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The influence of concentration on the release of drugs from gels and matrices containing Methocel®

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Summary

The release of propranolol hydrochloride from hydroxypropylmethylcellulose and methylcellulose matrices has been examined at constant cellulose ether contents. As the drug content decreased, the release rate of propranolol became disproportionately higher. HPMC K4M, HPMC F4M and HPMC E4M all performed similarly. However, with methylcellulose matrices, a burst release at low drug levels was apparently due to a failure of the matrix to maintain integrity. Explanations were sought on the basis of diffusional studies. Apparent diffusion coefficients were in the order of $3.1–3.8 \times 10^{-6}$ cm^2 s^{-1} for propranolol hydrochloride. Each of the four grades performed similarly. Using similar diffusional studies, but HPMC K15M as the polymer, an apparent diffusion coefficient of 3.6×10^{-6} cm^2 s^{-1} was derived, indicating that the coefficient was independent of molecular weight. The coefficient was dependent on HPMC content decreasing from approx. 5.5×10^{-6} to 3×10^{-6} cm^2 s^{-1} as the HPMC content was increased from 5 to 15% w/w. The diffusion coefficients of tetracycline hydrochloride were lower and conversion to the free base is postulated as the explanation of previously described anomolous release for this drug from matrix tablets. The tortuosity of the gels was independent of the included drug.

Introduction

Hydroxypropylmethylcellulose, a cellulose ether, is well recognised as forming the basis of matrix tablets which provide a control of drug release. Its uses, and a comparison with performance to that of methylcellulose, have been reviewed by Alderman (1984). Drug release is controlled, for water soluble drugs, by diffusion or, for poorly water soluble drugs, by erosion (Ford et al., 1991a). Consequently, the roles played by drug/cellulose ether ratio (Ford et al., 1985a, 1987, 1991a), viscosity grade (Salomen et al., 1979; Ford et al., 1985a,b), compaction pressure (Lapidus and Lordi, 1966; Huber and Christienson, 1968; Ford et al., 1985a), drug particle size (Ford et al., 1985a–c) and external environments such as the composition of the dissolution fluid (Mitchell et al., 1990a) have been thoroughly researched.

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In 1987, Ford et al. considered that certain drugs such as tetracycline hydrochloride may interact with the hydration processes of HPMC following contact with water. By using thermal analysis, Mitchell et al. (1989) were able to show that propranolol hydrochloride modified the equilibrium water/HPMC content in HPMC gels. Additionally, it was postulated that water soluble drugs such as propranolol hydrochloride and tetracycline hydrochloride contributed to the extent of swelling in methylcellulose and hydroxypropylmethylcellulose based gels (Mitchell et al., 1991).

Until now, much of the basic research into HPMC matrices has involved altering the HPMC content whilst monitoring at a constant drug level. This paper describes the influence of varying the drug level but at constant cellulose ether levels within matrices and gels. This approach has also been used to determine the diffusion coefficient of drugs in HPMC gels. Previous papers which have investigated the propranolol hydrochloride HPMC system include those by Ford and co-workers (1985b, 1987, 1991b) and Mitchell and co-workers (1989, 1990b, 1991) and for tetracycline hydrochloride (Ford et al., 1987) where anomalous release was described.

Materials and Methods

Materials

Propronolol hydrochloride and tetracycline hydrochloride were of B.P. standard. Magnesium stearate was reagent grade (British Drug Houses). The Methocels used were Methocel A4M, Methocel E4M, Methocel F4M and Methocel K4M manufactured by Dow Chemicals (U.S.A.) and supplied by Colorcon Ltd (Kent, U.K.). These correspond to USP types methylcellulose and hydroxypropylmethylcellulose (HPMC) types 2910, 2906 and 2208, respectively.

Matrix preparation

Cellulose ethers, hydroxypropylmethylcellulose grades K4M, E4M or F4M or methylcellulose A4M were used to produce the matrices (7.94 mm; shallow convex). Tablets contained 150 mg of Methocel, 20, 40, 80 or 160 mg propranolol hydrochloride, and 0.75% magnesium stearate and were prepared by direct compression of the powder blends using a Manesty F3 tableting machine.

