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The influence of drugs on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropylmethylcellulose

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)*

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Summary

The cloud points, matrix swelling and gel layer formation in matrices containing cellulose ethers and indomethacin, propranolol hydrochloride or tetracycline hydrochloride have been investigated. The two hydrochloride salts contributed to the matrix swelling and gel layer formation, maintaining the integrity of matrices containing methylcellulose. Gel layer formation, measured by thermomechanical analysis was most rapid, and the layer thickest, in matrices containing propranolol hydrochloride. This mimicked cloud point determination where propranolol salted the cellulose ethers into solution to a greater extent than tetracycline. The poorly soluble indomethacin failed to contribute to swelling and gel layer formation. Studies, using U-tube viscometry, indicated that the viscosity of gels containing HPMC E4M, HPMC F4M, HPMC K4M and methylcellulose reduced on storage. This appeared to be further catalysed by the inclusion of drugs, and especially of tetracycline hydrochloride in the gels.

Introduction

Hydroxypropylmethylcellulose (HPMC) or methylcellulose are cellulose ethers which are frequently used to provide a controlled release of drugs from matrix tablets (Melia, 1991). Although the release rates from such products may be modified by careful control of drug particle size (Ford et al., 1985a,b), drug/cellulose ether ratio (Ford et al., 1985a,b, 1987) or even matrix shape (Ford et al., 1987), there is evidence that varying the substitution type of methylcellulose may effect a control on drug release. This was adjudged to be due to different hydration rates, the order being HPMC K > HPMC E > HPMC F > methylcellulose (Alderman, 1984). Hydroxypropylmethylcellulose K grade is therefore purportedly the fastest to hydrate, although Mitchell et al. (1990a), using differential scanning calorimetry, found no evidence to collaborate such assumptions.

Undoubtedly, however, in a matrix tablet the presence of a drug will modify how water is

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

bound to, or taken up by, the cellulose ether. Thermal analysis showed a variation induced in the water distribution within HPMC gels caused by the presence of propranolol hydrochloride (Mitchell et al., 1989).

One controlling factor in the release of drugs from HPMC or MC matrices is the production of a gel layer around the matrix on initial contact with water (Alderman, 1984). Drug release is controlled, for soluble drugs, by the rate of diffusion through such a gel, or for poorly water soluble drugs, by a combination of diffusion and gel erosion (Ford et al., 1991). However, since drugs alter water distribution within such matrices it follows that they will modify the matrix structure. Already Ford et al. (1987) have compared the release of several dissimilar drugs from HPMC K15M matrices and Mitchell et al. (1993) have demonstrated that factors such as the cloud point of the cellulose ether, the type of ether and gel strength are factors which may influence the performance and properties of gels containing HPMC or methylcellulose. This paper, using thermomechanical analysis as its focal experimental technique, attempts to elucidate the role played by drugs in modifying the performance of HPMC and methylcellulose matrices. Cloud points and viscosity data are used to supplement the results. The presence of low levels of electrolytes has been shown to effect drug release from HPMC matrices (Mitchell et al., 1990b). It would seem reasonable, therefore, that drugs play an active role in determining their own release rates.

Materials and Methods

Methocel A4M, Methocel E4M, Methocel F4M, Methocel K4M, each manufactured by Dow Chemicals, U.S.A. and equivalent to USP types methylcellulose, hydroxypropylmethylcellulose (HPMC) 2910, HPMC 2906 and HPMC 2208, respectively, were used as supplied throughout the study. Additionally, HPMC K15M, similarly supplied, was used. Propranolol hydrochloride B.P., tetracycline hydrochloride B.P., indomethacin B.P. and magnesium stearate (Analar grade, British Drug Houses) were used as supplied.

Thermomechanical analysis

Approx. 25 mg samples were compressed into tablets, 3 mm flat faced, using a Manesty SP single punch tableting machine. These tablets contained solely methylcellulose A4M, HPMC E4M, HPMC F4M or HPMC A4M. Alternatively, tablets contained 50% of methylcellulose A4M, HPMC E4M, HPMC F4M or HPMC K4M and 50% propranolol hydrochloride, tetracycline hydrochloride or indomethacin. No lubricant was employed.

