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Multilayer drug-coated cores: A system for controlling drug release

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Summary

The present study was undertaken to develop a new controlled release model system using multilayer coated granules prepared by consecutively spraying aqueous solutions of diphenhydramine · HCl, dissolved in methylcellulose (MC) of various viscosity grades, onto lactose granules in a fluidized bed. The in vitro drug release profiles of the coated product were shown to be a function of the polymer viscosity grade and the sequential order of application of the polymeric component layers on the lactose granules. The permutation and the mass fraction of the component layers on the multilayer coated granules could be altered to provide different drug release rates. Although the equilibrium hydration and swelling of each component layer influenced drug diffusion to some extent, the overall release was not entirely governed by it. The drug release profiles were also modulated by the dissolution characteristics, particularly the particle size of the recrystallized drug that is embedded in the polymeric coat. This approach on controlled-release provides an outline for further work in this field.

Introduction

A number of controlled or sustained-release delivery systems have been described in the literature whereby the active ingredient is incorporated within inert polymer films. Such products can be adapted to different routes of administration by direct utilization or in the form of coatings in oral dosage forms (Sciarra and Gidwani, 1972; Borodkin and Tucker, 1974; Donbrow and Friedman, 1975b). Drug release rates may be altered by the use of additives or polymers selected on the basis of hydrophilicity (Samuelov et al., 1979; Okor, 1982) and hydrophobicity properties (Benita et al., 1984).

Hydrophilic polymers such as the cellulose ethers are commonly utilized in the design of drug delivery systems. An advantage of these cellulose derivatives is their availability in a wide range of viscosity grades which afford the formulator flexibility in developing dosage forms with specific characteristics without greatly altering the chemical and toxicological properties of the system (Alderman, 1984; Rowe, 1986; Doelker, 1987). The objective of the present work is to

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evaluate the concurrent use of different viscosity grades of a water-soluble cellulose ether, methylcellulose (MC), as drug-containing polymer films layered separately onto the same granule particle in controlling the drug release characteristics of the coated product. The multilayer coated granules are prepared by consecutively spraying aqueous solutions of diphenhydramine · HCl in MC of different viscosity grades onto lactose granules in a fluidized-bed. An attempt is made to identify the release kinetic patterns for such multilayer coated granules.

TABLE 1

Summary of the process conditions used in the preparation of the multilayer coated granules

Parameter	Setting
Fluidizing airflow 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
Spray interval	intermittent
Postcoating drying conditions	80°C, 10 min
Lactose granule load (g)	200

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, 20–30, 80–120, 350–550 and 800–1200 cps) was selected as the coating polymer. Distilled water was used for the preparation of the

TABLE 2

Coating formulations used in the production of multilayer coated granules

Batch No.	Formulation						
	Location of layer [a]	Diphenhydramine · HCl (g) [b]	MC [c] 13–18 cps (g)	MC [c] 350–550 cps (g)	MC [c] 20–30 cps (g)	MC [c] 80–120 cps (g)	MC [c] 800–1200 cps (g)
LH13	I	18.8	5 (2)	–	–	–	–
	O	56.2	–	15 (2)	–	–	–
LH11	I	37.5	10 (2)	–	–	–	–
	O	37.5	–	10 (2)	–	–	–
LH31	I	56.2	15 (2)	–	–	–	–
	O	18.8	–	5 (2)	–	–	–
HL13	I	18.8	–	5 (2)	–	–	–
	O	56.2	15 (2)	–	–	–	–
HL11	I	37.5	–	10 (2)	–	–	–
	O	37.5	10 (2)	–	–	–	–
HL31	I	56.2	–	15 (2)	–	–	–
	O	18.8	5 (2)	–	–	–	–
LH22	I	37.5	–	–	10 (2)	–	–
	O	37.5	–	–	–	10 (2)	–
HL22	I	37.5	–	–	–	10 (2)	–
	O	37.5	–	–	10 (2)	–	–
LH44	I	37.5	–	–	10 (2)	–	–
	O	37.5	–	–	–	–	10 (1.7)
HL44	I	37.5	–	–	–	–	10 (1.7)
	O	37.5	–	–	10 (2)	–	–

[a] I and O represent inner and outer layer, respectively.

[b] The drug : MC ratio is held constant at 3.75 : 1 in all the layers.

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

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

Batches of about 200 g of lactose granules (600–710 μm) were coated in a bottom-spray fluidized-bed Aerocoater® (Model Strea-1, Aeromatic AG, Switzerland). The intermittent spray conditions adopted in a previous study (Wan and Lai, 1991) were used in the coating process. The process conditions are summarized in Table 1. The coating conditions were kept almost identical throughout this study. The lactose granules were sprayed consecutively with solutions of different composition, resulting in the formation of multilayer coated granules. The composition of the various drug-polymer formulations is listed in Table 2. The total drug and polymer loadings were fixed at 75 and 20 g, repectively, while the drug-to-polymer ratio of 3.75 : 1 was maintained for the different formulations. After coating and drying in the fluidized bed, the coated granules were mechanically sieved (Endecotts Sieve Shaker, Model EVS1, U.K.) to remove agglomerates and the sieve fraction of 600–850 μm was used for further evaluation.

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, U.S.A.) at 256 nm. All the assays were carried out in triplicate and the mean values were used for subsequent calculations.

Dissolution studies

In vitro dissolution tests were conducted in 900 ml of distilled water at 37 $\pm$ 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 (Wan and Heng, 1987). 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.

Preparation of cast films

The cast films were prepared by pouring a fixed volume (5 ml) of the aqueous drug-polymer solution onto a standard size glass petri dish and allowing it to spread over the entire surface. A fixed volume of solution was necessary to obtain approximately constant film thickness for each sample. The composition of the various drug-polymer solutions corresponded to that employed for the spray coating process (Table 2). The films were placed in a hot air oven at 80°C until they were completely dried. The dried films were then stored in a vacuum desiccator until further evaluation. The casting procedure was repeated to ensure reproducibility.