Dissolution methodology

Dissolution was measured using a Series 8000 dissolution tester, (Copley Instruments, Nottingham, U.K.) and continuously monitored by a Spectrophotometer (Kontron, Uvikon 810) according to the methods described by Ford et al. (1985b). The USP I basket method was used rotating at 100 rpm in 1000 ml glass-distilled water maintained at 37°C, monitoring propranolol at 288 nm. The results reported are the means of six tablets for each batch of tablets.

Gel preparation and diffusion studies

Hydroxypropylmethylcellulose and methylcellulose gels were prepared by heating one third of the total amount of freshly distilled water to 80°C and then adding the required amount of cellulose ether and dispersing it. The required amounts of drug were dissolved in distilled water and their solution added to the cellulose ether suspensions. Cold water was then added to make the gels up to weight. Approx. 50 g of gels were prepared containing 5, 10 or 15% HPMC E4M, HPMC F4M, HPMC K4M or HPMC K15M, or methylcellulose A4M and 3.2 or 6.4% propranolol hydrochloride or 5, 10 or 20% tetracycline hydro-

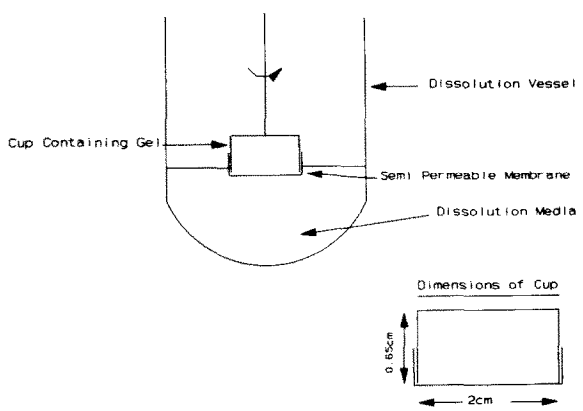

Fig. 1. Apparatus used to measure drug diffusion through hydroxypropylmethylcellulose and methycellulose gels.

chloride. The apparatus used to measure diffusion is shown in Fig. 1. Quantities of gel (2.5 g) were weighed into the 'cup' with a one way semi-permeable membrane (Medical International, London) covering it. The cup was then mounted on the lower surface of the disc of the driving shaft of the United States Pharmacopeial dissolution test apparatus part of the Copley Series 8000 Dissolution Tester. The cup was lowered so that the semi-permeable membrane just dipped into 300 ml of distilled water maintained at 37°C rotating the disc at 100 rpm. Four determinations were carried out for each gel formation tested. Flow through facilities, as described under *Dissolution methodology* were used to monitor the release of propranolol hydrochloride at 288 nm and tetracycline hydrochloride at 390 nm.

Results and Discussion

The dissolution data for the release of propranolol hydrochloride, from the matrices containing the various cellulose ethers, when plotted as a function of the square root of time, produced straight line plots for the data corresponding to 5–70% drug release (as Ford et al., 1985b). The correlation coefficients for all data were > 0.997 and the release rates, both as % $min^{-1/2}$ and mg $min^{-1/2}$, are given in Table 1.

As the content of propranolol hydrochloride in the matrices was reduced, in matrices containing 150 mg cellulose ether, the ability to sustain drug release decreased. In matrices containing methylcellulose A4M, the dissolution rate (estimated as % $min^{-1/2}$) increased from 4.55 to 20.58% $min^{-1/2}$ as the content of propranolol was lowered from 160 to 20 mg. Obviously the dissolution rates, as estimated as mg $min^{-1/2}$ (Table 1), decreased from 7.28 to 4.12 mg $min^{-1/2}$ over the similar range of drug but it must be emphasised that this 40% reduction in dissolution rate was achieved with a 87.5% reduction in matrix content of propranolol and the overall release rate of drug from the matrix, considering the reduction in dose, increased. Over similar drug contents, the matrices containing HPMC E4M, HPMC F4M or HPMC K4M displayed a smaller, but still apparent increase in dissolution rates. Fig. 2 illustrates the change in propranolol dissolution rates with change in drug content within the matrices.

