International Journal of Pharmaceutics, 100 (1993) 143–154

IJP 03290

The influence of substitution type on the performance of methylcellulose and hydroxypropylmethycellulose in gels and matrices

K. Mitchell [a], J.L. Ford [a], D.J. Armstrong [a], P.N.C. Elliott [a], J.E. Hogan [b] and C. Rostron [a]

[a] *Drug Targeting Research Group, School of Pharmacy, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF (UK) and* [b] *Colorcon Ltd, St. Paul's Cray, Orpington (UK)*

(Received 17 February 1993)
(Accepted 16 April 1993)

Key words: Methylcellulose; Hydroxypropylmethylcellulose; Methocel; Substitution type; DSC; Thermomechanical analysis; Gel; Matrix tablet; Swelling; Polymer hydration

Summary

The characteristics of matrices containing hydroxypropylmethylcellulose (HPMC) grades E4M, F4M or K4M, or methylcellulose A4M have been compared using thermomechanical analysis, differential scanning calorimetry (DSC), laser analysis, cloud points and via the dissolution of a model drug, propranolol hydrochloride, from matrices containing the cellulose ethers and prepared by direct compression. Dissolution rates of propranolol varied according to the drug/cellulose ether ratio within the matrix. Propranolol release from methylcellulose matrices was least affected by this ratio but the performance differences of the three grades of HPMC could not be distinguished. In the absence of drug, matrices containing methylcellulose disintegrated at 37 and 44°C. Water uptakes, as measured by DSC and gel layer thicknesses, were similar for each grade of cellulose ether. Matrices containing HPMC K4M tended to swell to the greatest extent. For all grades, swelling was greater in the axial rather than radial direction. Cloud points provided the best prediction of matrix performance.

Introduction

The ability of hydroxypropylmethylcellulose (HPMC) to form the basis of matrices which provide the extended release of both poorly soluble and freely water soluble drugs is now unequivocal (Alderman, 1984). The release characteristics of drugs from HPMC matrices have been well characterised. These include the influences of the viscosity grade of HPMC (Ford et al., 1985b–d, 1987), temperature (Mitchell et al., 1990b; Ford et al., 1991a), included surfactants (Ford et al., 1991b) or diluents (Ford et al., 1987), drug solubility (Ford et al., 1985d, 1987), pH and composition of dissolution fluids (Ford et al., 1985a; Mitchell et al., 1990a) and HPMC/drug ratio (Ford et al., 1985b–1985d, 1987).

There is uniform acceptance that the retardation of drug release is brought about by the production of a gel layer around the matrix when it is placed in contact with aqueous fluids (Alderman, 1984). On initial contact with water the

Correspondence to: J.L. Ford, Drug Targeting Research Group, School of Pharmacy, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, U.K.

HPMC starts to swell and the tablet thickness increases. Soon after this the polymer begins to dissolve in the solvent due to chain disentanglement leading to a slow erosion of the gel. The release of water soluble drugs is controlled by diffusion of the drug through the gel and that of insoluble drugs is controlled by erosion of the gel exposing fresh surfaces containing undissolved drug.

Since diffusion plays such a prominent role in controlling drug release, the release kinetics are ever changing because of the changing diffusional path length. Indeed, the release kinetics follow the kinetics of swelling (Colombo et al., 1990). Consequently, a non-static phenomenon is developed which has proved to be very difficult to study. Melia et al. (1990) have used cryogenic scanning electron microscopy to picture the gel network at the surface of the tablet. Thermal analysis has been frequently used to examine the water content and distribution in hydrophilic polymers. Provisional findings into the use of thermal analysis in characterising the hydration of HPMC gels (Mitchell et al., 1989), the uptake of water into different substitution types of HPMC (Mitchell et al., 1990c) and the use of thermomechanical analysis to account for the swelling of HPMC matrices (Mitchell et al., 1991) have been recently described.

This paper attempts to rationalise the role that the substitution type of cellulose ethers play on the properties of matrices containing methylcellulose or HPMC. Thus, thermal analysis, both thermomechanical analysis and DSC, is used to evaluate the swelling of, and uptake of water into, matrices. The influence of the substitution type on drug release is followed using a model drug, propranolol hydrochloride.

Materials and Methods

Methocel A4M, Methocel E4M, Methocel F4M and Methocel K4M, each manufactured by Dow Chemicals, U.S.A. and equivalent to USP types methylcellulose, hydroxypropylmethylcelullose (HPMC) 2910, HPMC 2906 and HPMC 2208, were used throughout the study as supplied. Propranolol hydrochloride B.P. and magnesium stearate (Analar grade, British Drug Houses) were used as supplied.

DSC

Approx. 10 mg samples, accurately weighed, for each of the cellulose ethers, were compressed into wafers, 6.35 mm in diameter. For testing, the wafers were placed into aluminium sample pans into which had been accurately weighed approx. 10 mg quantities of double distilled water. 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. Empty aluminium sample pans were used as reference. Each sample was 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 then calculated from the differences between the water weighed into the pan and the amount of unbound water equivalent to the enthalpy of fusion.

Thermomechanical analysis

Approx. 25 mg samples of each of the Methocels were compressed into tablets, 3 mm flat faced, using a Manesty SP single punch tableting machine. Tablets contained the pure Methocels only and no lubricant. The sample arrangement used for testing is illustrated in Fig. 1. Each matrix tablet under test was placed in a 100 ml glass beaker in a water bath maintained at 24, 37 or 45°C for up to 100 min. The expansion probe was placed on top of the tablet and water was introduced into the beaker at the relevant temperature. Both the axial and radial dimensions of the tablets were measured to ± 0.001 cm using a Perkin Elmer Series 7 Thermal Mechanical Analyser (in expansion mode) controlled by a Perkin Elmer TAC 7 and calibrated using a five point calibration. Tests were carried out in duplicate.