Optical microscopy

The dried diphenhydramine · HCl cast films were examined using a light microscope (Olympus System Microscope Model BH-2, Japan) at different magnifications.

Scanning electron microscopy

The surface morphology and cross-sections of the coated granules were examined by scanning electron microscopy. The coated granules were sputter coated for 120 s under an argon atmosphere with gold (Bio-Rad Sputter Coater, Model SC502, U.K.) and then examined with a scanning electron microscope (Jeol JSM 5200, Japan).

Results and Discussion

Composition of the multilayer polymeric coat

The release profiles of the multilayer coated granules and the dissolution profile of pure diphenhydramine · HCl powder in distilled water are shown in Figs 1–5. The release rates of diphenhydramine · HCl from the coated granules were in all cases slower than from the pure drug powder.

The lactose granules were coated with two component layers comprising a high and a low viscosity grade of MC while keeping the drug-to-MC ratio and the total amount of material (polymer and drug) applied constant. The release patterns obtained are especially interesting in that a reverse in the order of deposition of the two layers of MC, each of a different viscosity grade, on the lactose granules resulted in vastly different drug release rates. A higher release rate is noted for batches HL11 (Fig. 1), HL22 (Fig. 2) and HL44 (Fig. 3) in which a lower viscosity grade of MC constituted the outer component layer compared with batches LH11, LH22 and LH44, respectively, where the high viscosity grade layer is located on the outside instead. This seemingly interesting 'two-sided' release behaviour of the double-layer coat described may be rationalized on the basis of the degree of hydration and swelling of the component polymer layers in water. Wan and Prasad (1990) have shown that MC films undergo rapid swelling when hydrated whereby the swelling rate is inversely related to the viscosity grade of the MC. Higher viscosity grades of MC have greater capacity to swell only when hydration is rapid. Slow hydration of the higher viscosity grade MC in the outer component layer of the coated granules probably allows viscous forces to exhibit their adhesive action and thereby limit the swelling phenomenon. In contrast, the lower viscosity grades of MC have the tendency to hydrate and swell fast. Their presence on the outer component layer of the composite coat could have facilitated water penetration, hydration and subsequent swelling of the high viscosity grade MC in the underlying layer.

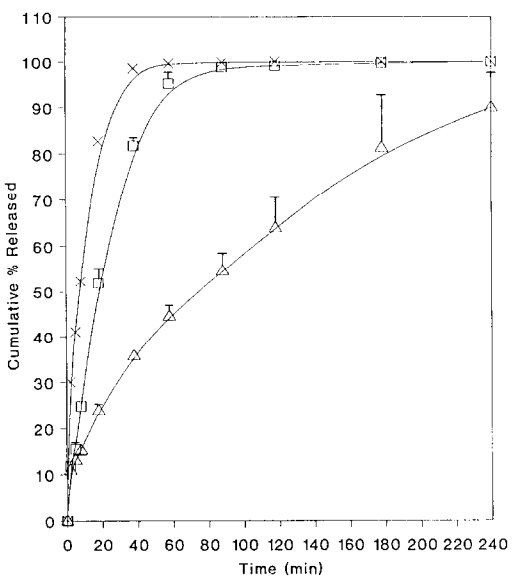

Fig. 1. Release of diphenhydramine·HCl from multilayer coated granules as a function of the order of deposition of the component layers; (□) HL11 (inner MC 350–550 cps, outer MC 13–15 cps); (△) LH11 (inner MC 13–15 cps, outer MC 350–550 cps); (×) diphenhydramine·HCl powder.

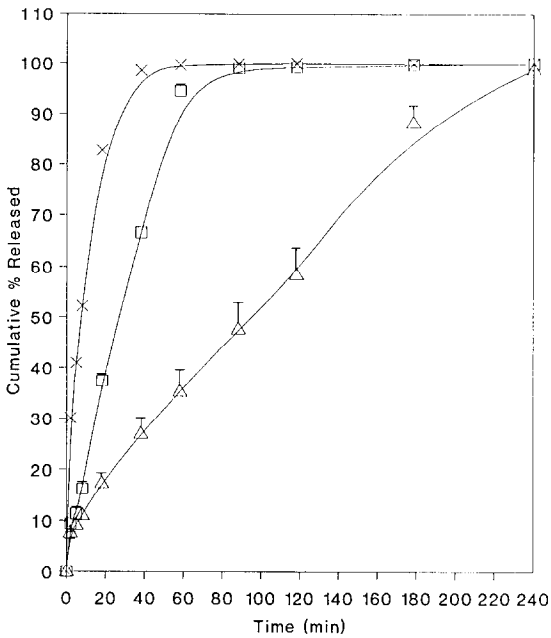

Fig. 2. Release of diphenhydramine·HCl from multilayer coated granules as a function of the order of deposition of the component layers; (□) HL22 (inner MC 80–120 cps, outer MC 20–30 cps); (△) LH22 (inner MC 20–30 cps, outer MC 80–120 cps); (×) diphenhydramine·HCl powder.