Full experimental details were described by Mitchell et al. (1993). The matrix tablet under test was placed in a 100 ml glass beaker in a water bath maintained at 37°C. The expansion probe was placed on top of the tablet and water was introduced into the beaker at a temperature of 37°C. 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. Tests were carried out in duplicate.

Gel layer thickness

Tablets, 400 mg 12.7 mm flat faced, and containing 50% HPMC K4M, 50% of tetracycline hydrochloride, propranolol hydrochloride or indomethacin and a further 0.75% magnesium stearate were compressed using a Manesty F3 single punch tableting machine. Using the method described by Mitchell et al. (1993) the thickness of the gel layer in the tablets was measured to ± 0.001 cm using a Perkin Elmer Series 7 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.

Cloud points

Cloud points were determined as per Mitchell et al. (1993). Gels were prepared containing 2% w/v HPMC K15M by heating one third of the total amount of freshly distilled water to 80°C, and then adding the required amount of polymer and dispersing it. Solutions of drugs were added at this stage before cold water was added to make the gels up to the weight. The concentrations of propranolol hydrochloride and tetracycline hydrochloride in the final gel were 0.02, 0.1 or 0.2 M.

Once prepared, the gels were stored overnight in a refrigerator. Samples were transferred to disposable 1 cm pathlength cuvettes (Elkay). Any air bubbles entrapped in the gels were removed by centrifugation. The samples were then placed in a water bath and the temperature gradually increased. Initially readings were taken at 5°C intervals which were reduced to 1°C increments near the cloud points. For reading, the samples were removed from the water bath. The samples were measured spectrophotometrically at 800 nm against a 2% w/w aqueous solution of the gel, maintained at room temperature, using a Uvikon 810 dual cell spectrophotometer. The cloud point was taken to be the temperature at which the light transmission was 50% of the reference held at room temperature.

Viscosity measurements

Dilute gels were prepared to contain 0.05, 0.1, 0.2 or 0.3% w/w HPMC K4M in the absence and presence of either 2.5% w/w propranolol hydrochloride or 2.5% w/w tetracycline hydrochloride. Tests were performed at 37°C, in U-tube viscometers, grade A (British Standard 188, 1957), which had previously been calibrated with distilled water at 20°C. Gels were maintained at a temperature of 37°C throughout the study. The dynamic viscosity of water at 20°C was taken to be 1.002 cP (British Standard 188, 1957). The time taken was a mean of three successive measurements, which were within 0.5% of each other. Each gel was tested several times over a 7 or 8 day period.

Results and Discussion

Both tetracycline hydrochloride and propranolol hydrochloride increased the cloud points of gels containing 2% HPMC K15M (Table 1). The relationship between cloud point and concentration was, for tetracycline, linear. However, for propranolol hydrochloride, positive deviation from linearity occurred indicating that, at the higher concentrations, the polymer was able to hydrate to a larger extent than at lower concentrations. Many electrolytes depress the gel points of polymers by affecting dehydration (Levy and Schwartz, 1958). Consequently, therefore, increase in cloud point must result from additional hydration. Interestingly, the value of the critical micelle concentration of propranolol hydrochloride of 29 mg/ml (Mitchell, 1992) lies between the 0.1 and 0.2 M concentrations.

Viscosity is one of the most widely utilized methods for the characterization of polymers, providing an easy and rapid means of determining molecular weight related data. A most obvious characteristic of HPMC and methylcellulose gels is their high viscosity, even when the content of the cellulose ether is small. Two parameters, the intrinsic viscosity $[\eta]$, and Huggins interaction constant k', provide indirect assessments of the ability of a solvent system to solve a polymer (Huggins, 1942; Alfrey, 1947).