Gel layer thickness

Tablets, 12.7 mm flat faced and containing approx. 400 mg HPMC K4M, E4M or F4M, were compressed using a Manesty F3 single punch tableting machine. Using a similar arrangement to Fig. 1, the thickness of the gel layer in the tablets was measured to ± 0.001 cm using the Perkin Elmer Thermal Mechanical Analyser in penetration mode and a specially modified probe (1 mm wide, with point 1.5 cm long). Distilled water, at 37°C, was introduced and maintained at this temperature throughout the test. At 1 h intervals, the size of the gel layer was measured by allowing the probe to sink into the gel with a force of 1000 mN. When a steady state reading was obtained the probe was lifted to the outer layer of the gel and then allowed to sink into the gel again. The reading was repeated four times and the mean determined.

Laser measurements

Tablets, approx. 200 mg and containing HPMC E4M, F4M or K4M or methylcellulose A4M, were compressed using a Manesty F3 single punch tableting machine and 10 mm flat face punches. For testing, one tablet was mounted on a drawing pin and placed in a glass container. A laser (Spectra-Physics, He-Ne laser) was mounted on a vernier microscope (The Precise Tool and Instruments Co., Ltd, Thornton Heath, Surrey). Measurements were taken by guiding the laser from

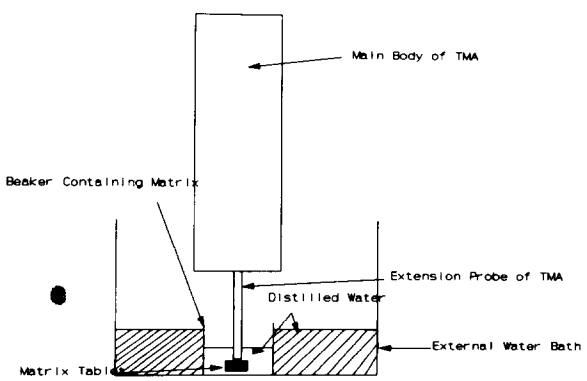

Fig. 1. The thermal mechanical analyzer as used to measure the rate and extent of swelling of cellulose ether matrix tablets.

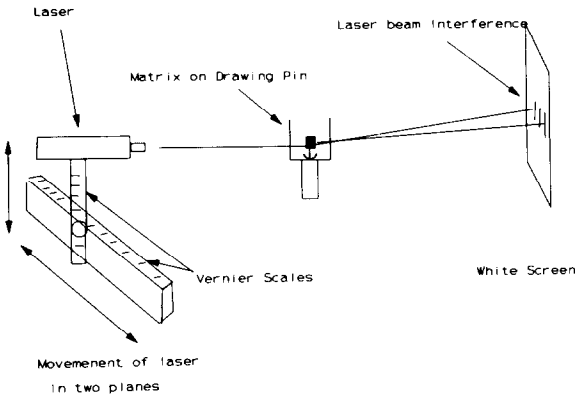

Fig. 2. Use of laser to measure the outer radius of the hydrating gel of a matrix tablet.

one side of the tablet to the other and from the top of the tablet to the bottom. When a clear, uninterrupted beam of light was detected on a sheet of white paper positioned 45 cm behind the tablet, a reading was taken on the vernier. When the laser beam passed through the outer limits of the gel layer interference could be seen on the screen. The edges of the gel layer were easily distinguished by the interface patterns produced by the laser passing through the gel. If the path of the laser was clear a sharp, bright circular image was seen on the screen. If the laser passed through the gel layer, Young's interference bands were apparent. Using this method, volume changes in the matrix tablets were measured accurately without disturbing the swelling matrix. The experimental set up is shown in Fig. 2. Water was then introduced at a temperature of 37°C which was maintained throughout the test by means of an external waterbath. The container was removed from the water bath for short periods of time and placed in the light beam during measurement. Readings were taken hourly for 6 h. The results presented are the means of two tablets for each grade of Methocel.

Cloud points

Gels were prepared containing 0.5, 1, 1.5 or 2% w/v methycellulose A4M or HPMC K4M, HPMC E4M or HPMC F4M, by heating one third of the required amount of freshly distilled

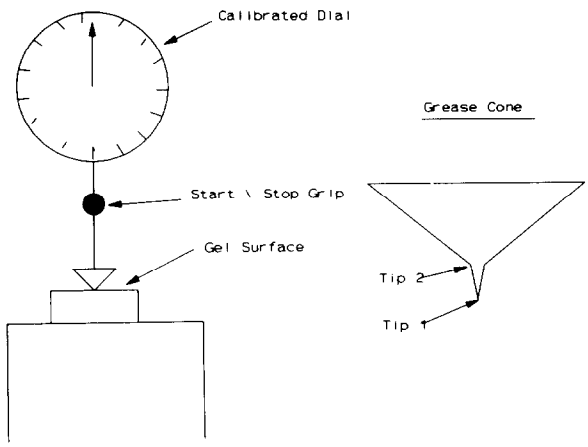

Fig. 3. Illustration of the penetrometer and the grease cone used to measure gel strength.

water to 80°C and then adding the required amount of cellulose ether and dispersing it. Cold water was added to make the gels up to the weight. 24 h old gels were tested.