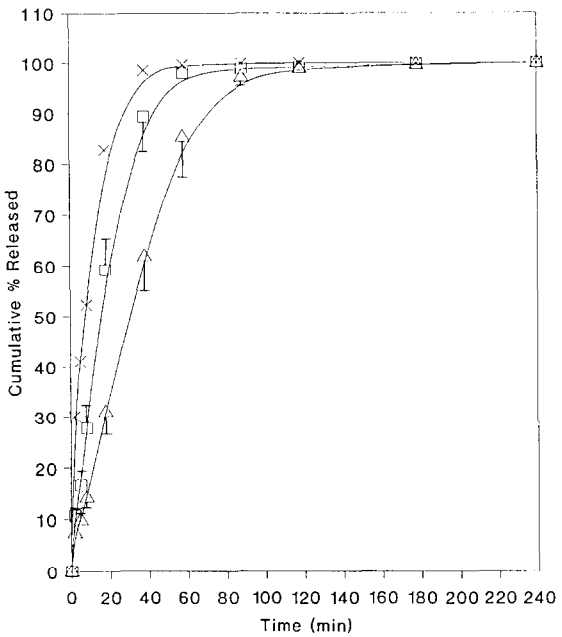

Fig. 3. Release of diphenhydramine·HCl from multilayer coated granules as a function of the order of deposition of the component layers; (□) HL44 (inner MC 800–1200 cps, outer MC 20–30 cps); (△) LH44 (inner MC 20–30 cps, outer MC 800–1200 cps); (×) diphenhydramine·HCl powder.

It has been well established that the diffusivity of a solute from a swollen polymer increases with the degree of swelling (Kim et al., 1980; Wood et al., 1982; Kojima et al., 1984). Thus, an increase in the diffusivity of diphenhydramine · HCl leading to comparatively higher release rates is observed in batches HL11, HL22 and HL44 in which the outer component layers of the coated granules are composed of the lower viscosity grade MC. In addition, dissolution of water-soluble polymers from polymer matrices may increase the rate of drug release (Donbrow and Friedman, 1975a). The more extensive erosion in the dissolution medium expected from the low viscosity grade gel in the outer layer may contribute further to the accelerated release observed in these batches.

It can be seen in Fig. 3 that the difference in the release rates between LH44 and HL44 whose component layers in the coat consist of MC 20–30 cps and MC 800–1200 cps is very much reduced compared with the other viscosity grade combinations (Figs 1 and 2). As has been discussed in an earlier report (Wan and Lai, 1991), one probable explanation is that the air entrapped in the porous lactose cores of the gelled granules during the fluidized-bed coating process imparts buoyancy to the final coated granules, resulting in a higher than expected release rate. A cross-sectional view of batch LH44 is shown in the scanning electron photomicrograph in Fig. 6. A number of air vacuoles could be seen in the outer region of the composite coat of the granule. It is postulated that air bubbles are continuously formed on the surfaces of the lactose granules during the coating process because of foam produced by spray atomization of the coating solutions (Savage, 1965). These bubbles are broken down rapidly during particle-to-particle collisions in the fluidized-bed. However, bubbles formed from spraying highly viscous coating solution being more stable and less readily collapsed would be entrapped in the dried coat as air vacuoles. While the exact nature of the interaction between the entrapped air vacuoles and drug release is not

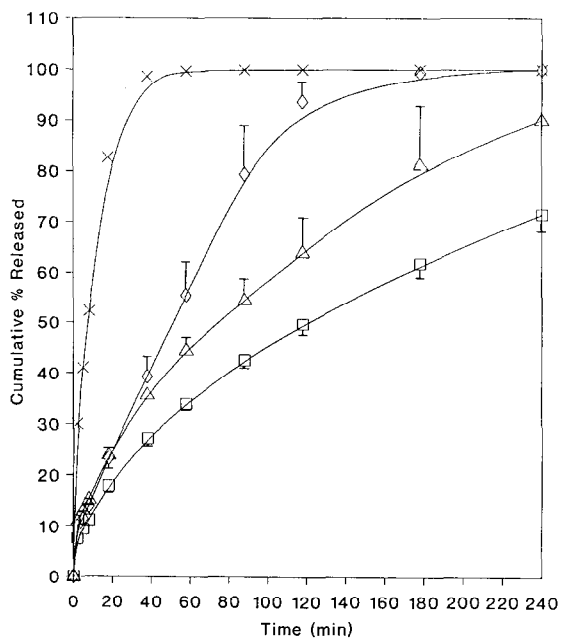

Fig. 4. Relationship between the mass ratio of the inner (MC 13–18 cps):outer (MC 350–550 cps) layers of the multilayer coated granules and their drug release rates; (◇) LH13 (1:3); (△) LH11 (1:1); (□) LH31 (3:1); (×) diphenhydramine·HCl.

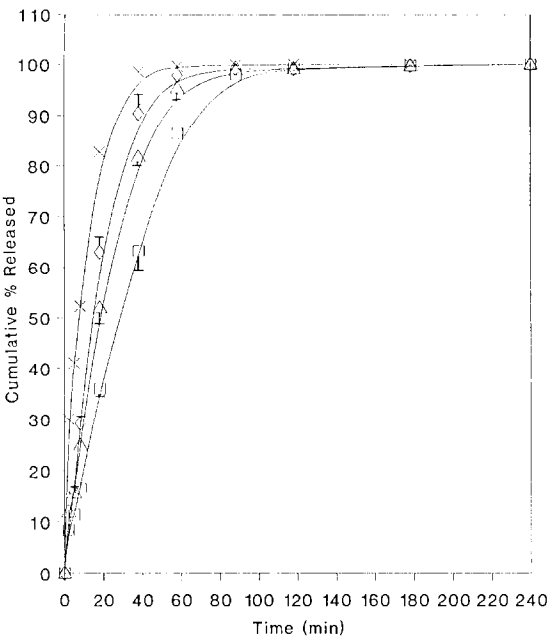

Fig. 5. Relationship between the mass ratio of the inner (MC 350–550 cps):outer (MC 13–18 cps) layers of the multilayer coated granules and their drug release rates; (◇) HL31 (3:1); (△) HL11 (1:1); (□) HL13 (1:3); (×) diphenhydramine·HCl.

immediately obvious, their presence would certainly contribute further to the buoyancy of the coated granules in the dissolution medium.