TABLE 1

The effect of concentration of propranolol hydrochloride or tetracycline hydrochloride on the cloud points of gels containing 2% hydroxypropylmethylcellulose K15M

Drug	Cloud point (°C)			
Concentration of drug (M):	0	0.02	0.1	0.2
Propranolol hydrochloride	66.0	67.3	71.5	83.5
Tetracycline hydrochloride	66.0	67.0	71.5	78.0

The intrinsic viscosity $[\eta]$ is an expression of the hydrodynamic interference between polymer and solvent and reflects the ability of a solvent to swell the polymer. It is unique to the polymer solvent system (Alfrey, 1947). Rigid polymer molecules, such as cellulose ethers, show relatively small diffferences in their values of $[\eta]$ due to solvent changes (Arwidsson and Nicklasson, 1989) and to an inability to expand greatly. Values of $[\eta]$ and k' were calculated by means of linear regression of the plots of reduced viscosity vs polymer concentration (c) according to Eqn 1 (Alfrey, 1947).

$$\eta_{sp}/c = [\eta] + k'[\eta]^2 c \qquad (1)$$

where η_{sp} is the specific viscosity, c denotes the concentration (g/dl), $[\eta]$ is the intrinsic viscosity (dl/g) and k' represents Huggins interaction constant.

The reduced viscosity (η_{sp}/c) can be represented by Eqn 2.

$$\eta_{sp}/c = ((\eta/\eta_0) - 1)/c \qquad (2)$$

where η is the viscosity of solution, η_0 denotes the viscosity of pure solvent and c is polymer concentration (% w/v).

Both the intrinsic viscosity and Huggins interaction constant can be calculated from a plot of reduced viscosity vs polymer concentration. The intrinsic viscosity is the point where the extrapolated line crosses the abscissa and the Huggins interaction constant k' can be calculated by dividing the gradient by the square of the value obtained for the intrinsic viscosity. The value of k' gives an indication of the polymer-polymer and polymer-solvent interactions, such that a positive slope is produced for a polymer which interacts weakly with the solvent and the slope becomes less positive as the interaction increases (Marriott, 1988).

Plots of reduced viscosity against polymer concentration for the four polymer grades (HPMC K4M, HPMC F4M, HPMC E4M, methylcellulose A4M) were generally straight lines, enabling an estimation of $[\eta]$ by regression of the plots. The solution viscosities of all the grades tested reduced over the test period. Consequently, the intrinsic viscosity also decreased. Such changes indicate either a change in polymer molecular weight or a change in the shape of the polymer according to the Mark-Houwink equation (Eqn 3).

$$(\eta) = KM^a \qquad (3)$$

where $[\eta]$ is the intrinsic viscosity, K denotes the proportionality constant, M is the average molecular weight of the polymer and a represents a constant.

The proprotionality constant is characteristic of the polymer and solvent system and therefore should remain constant over time. The constant a is a function of the shape of the polymer coil over time.

The values of intrinsic viscosity obtained were similar for HPMC E4M, HPMC F4M and HPMC K4M, but methylcellulose A4M gave higher values of intrinsic viscosity (Table 2). This indicates that either the average molecular weight of methylcellulose A4M was greater than HPMC E4M, HPMC F4M and HPMC K4M, or that the polymer coil of methylcellulose A4M possessed a greater exclusion volume (Staudinger, 1930). In constrast, k' increased over the test period for gels of methylcellulose A4M, HPMC F4M and HPMC K4 (Table 2). HPMC E4M was refractory to any changes in k' and seemed to be the most stable of the four grades of cellulose ethers tested.

Because it is known that the lower the value for k', the greater the polymer solvent interaction, it would appear that water is a better solvent for methylcellulose A4M than HPMC K4M, HPMC E4M or HPMC F4M grades. The excluded volume of the methylcellulose molecule is either greater than that of HPMC E4M, HPMC F4M and HPMC K4M, or there is stronger bonding between water and methylcellulose than between water and any of the HPMCs. This result is not apparently explainable since methylcellulose A4M contains only the hydrophobic methoxy substituent, and not the hydrophilic hydroxypropoxyl substituent.

TABLE 2

The effect of storage on the intrinsic viscosity [η] and Huggins interaction constant, k', for hydroxypropylmethylcellulose E4M, K4M or F4M or methylcellulose A4M gels stored at 37°C