Gel strengths

The apparatus consisted of a cone of known weight and tip angle. The cone was allowed to penetrate the gel, under its own weight, for a known period of time. The depth of penetration was measured and from these results the yield values of the test material were calculated. A grease cone was used, which is a double cone with one tip with a 30° angle which increases after 15 mm to an angle of 90°. This cone weighed 81.2 g and gels had to be used which could withstand this weight. Fig. 3 shows the apparatus used and illustrates the double tipped grease cone used in this study.

Approx. 150 g of 6% w/w gels (A4M, E4M, F4M, K4M) were prepared in the penetration cups to avoid disturbing the gels or introducing air bubbles when transferring the gels. They were prepared by the method outlined under *Cloud points* and then placed in a refrigerator overnight. Gels containing 2–5% w/w HPMC were tested but were too easily penetrated. Before testing, the gel surface was levelled with a sharp knife so it was at a 90° angle to the cone. The cone penetrometer (Hutchingsons) was calibrated in 0.1 mm. The cone was held in place at the surface of the gel and the instrument zeroed. The cone was released and allowed to penetrate into the sample for 5 s, after which the cone was clamped to avoid any more movement. Penetration depth was then read and samples were allowed to recover for 3 h before the exercise was repeated. Each experiment was duplicated using fresh samples.

Tablets and dissolution testing

Tablets, 7.94 mm, shallow concave, were prepared by direct compression of the drug-HPMC-lubricant blends. They contained 160 mg propranolol hydrochloride, 25, 50, 75, 100 or 150 mg HPMC E4M, HPMC F4M, HPMC K4M or methylcellulose A4M and 0.75% w/w magnesium stearate. Dissolution rates were determined using a Copley Series 8000 automatic dissolution tester into 1 l of distilled water maintained at 37°C using the British Pharmacopoeia (1988) basket method, rotating at 100 rpm and monitoring the release of propranolol hydrochloride at 288 nm (Ford et al., 1985c). Results presented are the mean of six tablets.

Results and Discussion

The dissolution of all tablets followed root time dependancy. Dissolution rates were determined by linear regression of the square root of time data. The correlation coefficients were > 0.997 for all data and the rates are summarised in Table 1. Each cellulose ether provided a sustained release. At higher HPMC contents there was little difference between the dissolution rates provided by each of the grades. Interestingly, differences were only detected at the very low levels of cellulose ether in the matrix (25 mg); the A4M grade provided the greatest sustained release although this is the grade purportedly the slowest to hydrate (Alderman, 1984). No one grade provided either the slowest or fastest release at all propranolol/HPMC ratios evaluated. It must therefore be concluded that the substitution grade has little effect on either the rate of hydration or the dissolution of the propranolol

TABLE 1

Dissolution rates of propranolol hydrochloride from matrices containing cellulose ethers

Quantity Methocel (mg)	Methocel substitution type			
	A	E	F	K
25	6.49	9.86	10.11	9.73
50	5.43	6.53	5.66	5.89
75	5.47	5.61	4.99	5.11
100	5.24	5.09	4.54	4.43
150	4.55	3.85	4.02	3.87

Dissolution rates expressed as mg $\%^{-1/2}$.

hydrochloride except in matrices containing low quantities of cellulose ethers. It is perhaps pertinent to note that the matrices described by Alderman (1984) included bulking agents (lactose) and glidants which may also have affected the release. In this study attempts were, therefore, made to further quantify any differences in the properties of the cellulose ethers.

The first attempt to evaluate the performance of the grades of methocel was by assessing their ability to imbibe water. This was accomplished by DSC. Over the period of 60 min the amount of water taken up by the polymer discs increased and typical results are shown in Fig. 4 which shows the DSC scans obtained for discs containing HPMC K4M and exposed to water for up to

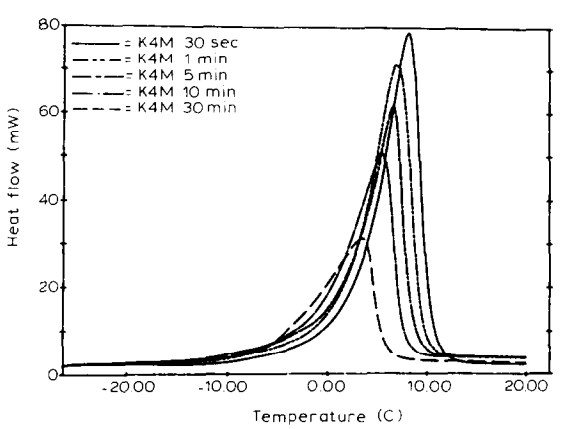

Fig. 4. Differential scanning calorimetry scans showing the melting endotherms of free water in contact with hydroxypropylmethylcellulose K4M discs from 30 s to 30 min.

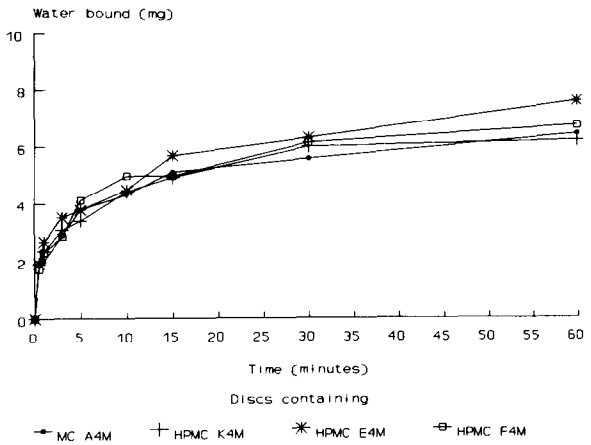

Fig. 5. The effect of time on the water bound by discs of hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M over a period of 60 min.