TABLE 1

The effect of propranolol hydrochloride content on the release rates (mg $min^{-1/2}$ or % $min^{-1/2}$) of propranolol hydrochloride from tablets containing 150 mg Methocel, 20, 40, 80 or 160 mg propranolol hydrochloride and 0.75% w/w magnesium stearate

Methocel substitution type	Propranolol hydrochloride content (mg)	Dissolution rates	
		% $min^{-1/2}$	mg $min^{-1/2}$
Methylcellulose	20	20.58	4.12
	40	10.82	4.33
	80	6.64	5.31
	160	4.55	7.28
HPMC E4M	20	6.05	1.21
	40	5.78	2.31
	80	5.15	4.12
	160	3.85	6.16
HPMC F4M	20	5.53	1.11
	40	5.57	2.23
	80	4.95	3.96
	160	4.02	6.43
HPMC K4M	20	5.40	1.08
	40	5.36	2.14
	80	5.16	4.13
	160	3.87	6.19

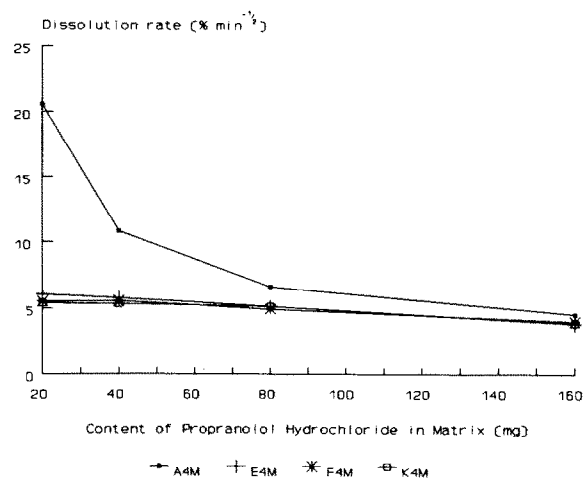

Fig. 2. Effect of propranolol content on dissolution rates of propranolol hydrochloride content from matrices prepared from 150 mg hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M.

The failure of matrices containing cellulose ethers to provide a sustained release of drugs has not previously been predicted. This is partly because earlier studies have maintained a constant drug level (dose) in the matrix and altered the drug/polymer ratio within the matrix by varying the content of cellulose ether. For instance, Ford et al. (1985a,b) in reporting the influence of drug/HPMC ratio on the release rates from matrices containing promethazine hydrochloride, aminophylline and propranolol hydrochloride, determined rates on the basis of constant doses of 25, 225 and 160 mg for the three drugs, respectively. These studies also neglected any influences that the drug had on the water distribution within the matrices. Using cloud point determinations, Mitchell (1992) demonstrated that propranolol hydrochloride, at concentrations of 0.02–0.2 M, increased the cloud point of HPMC and therefore increased the solubility of hydroxypropylmethylcellulose. Using differential thermal analysis, Mitchell et al. (1989) demonstrated that this drug altered the water distribution in HPMC gels. It could appear, therefore, from Table 1 and Fig. 2, that drug release is modified by effects that the drug produces within the cellulose ether matrices. The presence of propranolol helps to maintain the gel structure and to provide sustained release at higher drug levels. Interestingly, the three grades of HPMC (E4M, F4M, K4M) behaved similarly and the major difference was that methylcellulose A4M failed to sustain release at low drug content. Mitchell et al. (1993) have shown that the major difference in physical properties between HPMC grades K, E and F, and methylcellulose grade A, was their cloud point. When the temperature was below the cloud point, the polymer associated with a large amount of water and gelled rapidly. If temperatures exceeded the gelation temperature water was not taken up by the polymer. This is a gradual response; as the cloud point, or indeed gelation temperature, is approached, the polymer loses more and more water of hydration and the speed of gelation in a hydrating matrix would decrease. This also accounts for the results seen in Table 1. At 37°C, a matrix containing only methylcellulose A4M disintegrated (Mitchell et al., 1993). This was because the gelation temperature was below that of the dissolution media. However, when the matrix contained 160 mg propranolol hydrochloride, the drug salted in the polymer by increasing the gelation temperature above that of the dissolution media. As the quantity of propranolol hydrochloride in the tablet decreased, this salting-in effect was reduced and the gelation temperature of the polymer decreased. The low dose of 20 mg propranolol failed to salt-in the polymer in the matrices leading to a loss in integrity and rapid drug release.

