Inner layer		Middle layer		Outer layer	
	Drug (g)	MC [b] (g)	Drug (g)	MC [b] (g)	Drug (g)	MC [b] (g)
Gradient drug distribution						
GLM 1A	10.7	10 (13-18 cP)	21.4	10 (13-18 cP)	42.9	10 (13-18 cP)
GLM 1B	25.0	10 (13-18 cP)	25.0	10 (13-18 cP)	25.0	10 (13-18 cP)
GLM 1C	35.0	10 (13-18 cP)	25.0	10 (13-18 cP)	15.0	10 (13-18 cP)
GLM 1D	42.9	10 (13-18 cP)	21.4	10 (13-18 cP)	10.7	10 (13-18 cP)
GLM 1E	50.0	10 (13-18 cP)	16.7	10 (13-18 cP)	8.3	10 (13-18 cP)
Gradient viscosity distribution (viscosity grades)						
GLM 2A	25.0	10 (13-18 cP)	25.0	10 (80-120 cP)	25.0	10 (350-550 cP)
GLM 2B	25.0	10 (13-18 cP)	25.0	10 (20-30 cP)	25.0	10 (80-120 cP)
Gradient viscosity distribution (MC blends)						
GLM 3A [a]	25.0	9 / 1	25.0	4 / 6	25.0	2 / 8
GLM 3B [a]	25.0	6 / 4	25.0	5 / 5	25.0	4 / 6
GLM 3C [a]	25.0	5 / 5	25.0	5 / 5	25.0	5 / 5
GLM 3D [a]	25.0	2 / 8	25.0	4 / 6	25.0	9 / 1

[a] Each layer consists of a MC 13-18/350-550 cP blend. The amount of MC 13-18 cP and 350-550 cP used is indicated respectively by the figures before and after the slash.

[b] The numbers in parentheses indicate the viscosity grade of the MC.

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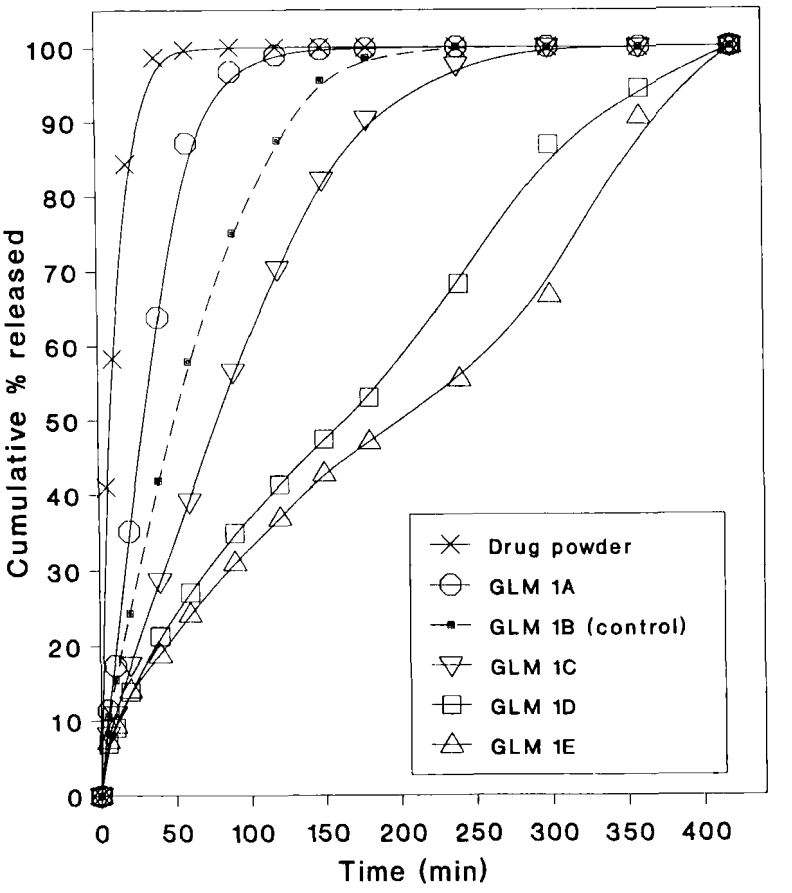

FIGURE 1
Relationship between the gradient distribution of the drug loading in the multilayer coat and the resultant release profiles.

layer resulted in longer release time, probably due to the formation of a more coherent swollen polymeric gel in the depletion zone during the dissolution event (4). Further, a steeper drug loading gradient across the film matrix resulted in a slower overall release rate. This is reflected in the $T_{50\%}$ values shown in Table 3. GLM 1E with the steepest drug loading gradient therefore had the longest $T_{50\%}$. In contrast, batch GLM 1A with a drug loading profile that was decreasing towards the inner component layer of the coated granules (opposite to GLM 1C, 1D and 1E) demonstrated a higher release rate than the control batch GLM 1B (uniform drug loading).