Effect of viscosity on recrystallization

Although diphenhydramine · HCl is soluble in the aqueous MC solution, the physical state of the drug in the applied coat when it is dried depends on the drug loading and the solubility of the drug in the polymer. Polymeric matrix systems have been classified as monolithic solutions or dispersions (Baker, 1987). The active ingredient is dissolved in the polymer in a monolithic solution while it is partly dissolved and partly dispersed in a monolithic dispersion. The diphenhydramine · HCl-MC films represented a monolithic dispersion as drug crystals are visible on scanning electron photomicrographs of the coated granules (Figs 7 and 8). The polymer matrix coat on the lactose granules can therefore be visualized as a heterogeneous system consisting of a continuous (polymer) phase with a discontinuous drug phase as precipitated drug particles dis-

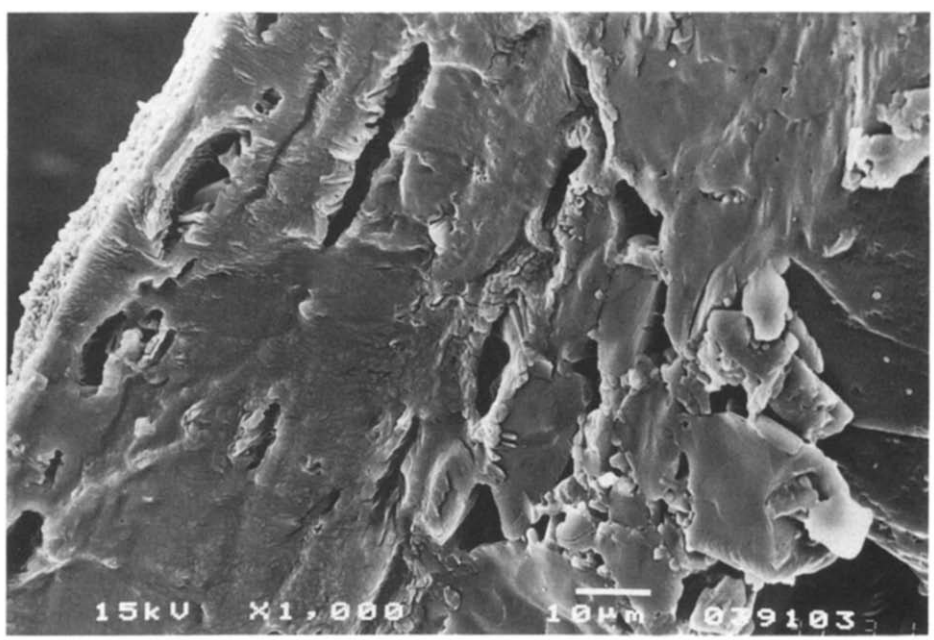

Fig. 6. Scanning electron photomicrograph of a sectioned multilayer coated granule from batch LH44 with MC 20–30 cps and MC 800–1200 cps as the inner and outer component layers, respectively, depicting the air vacuoles in the outer region of the coat.

persed throughout the matrix (Chandrasekaran and Hillman, 1980). Clearly, several of the properties of this heterogeneous system can influence the permeation of the drug, inter alia, the composition, shape, size and size distribution of the disperse phase, and interactions between the phases.

When the mass fraction of the MC 350–550 cps in the outer component layer was increased from 0.25 in batch LH31 to 0.5 in batch LH11