Polymer	Age (days)	$[\eta]$ (dl/g)	$[\eta]^2$ $(dl/g)^2$	Gradient	k'
HPMC K4M	1	5.24	27.45	35.80	1.31
	2	5.46	29.78	34.23	1.15
	5	4.82	23.23	33.64	1.45
	7	4.65	21.58	33.17	1.49
	8	4.56	20.79	32.90	1.58
HPMC E4M	1	4.73	22.42	37.83	1.68
	2	4.53	20.53	38.61	1.88
	5	4.65	21.65	35.77	1.65
	7	4.75	22.61	33.77	1.49
	8	4.67	21.81	33.88	1.55
HPMC F4M	1	5.39	29.11	29.79	1.02
	4	4.94	24.37	28.49	1.17
	5	4.72	22.35	27.54	1.23
	6	4.68	21.87	27.08	1.24
	7	4.51	20.35	27.14	1.33
Methyl cellulose A4M	1	7.32	53.55	24.71	0.46
	4	6.64	44.12	22.99	0.52
	5	6.52	42.57	24.06	0.56
	6	6.53	42.71	22.95	0.54
	7	6.41	41.07	22.52	0.55

Fig. 1 shows the changes in reduced viscosity of gels containing HPMC K4M and propranolol hydrochloride. The intrinsic viscosity decreased

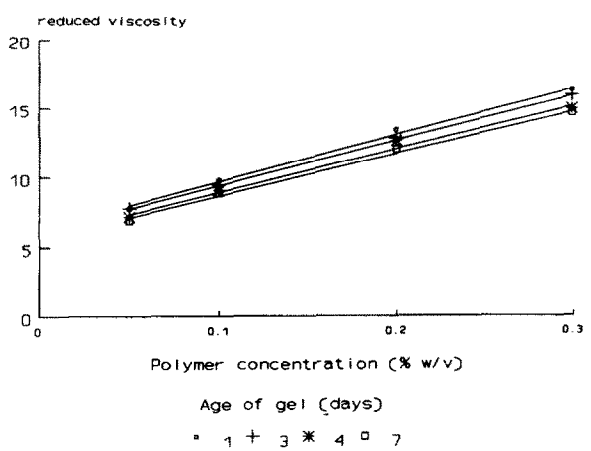

Fig. 1. The effect of storage at 37°C on the reduced viscosity of hydroxypropylmethylcellulose K4M gels containing 2.5% w/w propranolol hydrochloride.

TABLE 3

The effect of storage on the intfinsic viscosities [η] and Huggins interaction constants, k^1 for hydroxypropylmethylcellulose K4M gels containing 2.5% w/w propranol of hydrochloride or 2.5% w/w tetracycline hydrochloride stored at 37°C

Drug included	Age of gel (days)	Intrinsic viscosity ($dl\ g^{-1}$)	Huggins interaction constant
Propranolol hydrochloride	1	6.23	0.90
	3	6.17	0.87
	4	5.85	0.93
	7	5.33	0.91
Tetracycline hydrochloride	1	6.64	0.91
	4	5.68	1.17
	5	5.03	1.36
	6	4.16	1.87
	7	3.77	1.97

from 6.23 to 5.33 over the 7 day period but the Huggins interaction constant remained relatively constant (Table 3). These results indicate either a decrease in polymer molecular weight or a decrease in polymer excluded volume over the 7 day period. This may be explained by the occurrence of gel syneresis, which may have the effect of decreasing the excluded volume. Fig. 2 shows the changes in reduced viscosity of HPMC K4M gels containing tetracycline hydrochloride. Here a dramatic decrease in the intrinsic viscosity (Table

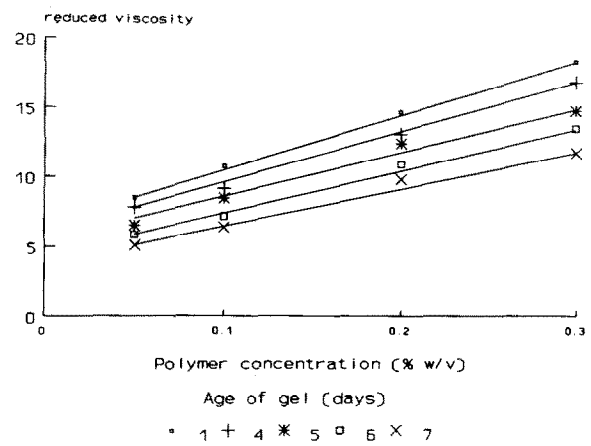

Fig. 2. The effect of storage at 37°C on the reduced viscosity of hydroxypropylmethylcellulose K4M gels containing 2.5% w/w tetracycline hydrochloride.