Fig. 2 shows the change in release rates in relation to the amount of cellulose ether in the matrix. Only the release rates from methylcellulose A4M matrices changed dramatically with polymer content. Cloud point determinations (Mitchell et al., 1993) showed that methylcellulose A4M dehydrated more readily with increase in temperature than the other grades of cellulose ether as the concentration of polymer increased. At low concentrations the cloud point of methylcellulose A4M was greater than those of HPMC K4M HPMC E4M or HPMC F4M, but this decreased rapidly with increase in temperature. There is an analogy with the results presented here, in that at high drug and low polymer contents methylcellulose A4M produced the sustained release but at low drug and high polymer content it allowed burst release.

It is claimed that the release mechanism from hydrophilic matrices is considered to be diffusion for soluble drugs (Alderman, 1984). Bamba et al. (1979) outlined several possible rate determining steps for the release of a drug from gelling matrices. These were the permeation of water, the gelation rate, the dissolution rate of drug into the permeating water and the diffusion rate of drug through the gel. Bamba et al. (1979) concluded that the diffusion of water into the tablet and diffusion of dissolved drug out through the gelled layer were the two processes which limited drug liberation.

Drug diffusion through most type of polymeric systems can be described by Fickian diffusion (Peppas, 1984). Fickian diffusion can be described by Eqn 1. The amount of substance, dm, diffusing in the x direction in time dt across an

area A is proportional to the concentration gradient dc/dx in the plane of that area.

$$dm = -DA(dc/dx)\,dt \quad (1)$$

Eqn 1 has a limitation in that it does not take into account the increase in size of a matrix due to polymer swelling. A second recognised type of diffusion is anomalous diffusion (Peppas and Franson, 1983; Peppas, 1984, 1985). Release from initially dry, hydrophilic glassy polymers that swell when added to water show anomalous diffusion as a result of relaxation of macromolecular chains. Diffusion can be Fickian or anomalous depending on the thermodynamic state of the polymer during release (Duda and Vrentas, 1970). Fickian diffusion occurs at low penetrant concentrations below the glass transition temperature of the polymer, whereas anomalous diffusion occurs at higher penetrant concentrations above the glass transition temperature of the polymer (Crank, 1975). A third class of diffusion has also been reported – Case II diffusion (Thomas and Windle, 1982). This type is characterised by linear drug release kinetics and a sharp diffusion front and generally occurs in polymer-penetrant systems in which the penetrant substantially swells the polymer (Thomas and Windle, 1982).

Diffusion is the main mechanism of release for water soluble drugs from HPMC matrices (Ford et al., 1991a). Therefore, the effect of drug type on diffusion through HPMC and methylcellulose gels using propranolol hydrochloride and tetracycline hydrochloride as model drugs was examined. The release rates of drugs from matrices have been described by W. Higuchi (1962) and T. Higuchi (1963). Higuchi (1962) derived Eqn 2 which describes the release of a drug with high aqueous solubility and which has dissolved when the matrix is hydrated.

$$W_r/t^{1/2} = 2W_o(S/V)(D'/\pi)^{1/2} \quad (2)$$

where W_r is the amount of drug dissolved in time t, W_o denotes the dose of the drug, S is the effective diffusional area, V represents the effective volume of the hydrated matrix, ϵ is the porosity of the hydrated matrix and D' is the apparent diffusion coefficient.