A positive deviation in the release profiles towards the later stage of the dissolution process (after about 60 % release) was observed in batches GLM 1D and GLM 1E (Figure 1). This could be associated with the hydration and release of the drug from the inner component layer of the film matrix in these two batches. The higher drug loading in this layer compared with the outer layers presumably overcompensated for the anticipated decline in release rate with time in a typical matrix system. Such observations were also reported by Foster and Parrott (7) in their study of

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TABLE 3
Time for 50 % of drug release ($T_{50\%}$) from the coated granules

Batch	$T_{50\%}$ ± SD (min)
GLM 1A	31.4 ± 4.6
GLM 1B	50.6 ± 7.2
GLM 1C	80.1 ± 7.0
GLM 1D	165.2 ± 6.7
GLM 1E	202.9 ± 16.6
GLM 2A	57.5 ± 11.6
GLM 2B	84.8 ± 22.6
GLM 3A	55.0 ± 10.0
GLM 3B	38.1 ± 4.7
GLM 3C	40.9 ± 7.1
GLM 3D	17.8 ± 1.7

multiple-layered hydrogenated castor oil matrices. Lapidus and Lordi (8,9) had attributed such deviation to a decrease in tortuosity which could be a function of the extent of hydration and the type of gel structure formed as water penetrated the different component layers of the film matrix. The higher drug load in the inner component layer induced a greater osmotic stress (10) causing the MC network to expand more than it would have with less or no drug. This has been shown to be true in glassy drug-loaded hydrogel beads (11) and gelatin matrices (12). Another contributing factor to the increased release could be the low polymer concentration in the inner component layer being insufficient to maintain matrix coherence.

The results obtained here were consistent with a previous finding that different loading concentrations of drug or excipient changed the structure of an ethylcellulose film matrix and the penetration constants of the solutes through the film were found to be dependent on their initial loading concentrations (13). Likewise, it is probable that the effective diffusivity of diphenhydramine hydrochloride in the different component layers of the MC film matrix would change according to the drug loading in that layer. The positive deviations of the release profiles thus suggested a large increase in diffusivity of the drug near the end of the release process.

Influence of the Variation in Polymer Viscosity of the Component Layers of the Multilayer Film Matrix

The release characteristics of a monolithic matrix coat on the lactose granules are governed by two main factors; that due to the barrier properties of the polymer coat and that attributed to the size of the embedded drug particles in the film matrix. The observed release profile of the coated granules is a manifestation of the relative magnitude of these two factors. The simultaneous operation of these two factors has been discussed in an earlier publication by the present authors (2). It is possible, on this basis, to provide explanations for the effect of the change in polymer viscosity across the multilayer film matrix on the resultant release characteristics of the coated granules.

The gradient distribution of polymer viscosity across the component layers of the film matrix on the lactose granules can be obtained by sequentially depositing different viscosity grades

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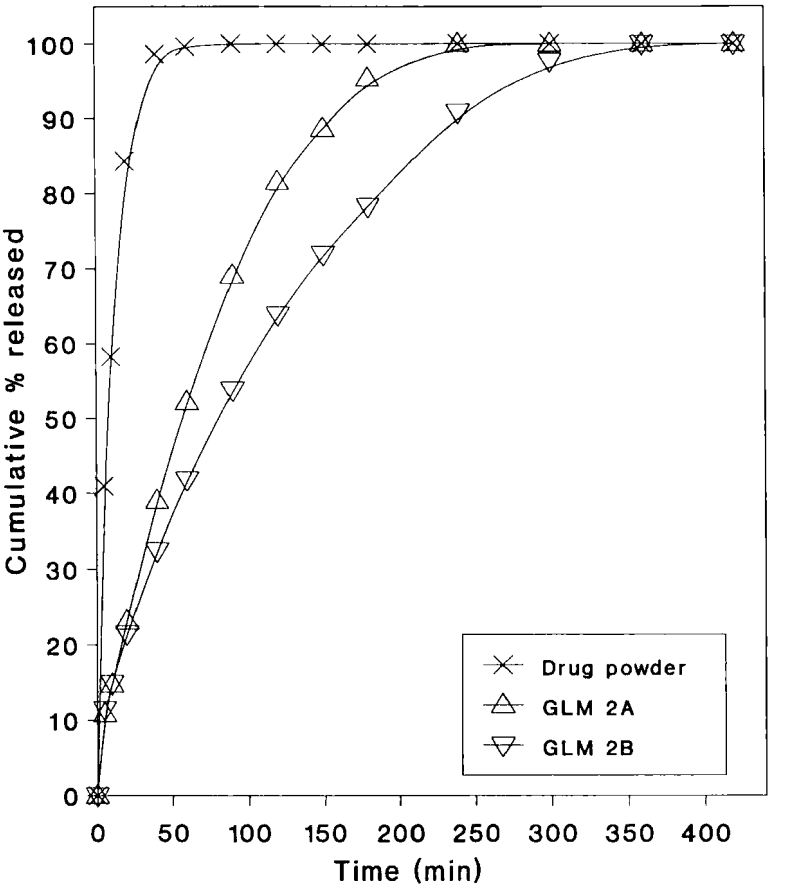