3) occurred and the Huggins interaction constant more than doubled.

The data in Table 3 indicated that both changes occurred in the molecular weight of the polymer and there were increases in solvent-polymer interactions. Tetracycline hydrochloride in solution gives an acidic pH, that of a 1% w/v solution being approx. 1.8 (Ali, 1984). It has been demonstrated that 0.1 M hydrochloric acid depolymerises HPMC (Mitchell, 1992). Therefore, the acidity of the hydrating gel may cause a similar decrease in molecular weight. The free tetracycline base was less soluble than tetracycline hydrochloride (Ali, 1984). This change in drug solubility may be the reason for increase in polymer-solvent interactions noted.

There are few published studies about the effects that drug or added excipients have on the swelling characteristics of HPMC or MC matrices. The swelling of p(HEMA) hydrogels has, however, been studied extensively, (Brannon-Peppas and Peppas, 1990; 1991). The swelling of p(HEMA) gels was sensitive to changes in internal and external conditions, which include excipients contained in the matrix and dissolution media. Subsequently, the effect of the three drugs propranolol hydrochloride, tetracycline hydrochloride and indomethacin on the swelling behaviour of HPMC and methylcellulose matrices was studied. These drugs were chosen because of their differing solubilities (Ford et al., 1987).

Propranolol hydrochloride had a profound effect on the swelling of all the grades of cellulose ether tested (Fig. 3). Its inclusion into methylcellulose A4M matrices caused them to swell rapidly for the whole test period. This was in direct contrast to the swelling behaviour of methylcellulose A4M in the absence of drugs (Mitchell et al., 1993) when the matrix swelled rapidly and collapsed (disintegrated) after approx. 15 min. The addition of propranolol hydrochloride therefore actively maintained the integrity of the methylcellulose A4M matrix. The mechanism by which propranolol hydrochloride maintained integrity would probably be by salting in the polymer. The polymer would in the presence of propranolol, be more soluble, thus increasing the amount of water associated with methylcellulose A4M; the

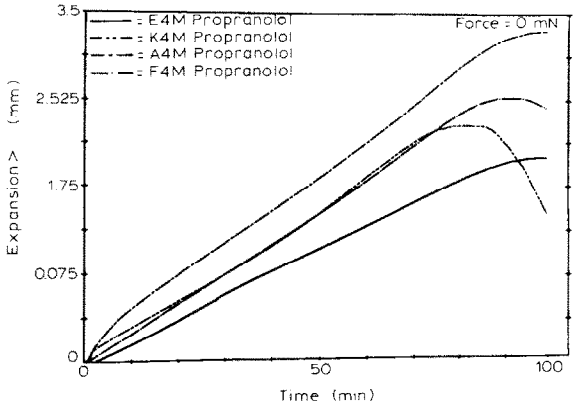

Fig. 3. The swelling profiles of matrices containing 50% hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M and 50% propranolol hydrochloride at 37°C.

polymer can therefore gel rapidly. A protective gel layer is thus formed before water entered the matrix and hydrated the inner layers.

The extent of swelling of the matrices containing methylcellulose A4M and propranolol hydrochloride was greater than that of the matrices containing propranolol hydrochloride and the HPMCs (Fig. 3). All matrices swelled to a maximum and then, in the case of matrices containing HPMC K4M and HPMC F4M, started to decrease in size before the end of the test period of 100 min. The HPMC E4M matrices were little effected by the addition of propranolol hydrochloride. This was surprising since the HPMC K grade was reported to have a higher gelation temperature (Sarkar, 1979) and cloud point (Mitchell et al., 1993) than the HPMC E grade. Therefore, the HPMC K grade would be expected to change least with changes in temperature and addition of additives.

