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The influence of the particle size of hydroxypropylmethylcellulose K15M on its hydration and performance in matrix tablets

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Summary

The dissolution rate of propranolol hydrochloride from matrices containing different sized fractions of hydroxypropylmethylcellulose K15M has been examined. Generally, the release rate decreased as the particle size of hydroxypropylmethylcellulose was reduced from > 355 μm to 150–210 μm. Further reduction in size caused no further decrease in dissolution rate. Burst release of propranolol occurred at the extremes of large particle size and low matrix contents of hydroxypropylmethylcellulose K15M. Measurements of surface area by nitrogen adsorption indicated that all the sieve fractions of hydroxypropylmethylcellulose were poorly porous. Water uptake studies, measured by differential scanning calorimetry, suggested that initially the larger sized fraction of hydroxypropylmethylcellulose imbibed water faster than the smaller sized fraction.

Introduction

Although a variety of drugs may be directly compressed with hydroxypropylmethylcellulose (HPMC) and various excipients to provide matrices which provide a sustained release of drugs (Alderman, 1984), the release may be further modified by the inclusion of surfactants (Ford et al., 1991), excipients such as lactose or calcium phosphate (Ford et al., 1987) or the inclusion of other polymers such as sodium carboxymethylcellulose (Bonferoni et al., 1992) or ethylcellulose (Feely and Davies, 1988).

Further modifications of release may be accomplished by variation in the drug: HPMC ratio (Ford et al., 1985a). Even the particle size of the drug may modulate release. Salomon et al. (1979) reported that differences in drug particle size had no effect on release rate when two contrasting particle sizes of potassium chloride crystals (63–100 and 315–400 μm) were used in HPMC matrices. Similarly, Ford et al. (1985a) reported that release rates of promethazine hydrochloride from HPMC matrices were unaffected by drug particle size, except in the extreme case where the polymer to drug ratio was low and particle size was high. Ford et al. (1985a,b) claimed that drug particle size only had a significant effect on the

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release rate at low levels of HPMC. Matrices containing 160 mg propranolol hydrochloride and only 57 mg HPMC K15M gave release rates of 8.0 and 28.3 mg $min^{-1/2}$ as the drug particle size increased from 180–250 to 250–500 μm, respectively, but were unchanged from tablets containing 285 mg HPMC K15M and similar particle size ranges of propranolol hydrochloride (Ford et al., 1985b). Similar results were noted with promethazine hydrochloride (Ford et al., 1985a).

The effects of particle size of HPMC are less understood. Coarse fractions of HPMC are thought to hydrate too slowly to allow sustained release (Alderman, 1984). Matrices prepared with coarse particle sizes disintegrated before complete hydration of the external layers occurred. The production of the external gel layer maintains the integrity of the matrix and protects the drug in the inner part of the matrix from dissolution. Small size fractions of HPMC allowed uniform hydration into the matrix, thereby effectively retarding release (Alderman, 1984).

This paper examines the importance of particle size of HPMC K15M on its hydration rates and the dissolution of a model drug, propranolol hydrochloride from its matrices. An earlier paper (Mitchell et al., 1993) detailed the experimental methods using thermal analysis to determine the water uptake. Brunauer-Emmett-Teller (BET) surface area determinations were performed on fractions of differing particle size in an attempt to find any differences in porosity of the various sized fractions.

Materials and Methods

Hydroxypropylmethylcellulose K15M (Methocel K15M, Dow Chemicals, U.S.A.) was used. Five particle size fractions, < 75, 75–150, 150–210, 210–355 and > 355 μm, were produced by sieving. Propranolol hydrochloride was BP standard and magnesium stearate (British Drug Houses) was analar reagent.

Tableting

Tablets, 7.94 mm, shallow concave, were made from each of the five sieve fractions of HPMC and unsieved HPMC (as supplied) by direct compression, using a Manesty F3 tableting machine. Tablets contained 160 mg propranolol hydrochloride, 57, 95, 140 or 285 mg HPMC K15M and 0.75% magnesium stearate as lubricant. All tablets were compressed to a hardness of 140 N, as determined by a Schleuniger Hardness Tester, except those containing the > 355 μm fraction of HPMC K15M which were difficult to compress. The latter were therefore compressed to as high a crushing strength as possible.