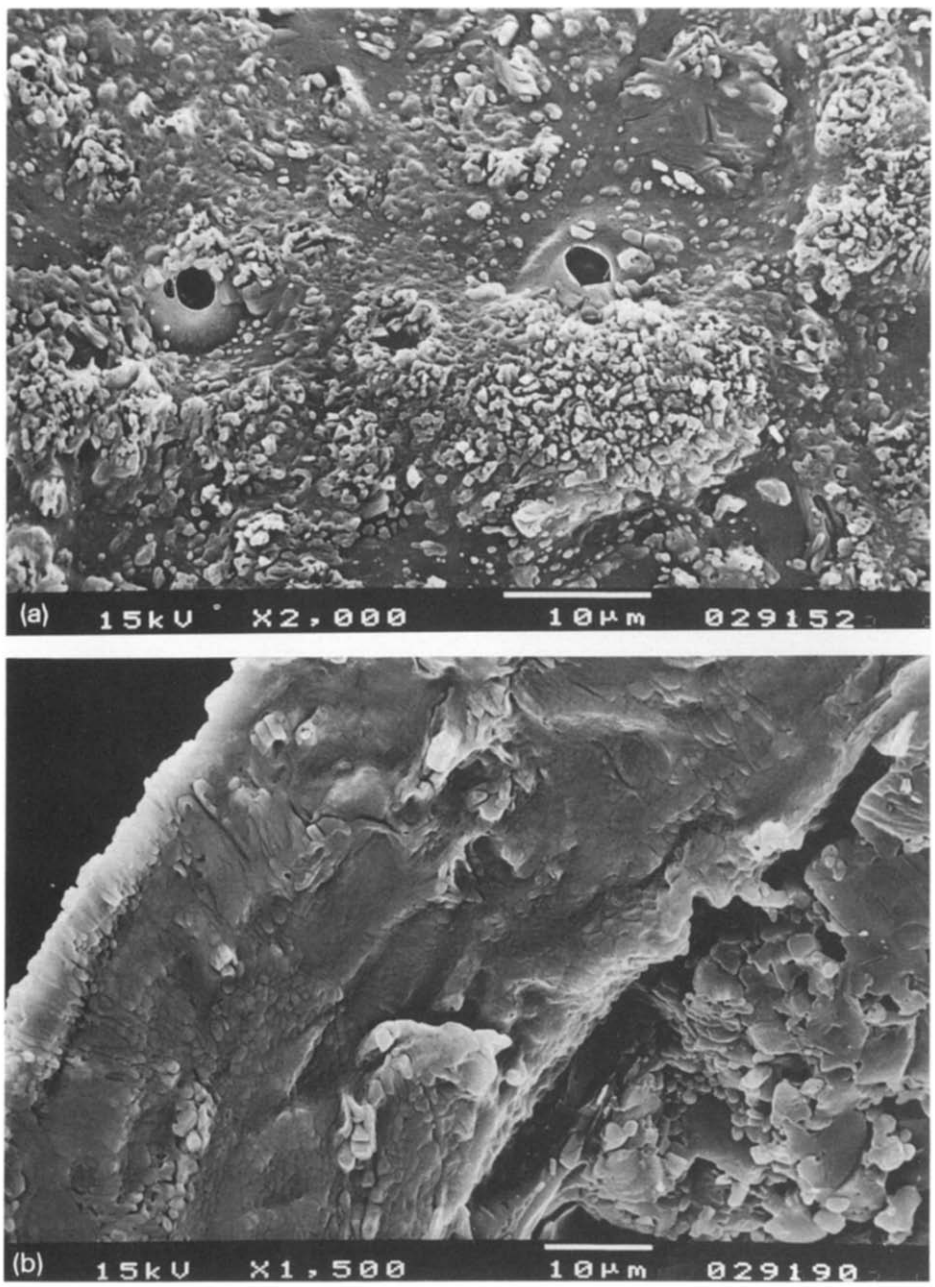

Fig. 7. Scanning electron photomicrographs showing (a) the surface morphology and (b) the cross-section of a lactose granule coated with diphenhydramine · HCl-MC 350–550 cps solution.

and then further to 0.75 in batch LH13 (Table 2), a progressive increase was observed in the overall release rate (Fig. 4). Since the opposite is normally expected, i.e., a decrease in release rate with increase in the viscosity of the hydrated gel, it must be inferred that the overall release rate

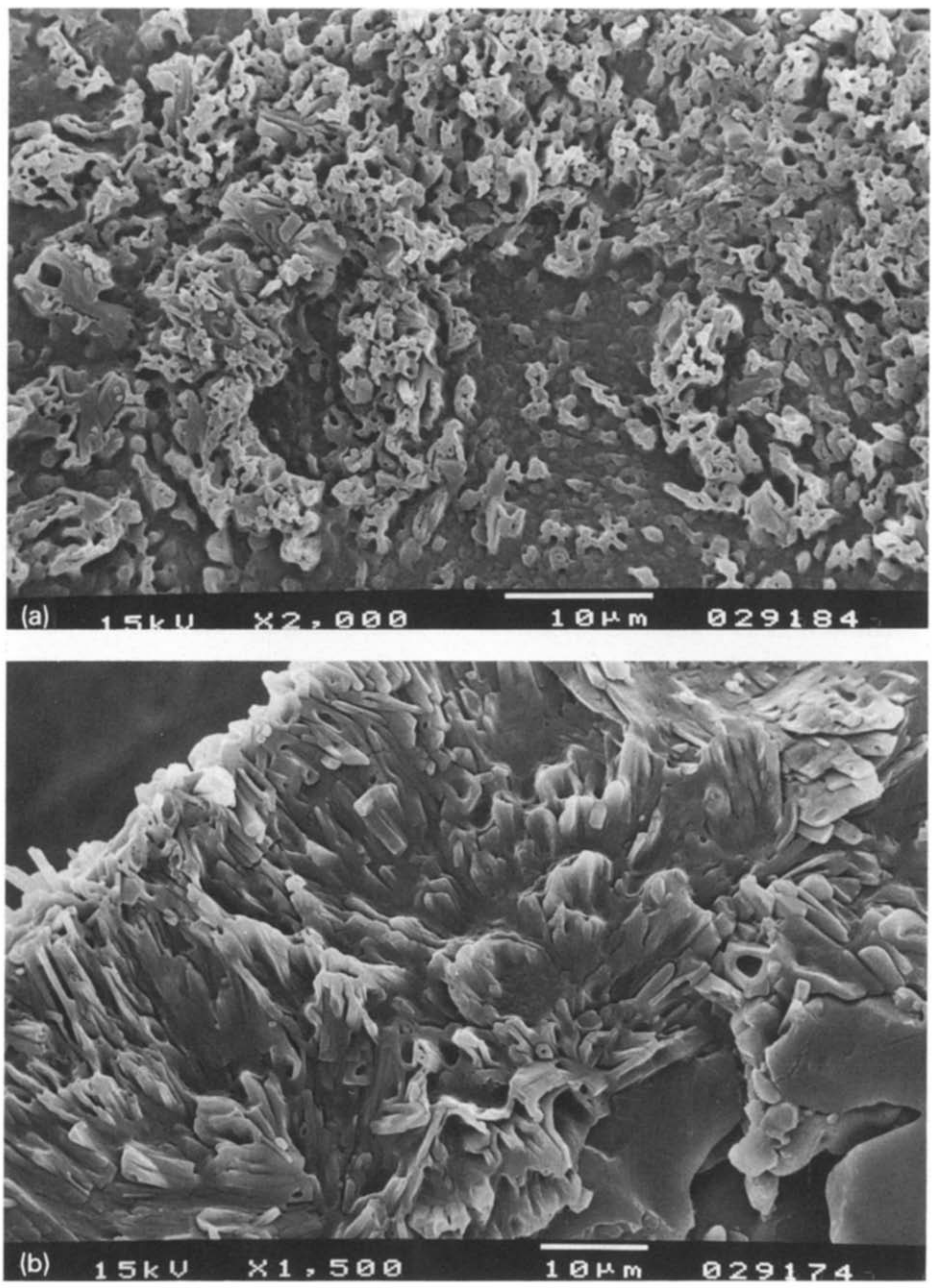

Fig. 8. Scanning electron photomicrographs showing (a) the surface morphology and (b) the cross-section of a lactose granule coated with diphenhydramine · HCl-MC 13–18 cps solution.