The plateau seen in the swelling profiles of the matrices containing propranolol hydrochloride may be due either to the solvent fronts on each face of the matrix meeting in the centre of the tablet (thus there was no further unhydrated polymer to hydrate and expand) or to the protective gel coat only allowing a small quantity of water to diffuse into the inner core. The plateau would therefore then represent the stage where the water entering the tablet and hydrating its

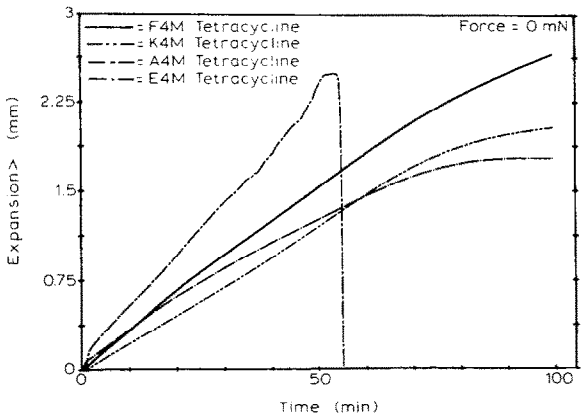

Fig. 4. The swelling profiles of matrices containing 50% hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M and 50% tetracyline hydrochloride at 37°C.

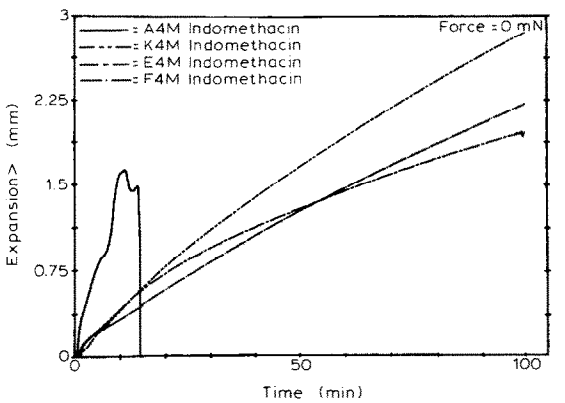

Fig. 5. The swelling profiles of matrices containing 50% hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M and 50% indomethacin at 37°C.

inner layers is equivalent to the relaxation of the gel layer. The time at which the tablet starts to reduce in size represents the point when the relaxation of the gel exceeds the speed at which water is diffusing into the tablet.

Tetracycline hydrochloride had a similar, but less profound, effect to propranolol hydrochloride on the swelling of the polymer (Fig. 4). This was seen particularly with the methylcellulose A4M matrix. The inclusion of tetracycline hydrochloride in this matrix allowed the integrity to be maintained for approx. 50 min. This was 35 min longer than in the absence of drug (Mitchell et al., 1993) but not as long as in the presence of propranolol hydrochloride. Since tetracycline hydrochloride is almost twice as soluble as propranolol hydrochloride, the results suggest that the manner in which the integrity of the methylcellulose A4M matrix was maintained was unlikely to be related to the solubility of the drug concerned. It was shown in Table 1 that, at high concentrations, propranolol hydrochloride increased the cloud point more than tetracycline hydrochloride. Thus, although tetracycline hydrochloride salted in the polymer to a certain extent which was why the integrity of the methylcellulose A4M matrix was maintained for 50 min, propranolol hydrochloride salted in the polymer to a greater extent and gave greater protection to disintegration.

The HPMC E4M grade was again little affected by the addition of tetracycline hydrochloride. Although methylcellulose A4M, was the fastest to swell, matrices with HPMC F4M swelled to a greater extent over the whole of the test period (Fig. 4). Indomethacin is practically insoluble in water and hence it would be anticipated to have very little influence on the swelling of methylcellulose and HPMC matrices. The only effect it produced appeared to be one of dilution (Fig. 5). It did not increase the integrity of meth-

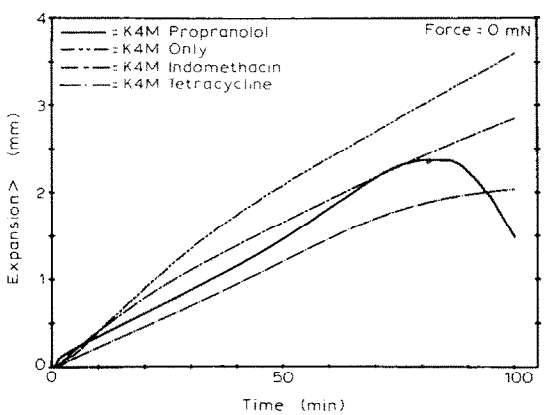

Fig. 6. The swelling profiles of matrices containing 50% hydroxypropylmethylcellulose K4M and 50% propranolol hydrochloride, tetracycline hydrochloride or indomethacin at 37°C.

ylcellulose matrices nor did it cause changes in the swelling profiles of the HPMC matrices.