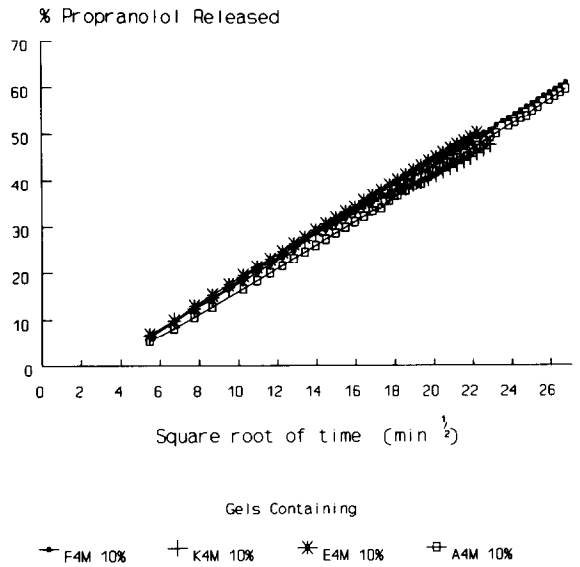

Fig. 3. The effect of substitution grade of cellulose ether on the release of propranolol hydrochloride from gels containing 10% w/w hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose and 6.4% propranolol hydrochloride.

Both equations predict a square root time dependent dissolution rate which assumes Fickian diffusion of the drug molecules through the hydrated matrix.

Eqn 2 was used to calculate the apparent diffusion coefficients of propranolol hydrochloride and tetracycline hydrochloride in the hydrated gels. The release data were plotted as the square root of time vs the % drug dissolved (for example, Fig. 3). The values of $W_r/t^{1/2}$ equal the slopes obtained from this plot; W_o is equal to the amount of drug in the gel at the beginning of the test. The values for S (effective diffusional area) and V (effective volume of the hydrated matrix) were constant because the gel is held in a rigid position, and therefore unable to expand throughout the test period. Eqn 2 was therefore rearranged to give Eqn 3 (Lapidus and Lordi, 1968).

$$D' = (\pi/60)(\text{slope } V/2W_oS)^2 \quad (3)$$

where slope denotes the gradient of a square root time vs % dissolved plot.

The factor of 60 was required to convert the units of apparent diffusion coefficient from cm^2 min^{-1} to cm^2 s^{-1}.

The diffusion of propranolol hydrochloride through gels containing HPMC K4M, HPMC E4M, HPMC F4M and methylcellulose A4M was examined. The data were plotted as square root of time vs percentage of drug released. The plots showed a straight line relationship with correlation coefficient > 0.998 (Fig. 3). The release rates and apparent diffusion coefficients (as determined by Eqn 3) are given in Table 2.

There were little differences in the calculated values of apparent diffusion coefficients from the various substitution types of cellulose ethers. This mirrored the dissolution rates from matrices prepared using the same polymer types as in this study (Ford et al., 1985a, 1987). The apparent diffusion coefficients for propranolol hydrochloride in the four 10% w/w cellulose ether gels were between 3.1 and 3.8×10^{-6} cm^2 s^{-1}. Other values for the apparent diffusion coefficients of various drugs in HPMC gels include 8×10^{-6} cm^2 s^{-1} for chlorpheniramine maleate (Lapidus and Lordi, 1968), between 6 and 10×10^{-6} cm^2 s^{-1} for salbutamol sulphate in 2.5% w/v HPMC E4M gels (Ferdinando-Bain et al., 1991), and between 1 and 1.5×10^{-6} cm^2 s^{-1} for verapamil hydrochloride in 10% w/v HPMC E4M gels (Ferdinando-Bain et al., 1991).

Two viscosity grades, HPMC K4M and HPMC K15M, were used to evaluate the effect of viscosity type of HPMC on the diffusion of propranolol. Again, a straight line relationship existed between % propranolol released and the square root of time. The apparent diffusion coefficients and diffusion rates are shown in Table 3. This shows that, despite the difference in molecular weight between the HPMC in the two gels, the diffusion rates of propranolol hydrochloride were similar.