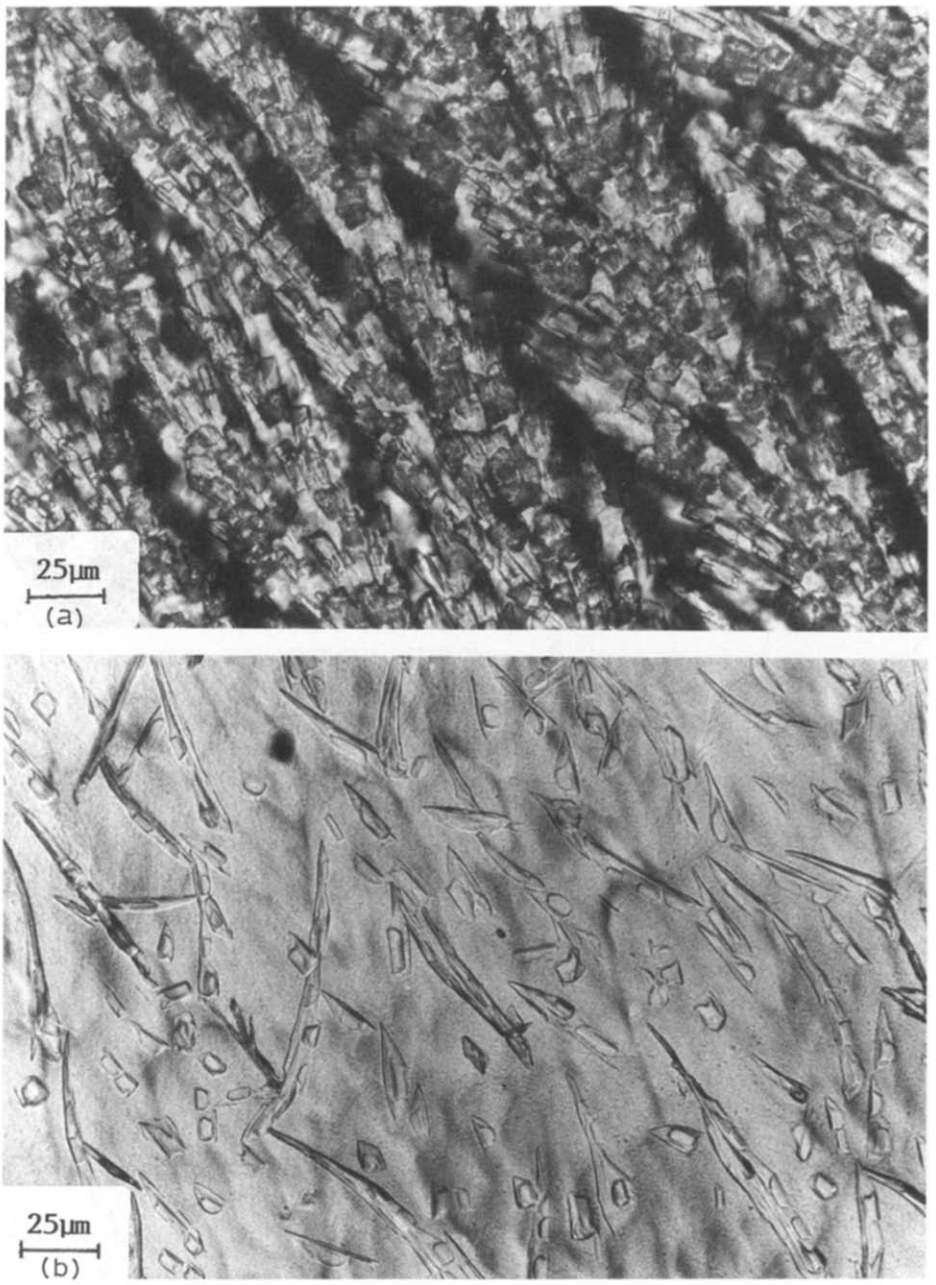

Fig. 9. Photomicrographs of cast films at 400 × magnification obtained from solutions of diphenhydramine · HCl dissolved in MC of different viscosity grades: (a) 13–18 cps and (b) 350–550 cps.

depends not only on the viscosity of the gel layer formed when the MC hydrates, but also on the size of the drug particles in the polymer matrix.

When the viscosity grade of the MC in the applied layer is increased, the crystallization of the drug is retarded due to the dampening of

TABLE 3

Parameters relating to diphenhydramine·HCl release from multilayer coated granules assuming first-order, square-root of time and zero-order equations ($n \geq 3$)

Batch No. [a]	Mass ratio of inner:outer layers [b]	First-order			Square-root of time			Zero-order		
		Rate constant (min^{-1})	Coefficient of determination (r^2)	Lag time (min)	Rate constant (% $min^{-1/2}$)	Coefficient of determination (r^2)	Lag time (min)	Rate constant (% min^{-1})	Coefficient of determination (r^2)	Lag time (min)
Inner, MC 350–550 cps; outer, MC 13–18 cps										
HL31	3:1	0.0661	0.9997	2.7	19.1237	0.9835	1.6	2.1893	0.9384	−5.4
HL11	1:1	0.0451	0.9945	0.8	15.6266	0.9828	1.0	1.9968	0.9793	−4.4
HL13	1:3	0.0345	0.9766	3.7	14.0797	0.9972	2.5	1.4192	0.9912	−4.7
Inner, MC 13–18 cps; outer, MC 350–550 cps										
LH13	1:3	0.0164	0.9644	0.3	8.6927	0.9643	1.0	0.8155	0.9997	−9.8
LH11	1:1	0.0090	0.9943	−8.5	5.8922	0.9973	0.0	0.3428	0.9485	−51.1
LH31	3:1	0.0048	0.9977	−24.4	4.7874	0.9999	0.3	0.2522	0.9592	−63.2

[a] Codes refer to the formulations listed in Table 2.