Fig. 6 shows the typical swelling profiles of HPMC K4M matrices containing 50% propranolol hydrochloride, tetracycline hydrochloride or indomethacin or solely HPMC K4M. The latter matrix swelled to the greatest extent, followed by the matrix containing HPMC K4M : tetracycline hydrochloride. The HPMC K4M : propranolol hydrochloride matrix was next but decreased in size before the end of the test. The HPMC K4M : indomethacin matrix swelled the least. All the matrices that contained 50% drug swelled to more than 50% of the extent of matrices which containing solely HPMC K4M swelled. This suggests that even the addition of the insoluble drug, indomethacin, resulted in an increase in the extent of swelling.

Since all of the drugs effected the swelling of the polymer, it was considered necessary to investigate the effect of these drugs on the thickness of the gel layer forming at the matrix surface. When in contact with water, cellulose ether matrices have two boundaries. One is the swelling front which is a boundary between the hydrated matrix and the solvent (water). This can be measured by a thermomechanical analyzer in expansion mode (Mitchell et al., 1993). The other boundary is between the rubbery matrix (hydrating polymer) and the glassy matrix (dry polymer) which can be measured by a thermal mechanical analyzer in penetration mode (Mitchell et al., 1993). The difference between these two boundaries is the gel layer thickness. Since drugs changed the swelling profiles of HPMC and methylcellulose matrices they should also change the rate at which the gel layer is produced.

The rate at which the gel layer was produced varied with the addition of drug to the matrix (Fig. 7). In matrices containing propranolol hydrochloride and tetracycline hydrochloride the production of the gel layer was very rapid over the first hour but was relatively constant thereafter. This was in contrast to the gel layer production in the absence of drugs when gel production was rapid for the first 4 h and then decreased over time (Mitchell el al., 1993). Thicker gel layers were produced in the absence of drugs over

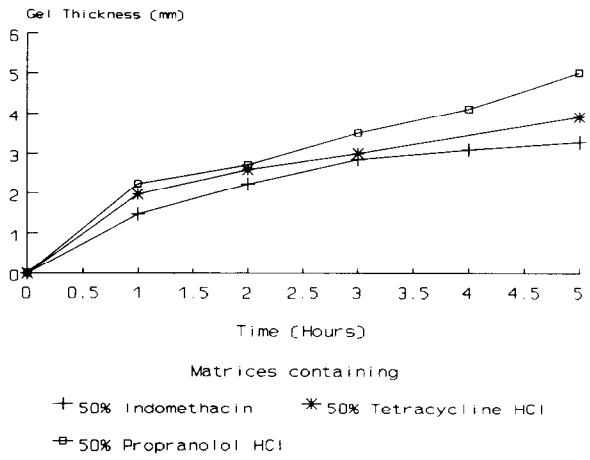

Fig. 7. The effect of time on the gel layer thickness of matrices containing 50% hydroxypropylmethylcellulose K4M and 50% of propranolol hydrochloride, tetracycline hydrochloride or indomethacin during contact with water at 37°C.

the test period. Matrices containing propranolol hydrochloride produced a thicker gel layer after five hours than matrices containing tetracycline hydrochloride or indomethacin. This mirrored the results from the swelling studies (Figs 4 and 5), where matrices containing propranolol hydrochloride swelled to a greater extent than those containing tetracycline hydrochloride or indomethacin. Indomethacin had little effect on the solubility of HPMC K4M and thus caused no extra swelling; its presence in the matrix simply acted as a diluent. The gel production profile for indomethacin (Fig. 7) was similar to that produced when no drug was present in the matrix (Mitchell et al., 1993).

Conclusions

The effects of drugs on the hydration, viscosity, swelling and gel layer of HPMC and methylcellulose gels and matrices production have been investigated. Propranolol hydrochloride and tetracycline hydrochloride were shown to play an active role in the swelling behaviour of HPMC and methylcellulose matrices. The mechanism for this was thought to be by salting in the polymer.

In addition, these drugs modified the ageing characteristics of gels containing cellulose ethers.

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