FIGURE 2
Release profiles of multilayer drug-coated granules prepared by sequential deposition of different MC viscosity grades.

of MC or by depositing MC blends comprising one low and one high viscosity grade in different proportions. For formulations in the GLM 2 series where the viscosity gradient in the multilayer polymeric coat was formed by sequential layering of different viscosity grades of MC, the significant disparity in the size of the recrystallized drug particles in a low viscosity compared to a high viscosity grade MC suggested that this factor would predominate. Photomicrographs obtained from both scanning electron and optical microscopic analyses of the coated granules and cast drug-MC films by Wan and Lai (2) corroborated this fact. Hence the release rate was faster in GLM 2A ($T_{50\%}$ = 57.5 min) than in GLM 2B ($T_{50\%}$ = 84.8 min) despite the fact that the film matrix in GLM 2A was composed of MC of higher viscosity grades (Figure 2). Apparently the more viscous film matrix in GLM 2A led to the formation of fine recrystallized drug particles (14,15) which tended to neutralize the retardant function of viscosity on release. Such particle size effect was also demonstrated by Haleblian et al. (16) in a study on the release of chlormadinone acetate from silicone elastomer.

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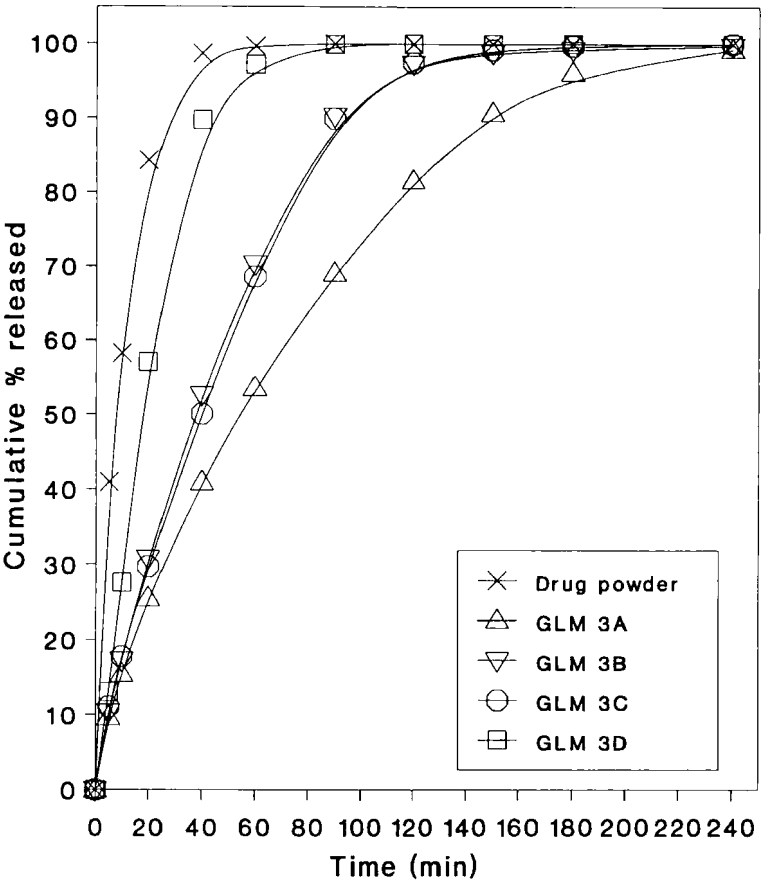

FIGURE 3
Release profiles of multilayer drug-coated granules formed by sequential deposition of MC blends of 13-18 cP and 350-550 cP in varying proportions.