30 min. The onset temperatures of the melting endotherms decreased from -10 to -17°C as the sample hydration time increased from 30 s to 30 min. Fig. 5 shows the mean uptake of water into the discs containing HPMC E4M, HPMC F4M, HPMC K4M or methylcellulose A4M. The ratio used, 1:1 water/Methocel, was based on HPMC KI5M requiring approximately its own weight of water to hydrate (Mitchell et al., 1989). The water uptakes of the various cellulose ethers were similar in the 1 h period of study. During the initial 5 min over 30% of the uptake occurred, but even in this period the water uptake was similar for each of the cellulose ethers; thereafter HPMC E4M imbibed water at a slightly faster rate than the other grades. Alderman (1984) considered that the speed at which the outer protective gel coat forms in the matrix tablets affects the release properties of drugs from cellulose ether matrices. Fig. 5 indicates that little difference occurred in hydration rates and that an alternative explanation for the claimed dissolution rate dependence on substitution type (Alderman, 1984) is required.

Several methods have been used to measure the extent and rate of swelling of polymers. For instance, Colombo et al. (1990) used a video camera to measure the rate and extent of swelling in matrices and Wan and Prasad (1990a,b) measured the rate and extent of swelling in particles

TABLE 2

Expansion (mm) of tablets in the axial (a) and radial (r) planes following 100 min emersion in water of 25 mg tablets containing methylcellulose A4M, HPMC E4M, HPMC F4M or HPMC K4M measured using TMA in expansion mode

Matrix	Temperature					
	24°C		37°C		45°C	
	a	r	a	r	a	r
A4M	2.75	0.41	1.67 [a]	0.26 [a]	–	–
E4M	2.53	0.34	2.95	0.45	3.23	0.47
F4M	3.25	0.34	4.21	0.41	6.08	0.30
K4M	2.50	0.09	3.67	0.22	4.58	0.22

[a] Results after 15 min, matrix disintegrated before the final testing period of 100 min.

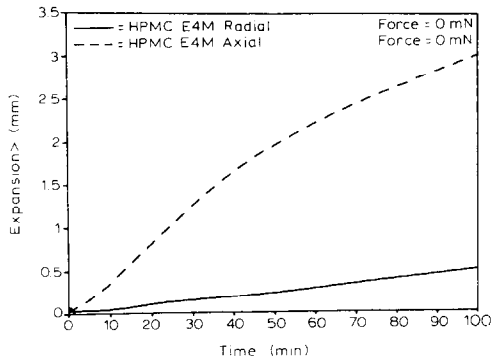

Fig. 6. The axial and radial expansion of a compact containing hydroxypropylmethylcellulose E4M as measured using a thermal mechanical analyser at a temperature of 37°C.

and films by video attached to a microscope. These methods have the advantage of being continuous and non-destructive. Attempts to similarly measure the cellulose ethers in this study proved abortive. The method was subjective since, at the beginning of the test period, the boundary between matrix and solvent was initially very clear cut but after some hours of testing, as the gel layer increased in volume, thickness and water content, the outer layer of the gel became almost transparent. Measurements of particle swelling by microscopy were also unreliable since the depth of field changed as the particles swelled. The focusing therefore was continually changed on the addition of water. Consequently, alternative methods were employed to measure swelling by thermomechanical analysis and by disruption of laser light passing through the matrices.

Table 2 gives the expansion of the matrices following 100 min exposure to water at 24, 37 or 45°C and measured by TMA. The methylcellulose A4M matrices disintegrated following around 20 min exposure to water. The aspect ratio (radial/axial ratio) before exposure to water was approximately unity for each of the matrices. This value changed as the test progressed since swelling proved to be isotropic. The swelling in the axial direction was much greater than the radial swelling. Figs 6–8 show the axial and radial swelling of HPMC E4M, F4M and K4M. Urdahal and Peppas (1987) explained this behaviour as an evident restriction to swelling due to a glassy core that limits the radial swelling of the matrix. Colombo et al. (1990) also noted that axial swelling of matrices was more prominent during the initial stages of swelling but in the later stages swelling fronts move in both directions. The radial swelling was very small and did not seem to be affected by temperature change. Rajabi-Siahboomi et al. (1992) also have shown larger expansion in the axial direction. The axial swelling was more prominent during the initial stages. The small compacts that were used showed very little

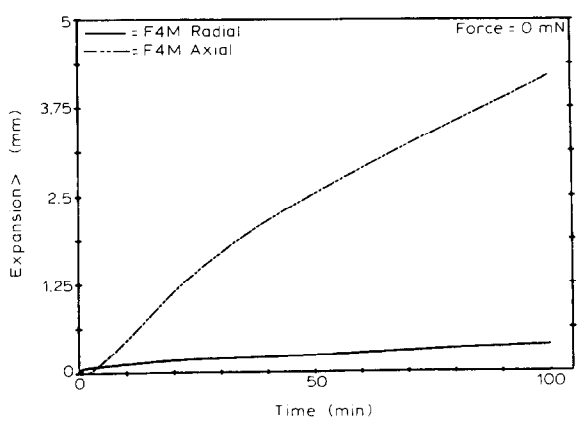

Fig. 7. The axial and radial swelling of a compact containing hydroxypropylmethylcellulose F4M measured using a thermal mechanical analyser at 37°C.