Dissolution testing

Dissolution was studied using a Copley Series 8000 automatic dissolution tester into 1 l of distilled water, using the British Pharmacopoeia 1988 method 1 and monitoring propranolol at 288 nm. All dissolution data were treated as amount dissolved against square root time to determine dissolution rates by linear regression. The means of six determinations are given.

Differential scanning calorimetry

The method of Mitchell et al. (1993) was used. Approx. 10 mg samples, accurately weighed of the < 75 and > 353 μm fractions of HPMC K15M were compressed into wafers, 6.35 mm in diameter and placed into aluminium DSC sample pans into which had been placed approx. 10 mg double distilled water, accurately weighed. Samples were held at room temperature for 0.5, 1, 3, 5, 10, 15, 30 or 60 min prior to analysis. After storage for the prescribed times, the pans and their contents were placed into the sample compartment of a Perkin Elmer DSC 7 Differential Scanning Calorimeter which had previously been cooled to -30°C to promote instant freezing of any unbound water. The samples were heated at 10°C min^{-1} to 20°C and the enthalpy of fusion of ice determined. This was used to determine the quantity of water which had not been bound into the HPMC. Each experiment was duplicated. The quantity of bound water was calculated from the differences between the water weighed into the pan and the weight equivalent to the enthalpy of fusion and representative of unbound water.

Surface area determination

The samples of five sieve fractions of HPMC were degassed on a Quantector (Quantachrome Corp., New York) for 24 h at a temperature of 70°C using helium as a purge gas. The degassed samples were then transferred to a Quantasorb (Quantachrome Corp., New York) where a mixture of nitrogen and helium at a relative pressure of 0.3 was allowed to flow over the powder for 1 h to equilibrate. The sample was cooled using liquid nitrogen, the potentiometer zeroed, and the sample then allowed to heat up to room temperature and the reading on the potentiometer noted. Using nitrogen as the calibration gas, a measured amount was injected into the Quantasorb which gave a reading to $\pm 10\%$ of the reading obtained for the sample tested. Assuming a linear relationship between volume of gas injected and potentiometer readings, the volume of nitrogen required to cover the surface area of powder was calculated. The cross-sectional area of N_2 was taken as 16.2×10^{-20} m^2.

Results and Discussion

It was impossible to compress the coarse (> 355 μm) fraction above a crushing strength of 35 N. The reason for this was unclear but is thought to be because HPMC is elastic and hence poorly compressible. These matrices were therefore compressed as hard as possible. The differences in crushing strengths were considered to be acceptable, since differences in compression force have been shown to little affect dissolution rates from HPMC matrices (Ford et al., 1985a). All dissolution data, plotted as amount dissolved against square root of time, produced straight line plots between 5 and 70% propranolol released. Table 1 gives the dissolution rates.

At low HPMC contents, the coarse (210– < 35 and > 355 μm) fractions gave faster propranolol dissolution rates than the sieved powder, but the matrices containing HPMC K15M below 210 μm in size gave similar dissolution rates to the matrices containing unsieved HPMC K15M. As the HPMC K15M content increased, the effect of particle size became less important and at high

TABLE 1

Effect of particle size of hydroxypropylmethylcellulose K15M (HPMC K15M) on the dissolution rates (% $min^{-1/2}$) from tablets containing 160 mg propranolol hydrochloride and 57, 95, 140 or 285 mg HPMC K15M

Content of HPMC K15M (mg)	Particle size of HPMC (μm)					
	Unsieved	< 355	210–355	150–210	75–150	< 75
57	8.07	44.72	10.91	7.77	7.69	8.49
95	6.86	56.70	6.47	6.74	6.56	6.57
140	6.02	35.20	5.66	6.04	5.76	5.67
285	4.44	3.90	4.19	4.16	4.05	4.09

(285 mg) HPMC K15M contents even the coarser fractions showed comparable dissolution rates to the fine fraction. Alderman (1984) reported rapid dissolution of riboflavin from matrices prepared with sieve fractions of HPMC K4M in excess of 150 μm. In contrast, generally only the fraction > 355 μm showed significant increases in dissolution. However, at low HPMC K15M (57 mg) content the 210–355 μm particle size fraction also showed a slight increase in propranolol dissolution rate.

The differences between the results reported here and those of Alderman (1984) may be accounted for by the use of adjuncts and low HPMC content in the matrices (85% lactose, 10% Methocel K4M, 5% riboflavin) described in the earlier study. From the results presented here, the particle size of HPMC plays an important role in controlling release rates from matrices of low HPMC content only.