[b] Drug:polymer ratio in all layers is held constant at 3.75:1.

solute migration and the difficulty in nucleation of the drug in the viscous medium (Buckley, 1963; Fox et al., 1963; Chiou and Riegelman, 1969). This effect is compounded during the coating process whereby the viscosity of the atomized coating droplets increases rapidly as they travel through the coating zone due to evaporation of the solvent. It has been found that polyvinylpyrrolidone could inhibit the crystal growth of sulphathiazole in water, even at a very low concentration (Simonelli et al., 1970). A recent study suggested that ultrafine crystals of chlorpropamide were precipitated from povidone and polyethylene glycol solutions because of the difficulty of crystal growth in a highly viscous medium of the polymer (Abd El-Bary et al., 1990). It was also observed by Sjökvist and Nyström (1988) that, in solid dispersions prepared by a solvent method, the drug was present in particulate form. For these dispersions, increased drug content was associated with increased particle size and decreased dissolution rate. The faster dissolution rate of the drug crystals formed in high viscosity grade MC solutions probably reflects a significant reduction in the size of the crystals following recrystallization from the polymer solution. Taking into consideration the effect of viscosity on crystal size, it is conceivable that as the mass fraction of the MC 350–550 cps component layer is increased, a larger proportion of the total drug load should be precipitated as small size crystals. The increase in surface area associated with a reduction in particle size appears to be the major factor responsible for the progressive enhancement in the release rates in batches LH31, LH11 and LH13 (Fig. 4). The opposite occurred in batches HL31, HL11 and HL13 (Table 2) where the outer component layer consists of MC 13–18 cps. The release rate in this case varied inversely with the mass fraction of the low viscosity MC in the outer component layer (Fig. 5).

The influence of viscosity of the MC on the crystal size of the drug can evidently be observed from the scanning electron microscopy analysis. Scanning electron photomicrographs show appreciable differences between the surface morphology as well as the cross-sections of the granules coated separately with MC 350–550 cps (Fig. 7) and MC 13–18 cps (Fig. 8) solutions containing diphenhydramine · HCl. In contrast to the granules coated with MC 350–550 cps, which exhibited a relatively smooth appearance in both the surface and cross-sectional views (Fig. 7), large drug crystals are seen embedded in or attached to the surface and cross-section of the granules layered with MC 13–18 cps (Fig. 8). The deductions from the scanning electron microscopy examinations are further supported by the results obtained from the corresponding cast films observed under the optical microscope. Distinct differences in crystal size of the drug could be noted between the MC 13–18 cps and MC 800–1200 cps films (Fig. 9).

Evaluation of the release kinetics

To analyse the mechanism of release of diphenhydramine · HCl from the multilayer

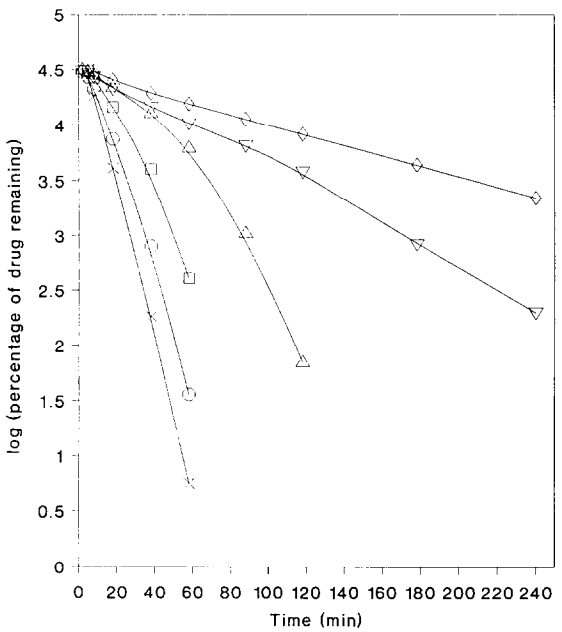

Fig. 10. Apparent first-order diphenhydramine·HCl release profiles of multilayer coated granules in the MC 13–18 cps/MC 350–550 cps combination system; (×) HL31 (inner MC 350–550 cps:outer MC 13–18 cps, 3:1); (○) HL11 (inner MC 350–550 cps:outer MC 13–18 cps, 1:1); (□) HL13 (inner MC 350–550 cps:outer MC 13–18 cps, 1:3); (△) LH13 (inner MC 13–18 cps:outer MC 350–550 cps, 1:3), (▽) LH11 (inner MC 13–18 cps:outer MC 350–550 cps, 1:1), (◇) LH31 (inner MC 13–18 cps:outer MC 350–550 cps, 3:1).

coated granules, the experimental data obtained for the MC 13–18/350–550 cps combination system are fitted to three commonly used models, namely, the first-order, zero-order and square-root of time equations (Higuchi's model). The values of the apparent release rate constants (k), lag time and coefficients of determination (r^2), following linear regression of the dissolution data from about 10 to 90% of the amount of drug released, are given in Table 3. Comparison of the r^2 values, lag times and the plots of the experimental data (Figs 10–12) showed that no single equation model tested could describe the release kinetics of all the various batches of coated granules. Although drug release from non-disintegrating polymer matrices generally follows a square-root of time relationship (Higuchi, 1963), the partial fit to two different kinetic models in batches such as HL13 and LH11 suggested that diphenhydramine · HCl release from the multilayer coated granules is likely to be due to the simultaneous operation of more than one release mechanism. This could have resulted from significant changes in the transport characteristics in the swollen matrices due to alteration of the structure and porosity of these hydrated matrices as dissolution and depletion of the embedded drug particles occur (Bhatia, 1986). The local drug concentration was found to affect the release kinetics and swelling behaviour of a drug-loaded hydrogel matrix (Lee, 1983) while deviations from the square-root of time dependence have also been reported in release studies carried out using cast hydrophilic polymer matrices (Korsmeyer and Peppas, 1981). Nevertheless, it could be demonstrated that apparent time-inde-