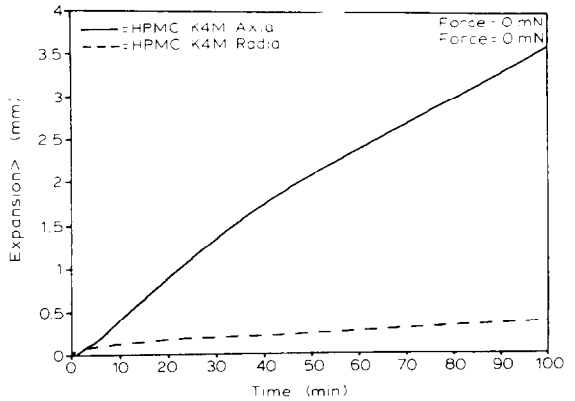

Fig. 8. The axial and radial expansion measured by thermal mechanical analyzer of a compact containing hydroxypropylmethylcellulose K4M at a temperature of 37°C.

radial swelling which was hardly affected by temperature changes.

The rate and extent of axial swelling increased with temperature whereas the extent of radial swelling did not significantly increase above 37°C. The extent of swelling was different for each of the grades. Thus, the ranking was HPMC F4M > HPMC K4M > HPMC E4M. Fig. 9 shows the axial swelling of the matrices containing HPMC K4M at 24, 37 and 45°C and indicates that the initial 15 min period is important in determining the extent of swelling. After this period the rates of axial swelling of the matrices containing the three HPMCs were similar, i.e., the swelling

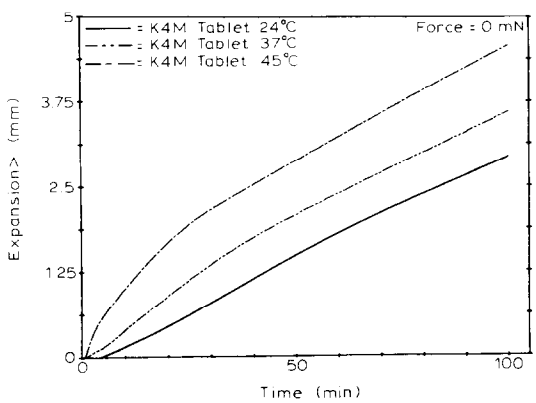

Fig. 9. The swelling profiles of compacts containing hydroypropylmethylcellulose K4M at 24, 37 and 45°C.

TABLE 3

Dimensional changes of matrices containing methylcellulose A4M, HPMC E4M, HPMC F4M or HPMC K4M at 37°C following emersion in water and using laser light to monitor thicknesses (mean of two determinations)

Time (h)	Width (cm)	Height (cm)	Volume (cm^3)	% increase in volume
E4M matrices				
0	0.985	0.673	0.512	0
1	1.159	0.943	0.995	94
2	1.241	1.108	1.340	161
3	1.220	1.200	1.403	174
4	1.310	1.262	1.701	232
5	1.348	1.213	1.731	238
6	1.371	1.318.	1.946	280
F4M matrices				
0	1.013	0.703	0.567	0
1	1.116	1.049	1.025	81
2	1.223	1.253	1.472	160
3	1.246	1.333	1.626	187
4	1.231	1.399	1.665	194
5	1.275	1.447	1.848	226
6	1.251	1.520	1.868	230
K4M matrices				
0	0.967	0.560	0.411	0
1	1.138	0.812	0.826	101
2	1.221	1.108	1.230	215
3	1.249	1.240	1.519	264
4	1.283	1.315	1.700	313
5	1.331	1.402	1.951	374
6	1.364	1.475	2.155	424

isotherms were parallel after this period. At all temperatures the matrices actually decreased in size slightly before beginning to swell. Compacts containing HPMC E4M were the least affected by the increase in temperature followed by HPMC K4M, HPMC F4M and methylcellulose A4M matrices. The latter swelled at 24°C and, compared to 37 and 45°C, did not disintegrate. At these higher temperatures the matrices containing methylcellulose swelled so rapidly that they failed to maintain their integrity.

Table 3 shows the results of laser analysis for the matrices tested. The matrices containing methylcellulose A4M disintegrated within 10 min and therefore no readings were obtained. Similar findings were apparent in the TMA expansion studies but it must be emphasised that no predic-

tion of this event would be apparent from the DSC studies which were not intended to assess dimensional changes. Matrices containing HPMC E4M, HPMC K4M or HPMC F4M expanded during the course of study. There was little difference, between the grades in the outer layer radius over the first 2 h of testing. After this period, all the matrices continued to expand but the HPMC K4M matrices swelled at a faster rate than the matrices containing HPMC F4M or HPMC E4M which performed similarly. For each of the three grades of HPMC, axial swelling was much faster than radial swelling which was similar for each of the E, F and K grades. The extent of axial swelling ranked as HPMC K4M > HPMC F4M > HPMC E4M. The rank order in volume increase was HPMC K4M > HPMC E4M > HPMC F4M. In fact, HPMC K4M swelled to an extent almost twice that of HPMC F4M. This mirrors the hydrophilic nature of the polymer.