On the contrary, for formulations in the GLM 3 series where the viscosity gradient was obtained by the blending of two MC viscosity grades, the effect of crystal size on the release profile of the coated product would be negligible. There was no observable difference between the size of the drug particles recrystallized in the cast films of the MC blends when they were subjected to examination under optical microscopy. Consequently, the relative effect of the barrier properties of viscosity on drug diffusion would become predominant. Rowe and Forse (18) had noted that blends of high and low molecular weight grades of a polymer can increase the effective toughness of the resultant polymer film and thus make it a more effective barrier to drug diffusion. Therefore, in formulations GLM 3A, 3B, 3C and 3D whereby the lactose granules were layered with MC blends, the overall release rate of the drug-coated granules would be dependent mainly on the overall viscosity of all the component layers in the multilayer film matrix. A higher overall viscosity would result in slower drug release (Figure 3).

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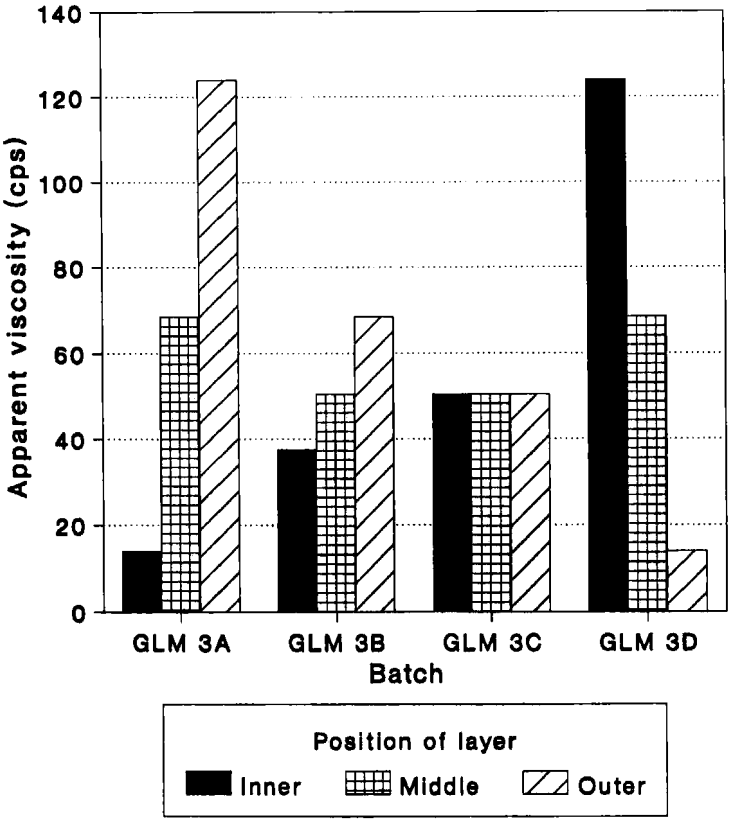

FIGURE 4
Apparent viscosity of coating solutions of drug-MC blends at 37 ± 0.5 °C used in the preparation of the gradient layered matrices.

Additionally, an interesting facet of the effect of polymer viscosity distribution in the multilayer film matrix could be noted. Figure 4 depicts the apparent viscosity values determined with a Brookfield viscometer, of solutions of drug-MC blends used in forming the component layers of the film matrices in GLM 3A, 3B, 3C and 3D. Although not a true representation of the viscosity of the film matrices, these values do provide an indication of the relative differences in the viscosity of the component layers when hydrated. The drug release rate of the coated granules was observed to vary inversely with the gradient of the polymer viscosity distribution (outer layer with the highest viscosity decreasing towards the inner layer) in the multilayer coat. A steeper viscosity gradient resulted in a slower release profile. This is most evident in GLM 3D which had a overall viscosity equivalent to GLM 3A (Table 2 and Figure 4) but with a reverse viscosity gradient instead (outer layer with the lowest viscosity increasing towards the inner layer). GLM 3D showed a much faster drug release ($T_{50\%}$ = 17.8 min) than GLM 3A ($T_{50\%}$ = 55.0 min). The similar release profiles for GLM 3B and GLM 3C (Figure 3) corresponded to their small relative differences in viscosity gradient across the multilayer film matrices as well as their similar overall viscosity (Figure 4).

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CONCLUSION

The gradient layered matrix approach has the advantages in the ease of fabrication and the latitude offered in modulating the release rate of the drug. The versatility of this approach provides an enhanced degree of design flexibility for obtaining useful, perhaps unique systems. The ability of the gradient layered matrix to extend the total duration of release at a relatively low polymer content was demonstrated in the study. This is useful in multiparticulate dosage forms particularly for water-soluble systems, which require a high coating level for prolonged release. The mechanism of release from the completely water-soluble systems investigated generally followed non-linear kinetics. Further work on the development of these systems is in progress.

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