Alderman (1984) also reported that coarser granules hydrated more slowly than fine granules and caused the matrices to disintegrate. This theory was examined using a DSC method for determining the amount of water taken up by the polymer (Mitchell et al., 1993). It is obvious that, contrary to hydrating slowly, the coarser particles bound water slightly faster than the finer particles (Fig. 1). After 60 min, however, the two samples imbibed the same quantity of water. However, the first few minutes of hydration are the most important, since that corresponds to the period when the protective gel coat is formed around matrices containing HPMC. After 1 min,

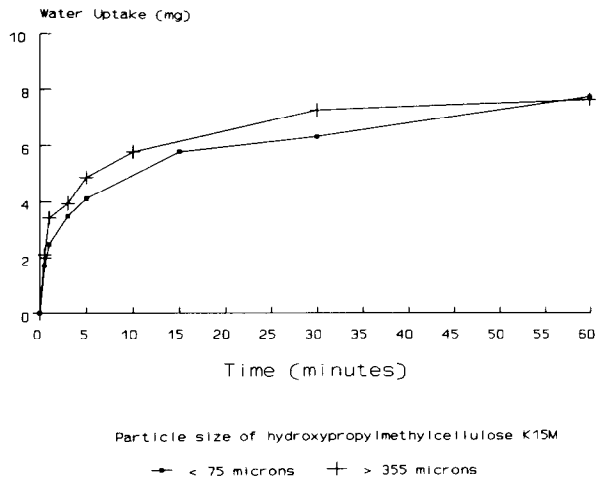

Fig. 1. The influence of particle size of hydroxypropylmethylcellulose on the water uptake into 10 mg, 6.35 mm wafers of hydroxypropylmethylcellulose as measured by differential scanning calorimetry.

the coarse particles absorbed nearly 40% more water than the fine particles which was contrary to the theory proposed by Alderman (1984).

Since, overall the two sieve fractions hydrated to similar extents, it was decided to determine the effect of particle size on the surface area of the HPMC samples. The surface areas of the various particle size fractions were low and indicated that the particles were relatively non-porous. Table 2 gives the values obtained. The surface area increased as the particle size decreased; the fine fraction (< 75 μm) had a surface area almost 3 times the size of the coarse fraction (> 355 μm).

TABLE 2

The surface area of the sieve fractions of hydroxypropylmethylcellulose determined by nitrogen adsorption using the Quantasorb

Sieve fraction (μm)	Surface area ($m^2\ g^{-1}$) ($\pm$SD)
< 75	1.091 ± 0.019
75–150	0.737 ± 0.008
150–210	0.543 ± 0.002
210–355	0.555 ± 0.005
> 355	0.382 ± 0.012

It is postulated that the increased dissolution rates were due to the relative lack of HPMC K15M in the matrix and not its particle size as reported by Alderman (1984). Burst release only occurred at low HPMC K15M contents ($< 50\%$). At such low quantities there are likely to be 'areas' at the surface of the tablet where there is an absence of HPMC. The finer material, which has approx. 3 times the surface area of the largest fractions, will spread further over the surface of the matrix and reduce the size of these HPMC free areas. Water would enter into the inner layers of the matrix through these areas and would hydrate the inner layers. Since the protective gel coat takes a finite time to form, water would continue to enter into the inner layers of the matrix before the gel coat is completely formed. The pressure caused by the inner layers hydrating would result in 'pores' within the matrix which would eventually disintegrate if the gel layer had not completely formed. If there was a sufficient quantity of the small HPMC K15M particle size in the matrix there would be fewer pores and a protective coat could form without water penetrating too far into the matrix. The surface areas of the HPMC samples were so low that they were unlikely to be porous and thus have low levels of intraparticulate pores. Penetration of water into the compacted matrix would be likely to occur through the interparticulate spaces with the resultant hydration holding the particles together. Faster dissolution from the larger size fraction of HPMC would be due to the size of these interparticulate pores. The water uptake studies implied that the larger sized fractions imbibed water at a faster rate, initially, than the smaller sized fractions. It must be presumed, therefore, that water penetrates into the centre of tablets at a faster rate for the tablets containing larger sized fractions of HPMC and that this ultimately results in burst release of the drug.

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