The previous experiments described expansion but not gel layer thickness. Therefore, TMA, in penetration mode, was used to quantify increases in gel layer thickness at the flat face of the matrices. The existence of sharply defined advancing boundaries during the swelling of polymers has long been recognised. Early studies by Hartley (1949) and Crank and Park (1951) showed sharply defined swelling boundaries. In most cases, where a boundary is apparent, it advances into the interior at a decreasing velocity (Haley, 1958). There are two moving boundaries in cellulose ether matrices. Therefore, in addition to studying the swelling ability of the HPMCs and methylcellulose, a penetration study was carried out which was designed to follow the solvent front moving into the tablet. Thermal mechanical analysis was used, in penetration mode, to measure gel layer thickness and discover what affect the substitution of cellulose ethers had on the rate of solvent penetration. Readings were taken at 37°C and consequently matrices containing methylcellulose A4M were excluded since they did not maintain integrity. Fig. 10 shows the increase in gel thickness as a function of time. All the HPMC grades behaved similarly.

In an attempt to explain the differences in the swelling behaviour between the various cellulose

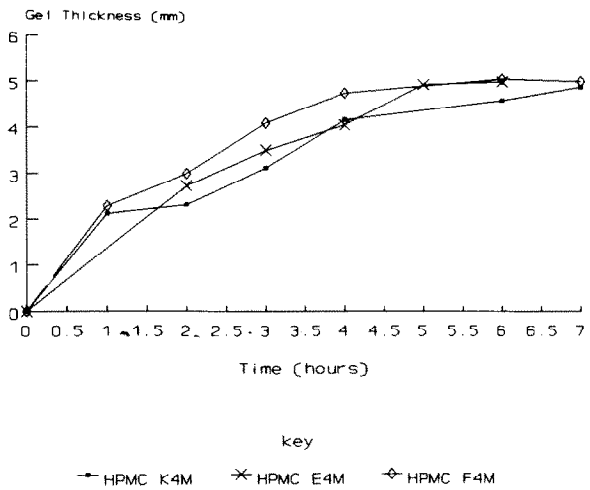

Fig. 10. The effect of time on the gel thickness of hydrating matrices containing hydroxypropylmethylcellulose K4M, E4M or F4M, measured using a thermal mechanical analyser in penetration mode.

ethers, cloud points were studied to determine their hydration status. The cloud points were determined over the concentration range of 0.5–2% w/v cellulose ether. The hydration of cellulose ethers is affected by temperature (Sarkar, 1979). As the temperature increases, the polymer loses its water of hydration and this is observed in gels as precipitation. This property may be measured by light transmission and the temperature at which light transmission reaches 50% of its original value is called the cloud point (Sarkar, 1979).

Fig. 11 shows a typical effect of temperature on the light transmission of various HPMC K4M gels. Fig. 12 shows the cloud point plots derived from the values obtained from such graphs, for methylcellulose A4M, HPMC K4M, HPMC, E4M and HPMC, F4M. The values are also given in Table 4. For 2% w/w gels, the cloud points were 46.0, 55.3, 58.1 and 70.7°C for methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M, respectively, a difference of 24.7°C between the lowest (methylcellulose A4M) and the highest (HPMC K4M) grades. The results were similar to the thermal gelation temperatures given by Sarkar (1979). Gels of HPMC E4M and HPMC F4M produced similar cloud points, but HPMC K4M

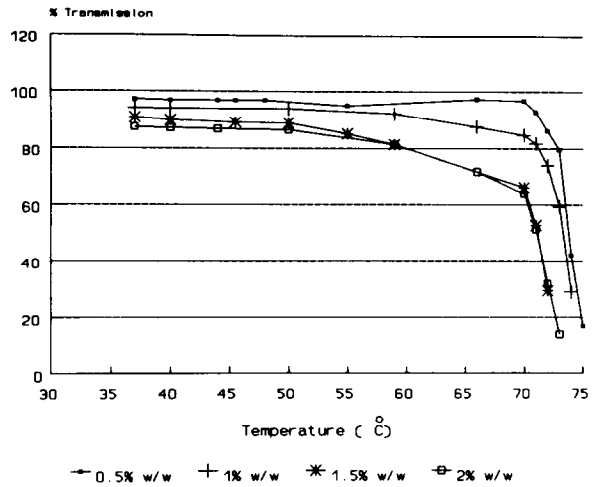

Fig. 11. The effect of temperature on the light transmission of various hydroxypropylmethylcellulose K4M gels.

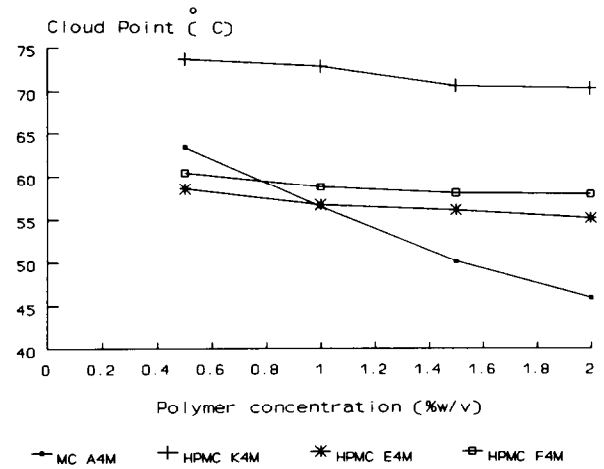

Fig. 12. The effect of polymer concentration on the cloud points of gels containing methylcellulose A4M, Hydroxypropylmethylcellulose K4M, E4M or F4M.