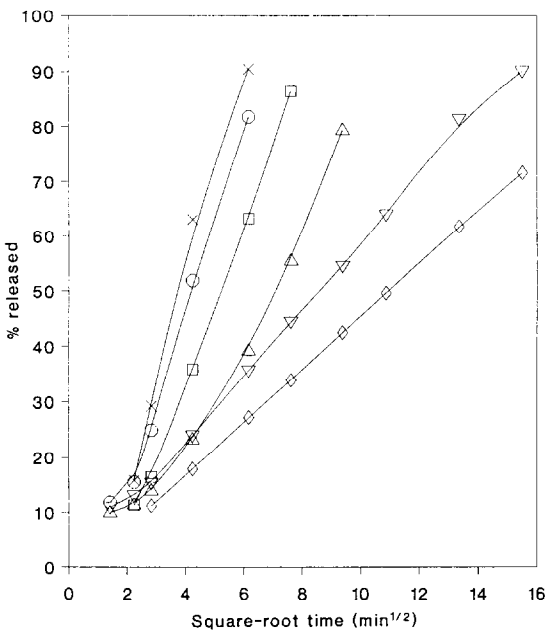

Fig. 11. Comparison of the square-root of time model to the release of diphenhydramine·HCl from multilayer coated granules in the MC 13–18 cps/MC 350–550 cps combination system; (×) HL31 (inner MC 350–550 cps:outer MC 13–18 cps, 3:1); (○) HL11 (inner MC 350–550 cps:outer MC 13–18 cps, 1:1); (□) HL13 (inner MC 350–550 cps:outer MC 13–18 cps, 1:3); (△) LH13 (inner MC 13–18 cps:outer MC 350–550 cps, 1:3), (▽) LH11 (inner MC 13–18 cps:outer MC 350–550 cps, 1:1), (◇) LH31 (inner MC 13–18 cps:outer MC 350–550 cps, 3:1).

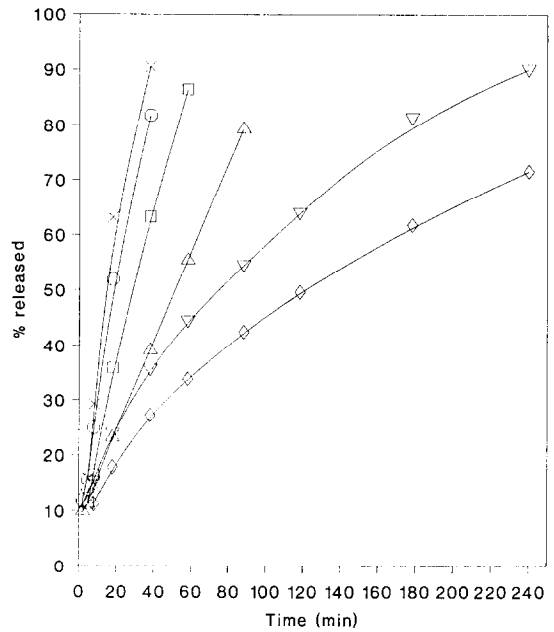

Fig. 12. Release profiles of multilayer coated granules in the MC 13–18 cps/MC 350–550 cps combination system assuming zero-order equation; (×) HL31 (inner MC 350–550 cps:outer MC 13–18 cps, 3:1); (○) HL11 (inner MC 350–550 cps:outer MC 13–18 cps, 1:1); (□) HL13 (inner MC 350–550 cps:outer MC 13–18 cps, 1:3); (△) LH13 (inner MC 13–18 cps:outer MC 350–550 cps, 1:3), (▽) LH11 (inner MC 13–18 cps:outer MC 350–550 cps, 1:1), (◇) LH31 (inner MC 13–18 cps:outer MC 350–550 cps, 3:1).

pendent release was attainable in batch LH13 (Table 3 and Fig. 12) for much of the release profile by a judicious choice of the combination of the viscosity grades and their proportion in the multilayer matrix coat.

The results obtained suggest that drug release from drug-dispersed hydrophilic matrix film is affected by many other rate-determining factors besides drug diffusion. These may include penetration of the aqueous solvent, swelling of the matrix, dissolution of the drug and polymers and relaxation of the polymeric chains. The relative contribution of each of these factors to the overall release process is difficult to assess and apparently varies with the composition of the multilayer polymeric coat on the lactose granules. It should be anticipated that different systems in which the water solubility of the polymer and the drug may be altered will provide additional information to further clarify the mechanism of drug release.

Conclusion

The multilayer matrix system under study is formulated from a combination of the different viscosity grades of MC as drug-containing component layers deposited onto the same lactose granule. The ability of the multilayer coated granules to release the drug at controlled rates over a delayed period appears to offer unique therapeutic and investigational possibilities, especially when the drug release profiles are also dependent on the permutation of the component layers in the granule coat. This phenomenon reveals the concept of utilizing non-uniform initial viscosity distribution as a means to modify drug release in the design of drug delivery systems. The simplicity of the approach arises from the use of just a single type of polymer in the system and the rapid, efficient and reproducible production of the coated granules in a fluidized bed. While this report deals only with the diphenhydramine · HCl-MC system, the underlying principles are believed to be sufficiently general to be extrapolated to other water-soluble drug-polymer systems.

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