TABLE 4

Cloud points of aqueous gels containing methylcellulose A4M, HPMC E4M, HPMC F4M or HPMC K4M

Methocel concentration (% w/w)	Cloud points (°C)			
	A4M	E4M	F4M	K4M
0.5	62.0	58.8	60.4	74.0
1.0	56.5	57.0	59.0	73.0
1.5	50.5	56.5	58.0	71.0
2.0	47.0	56.0	57.8	70.7

produced the highest cloud points at equivalent polymer concentrations. The gradients, i.e., change in cloud point with concentration, of the three HPMCs plots were similar whereas the gradient of the methylcellulose A4M plot was steeper, implying that it was more easily precipitated than the HPMCs. The cloud points of methylcellulose A4M gels dropped 15°C over the 1.5% concentration range studied. In contrast, the cloud points of HPMC E4M and HPMC F4M decreased by 2.8 and 2.6°C, respectively, over the same concentration range. The gels of HPMC possessed the highest cloud points whilst also displaying a small decrease (3.3°C) over the range examined.

This variation in cloud points between the grades can be explained by the type and quantity of substitution groups attached to the cellulose backbone of the polymers. Methylcellulose contains only a methoxy substituent which is hydrophobic. The hydroxypropoxy group is absent in methylcellulose A4M. This is a hydrophilic group and seems to retard the process of dehydration in the HPMCs tested. Hydroxypropylmethylcellulose grades E4M and F4M have a similar percentage of methoxy substituents to A4M (27.5–31.5%) but contain differing quantities of the hydroxypropoxy substituent (4–7.5 and 7–12%, respectively). The cloud points for HPMC E4M and F4M were similar (Fig. 12), showing that the presence of the hydroxypropoxy group increases the value of cloud points and the greater the percentage of hydroxypropoxy substituent the greater the value of the cloud point at a pro-rata concentration of the cellulose ether. Hydroxypropylmethylcellulose K4M has a similar hydroxypropoxyl constituent to HPMC E4M but the methoxy substituent is less, 19–24 compared to 28–30% for HPMC E4M. This reduction in methoxy substituent gives higher cloud points. The fact that methylcellulose gels of low concentrations produced cloud points greater than those of gels containing HPMC E4M or HPMC F4M even though no hydroxypropoxyl substituent was present, indicates that the methoxy substituent is the most important substituent in causing the cellulose ethers to precipitate. The relation between cloud point and concentration was approx-

imately linear. Following extrapolation to 37°C, the gel concentrations providing the cloud points at 37°C were 3.2, 15.2, 16.8 and 21.5% w/w for methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M, respectively. This low concentration for methylcellulose confirms that this particular grade was unable to form a stable matrix because of its poor ability to hydrate. It would be unable to form a protective gel and the matrix would fall apart.

The cloud points provided a partial explanation for the failure of methylcellulose to maintain matrix integrity during the swelling studies. As the temperature increased, the polymer would be associated with less water of hydration. This would decrease the rate at which the protective gel coat around the matrix was formed. Water could, therefore, penetrate further into the the compacts and hydrate the inner layers, causing an overall increase in polymer swelling. Thus, the swelling rate was promoted as the temperature increased. In the case of methylcellulose, which was much more sensitive to changes in temperature, the compact was unable to maintain integrity and disintegrated. The presence of drug during the dissolution studies appeared to maintain the integrity of the methylcellulose matrices.

Drugs are released from the cellulose ether matrices by both diffusion and erosion of the outer hydrated gel layers (Ford et al., 1991a). If the gel strength of the cellulose ethers was low the release by erosion would be fast since the gel would erode quickly. If, on the other hand, the gel strength of the cellulose ether was high, release by erosion would be slow. One method of testing the strength of a gel is by the use of a penetrometer (Haighton, 1959). The use of the 'grease cone' complicated the experiment since the angle of the tip of the cone changes as the cone penetrates through the gel (Haighton, 1959). This made the calculation of the yield values of the gels difficult. As a result, readings of penetration depth only, were determined. The penetration depth was measured twice for each sample, to determine the gel strength and thereafter to measure recovery from the trauma of the first test.

The results (Table 5) did not show great differences between the gel strengths of the different substitution types. In decreasing order the strength of the gels ranked as methylcellulose A4M > HPMC K4M > HPMC E4M > HPMC F4M. The resistance of the gels to erosion would be expected to be in a similar order. Differences in gel strengths have been reported by Sarkar (1979) using 2% w/v gels where a greater degree of the hydroxypropyl substituent resulted in greater gel strengths. It would seem that gels with no hydroxypropyl substituent have greater gel strengths than those with hydroxypropyl substituents. All gels recovered well, almost obtaining their original consistency. However, such small differences in gel strength would indicate a marginal contribution of this property to controlling drug release.

TABLE 5

Penetration depth into 6% w/w cellulose ether gels (mean of two determinations)

Cellulose ether used	Penetration depth (mm)	Recovery penetration depth (mm)
MC A4M	25.5	27.8
HPMC E4M	28.1	29.0
HPMC F4M	29.4	28.9
HPMC K4M	27.5	27.8

Conclusion

The DSC data clearly indicated the importance of the first 5 min of contact of the Methocel with water to the maintenance of a stable gel around a matrix tablet. If the gel coat did not form over this period, the system would not function as a sustained release matrix. The water uptake, determined from DSC, did not correlate with the hydrophilic or hydrophobic substituents in the individual cellulose ethers. Other properties of the polymer are, therefore, responsible for the differences previously attributed to the different substitution types of HPMC and methylcellulose (Alderman, 1984).

Thermomechanical analysis showed that, in the initial 15 min contact with water, the outer layers

of a matrix hydrated to form a protective gel. Once this gel is established the solvent will diffuse through the gel to hydrate the inner layers of the matrix thereby promoting swelling. Matrices containing HPMC E4M were the least affected by increases in temperature. Matrices containing methylcellulose A4M were so affected by increase in temperature that at 37 and 45°C the matrices swelled rapidly and were unable to maintain integrity. However, at 24°C the integrity of the methylcellulose matrices was maintained. An explanation for this behaviour lies with the degree of substitution associated with the different grades of cellulose ether. The cloud points for the different grades varied and were much lower for methylcellulose A4M. This is thought to be because this grade only contains the hydrophobic methoxy substituents. As the temperature increases, the cellulose ethers were associated with less and less water of hydration. Thus, the polymer is steadily dehydrating and when the cloud point is reached the interactions within the polymer prevent a complete protective gel layer from forming rapidly around a matrix. Hence, water penetrates into and hydrates the polymer in the inner layers. This promoted the swelling and, in the case of the methylcellulose matrices, caused disintegration of the matrix. The dissolution data, however, indicated little difference in the performance of the four grades of cellulose ether in modulating the release of propranolol hydrochloride. The explanation must lie in the drug further modifying the intrinsic properties of the cellulose ethers, thereby, swamping out the subtle differences noted between the grades in the absence of drug.

References

Alderman, D.A., A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int. J. Pharm. Technol. Prof. Mfr*, 5 (1984) 1–9.

Colombo, P., Conto, U., Gazzaniga, A., Maggi, L., Sangalli, M.E., Peppas, N.A. and La Manna, A., Drug release modulation by physical restrictions of matrix swelling. *Int. J. Pharm.*, 63 (1990) 43–48.

Crank, J. and Park, G.S., Diffusion in high polymers. *Trans Faraday Soc.*, 47 (1951) 1072–1084.

Ford, J.L., Mitchell, K., Rowe, P., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., Mathematical modelling of drug release from hydroxypropylmethylcellulose matrices: effect of temperature. *Int. J. Pharm.*, 71 (1991a) 95–104.

Ford, J.L., Mitchell, K., Sawh, D., Ramdour, S., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., Hydroxypropylmethylcellulose matrix tablets containing propranolol hydrochloride and sodium dodecyl sulphate. *Int. J. Pharm.*, 71 (1991b) 213–221.

Ford, J.L., Rubinstein, M.H., Changela, A. and Hogan, J.E., Influence of pH on the dissolution of promethazine hydrochloride from hydroxypropylmethylcellulose controlled release tablets. *J. Pharm. Pharmacol.*, 37 (1985a) 115P.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 24 (1985b) 327–338.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *Int. J. Pharm.*, 24 (1985c) 339–350.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Dissolution of a poorly water soluble drug, indomethacin from hydroxypropylmethylcellulose controlled release tablets. *J. Pharm. Pharmacol.*, 37 (1985d) 33P.

Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E. and Edgar, P.J., Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Int. J. Pharm.*, 40 (1987) 223–234.

Haighton, A.J., The measurement of the hardness of margarine and fats with core penetrometers. *J. Am. Oil. Chem. Soc.*, 36 (1959) 345–348.

Haley, A.R., Interaction of wool and water. *Aust. J. Appl. Sci.*, 9 (1958) 410–419.

Hartley, G.S., Diffusion and swelling of high polymers. *Trans Faraday Soc.*, 45 (1949) 820–832.

Melia, C.D., Binns, J.S.D. and Davies, M.C., Polymer hydration and drug distribution within the gel layer of hydrophilic matrix devices during drug release. *J. Pharm. Pharmacol.*, 42 (1990) 125P.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., Differential thermal analysis of hydroxypropylmethylcellulose gels: influence of water content and propranolol hydrochloride. *J. Pharm. Pharmacol.*, 41 (1989) 59P.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrix tablets. *Int. J. Pharm.*, 66 (1990a) 233–242.

Mitchell, K., Ford, J.L., Rostron, C., Armstrong, D.J., Elliott, P.N.C., and Hogan, J.E., Swelling behaviour of cellulose ether matrix tablets. *J. Pharm. Pharmacol.*, 43 (1991) 77P.

Mitchell, K., Sogo, T., Armstrong, D.J., Elliott, P.N.C., Ford, J.L., Rostron, C. and Hogan, J.E., Temperature effects on

the dissolution of promethazine hydrochloride from hydroxypropylmethylcellulose matrix tablets. *J. Pharm. Pharmacol.*, 42 (1990b) 127P.

Mitchell, K., Sogo, T., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., The influence of cellulose ether substitution type on water-uptake and dissolution of propranolol hydrochloride. *J. Pharm. Pharmacol.*, 42 (1990c) 124P.

Rajabi-Siahboomi, A.R., Melia, C.D., Bowtell, R.W., McJury, M., Sharp, J.C. and Mansfield, P., Imaging the internal structure of the gel layer in hydrophilic matrix systems by NMR microscopy. *J. Pharm. Pharmacol.*, 44 (1992) 41P.

Sarkar, N., Thermal gelation properties of methyl- and hydroxypropylmethylcellulose. *J. Appl. Polym. Sci.*, 24 (1979) 1073–1087.

Urdahal, K.G. and Peppas, N.A., Anamolous penetration transport in glassy polymers V. Cyclohexane transport in polystyrene. *J. Appl. Polym. Sci.*, 33 (1987), 2669–2687.

Wan, L.S.C. and Prasad, K.P.P., A study of the swelling of tablet excipients using video recording. *Drug Dev. Ind. Pharm.*, 16 (1990a) 921–933.

Wan, L.S.C. and Prasad, K.P.P., Relationship between temperature and swelling of methylcellulose in tablets. *Drug. Dev. Ind. Pharm.*, 16 (1990b) 945–950.