TABLE 2

Release rates and apparent diffusion coefficients (D') for propranolol through hydroxypropylmethylcellulose K4M, E4M, F4M or methylcellulose A4M gels

Gel type	Drug release rate (% $min^{-1/2}$)	Apparent diffusion coefficient ($\times 10^6$) (cm^2 s^{-1})
10% K4M 6.4% PHCl	2.36	3.1
10% A4M 6.4% PHCl	2.59	3.7
10% E4M 6.4% PHCl	2.62	3.8
10% F4M 6.4% PHCl	2.59	3.7

TABLE 3

The effect of polymer viscosity type on the apparent diffusion coefficients of propranolol hydrochloride from hydroxypropylmethylcellulose gels

Gel type	Release rate (% $min^{-1/2}$)	Apparent diffusion coefficient ($\times 10^6$) (cm^2 s^{-1})
5% K15M 6.4% PHCl	3.21	5.7
10% K15M 6.4% PHCl	2.54	3.6
15% K15M 6.4% PHCl	2.40	3.2
5% K4M 6.4% PHCl	3.34	6.2
10% K4M 6.4% PHCl	2.36	3.1
15% K4M 6.4% PHCl	2.32	3.0

PHCl, propranolol hydrochloride.

Therefore, increasing the molecular weight, and hence the chain length of the polymer, had little effect on the apparent diffusion coefficients. These results concur with the findings of Ford et al. (1985a) which showed that the dissolution rates of promethazine from matrices prepared from HPMC, K4M and HPMC K15M were similar. Therefore, the molecular weight of HPMC is of little importance in the control of drug release from matrices.

The release rates of propranolol hydrochloride decreased as the gel concentration of HPMC increased (Tables 3 and 4) from 5 to 15% w/w. This may be explained by an increasing polymer chain entanglement in gels containing higher contents of HPMC. This would result in a more concentrated gel and increased gel tortuosity. Thus, the diffusional path would become more convoluted and the diffusion rate would therefore decrease. The apparent diffusion coefficient did not change appreciably with increases in molecular weight, e.g., from K4M to K15M. It may therefore be postulated that gel tortuosity does not increase with polymer molecular weight.

The diffusion rates of both propranolol hydrochloride and tetracycline hydrochloride were

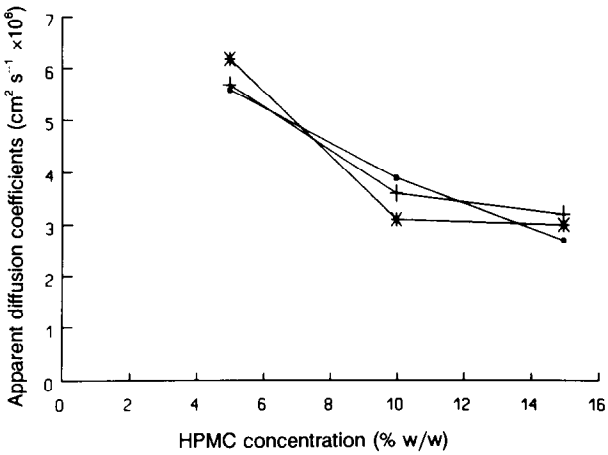

Fig. 4. The effect of the gel concentration on the apparent diffusion coefficients of propranolol hydrochloride in hydroxypropylmethylcellulose KI5M and K4M gels. Gels containing: (■) 3.2% propranolol:K15M; (+) 6.4% propranolol:K15M; (*) 6.4% propranolol:K4M.

studied to determine their true diffusion coefficients and the tortuosity of the HPMC gel. The apparent diffusion coefficients obtained for propranolol hydrochloride were similar at different drug loadings despite different HPMC molecular weights (Fig. 4). The apparent diffusion coefficients obtained for tetracycline hydrochloride were not (Table 4). Large variations in apparent diffusion coefficients were apparent with changes in drug loading (Fig. 5). As drug loading increased the apparent diffusion coefficients of the drugs decreased. The reason for this behaviour was probably due to the nature of tetracycline hydrochloride. On standing in water tetracycline hydrochloride converts to tetracycline base which is less soluble than tetracycline hydrochloride (Ali, 1984). This was demonstrated by preparing a solution of tetracycline hydrochloride in water and leaving it to stand for several hours. When high concentrations of tetracycline hydrochloride were used in the gels, i.e., 1 and 2% w/v, precipitation was observable in the gel. The effect of this precipitation would be to hinder diffusion of tetracycline hydrochloride through the gel and thus decrease the apparent diffusion coefficient. Ford et al. (1987) reported that tetracycline hydrochloride gave complex release kinetics from HPMC K15M matrices, showing a sigmoidal release pattern, when % drug released vs square root time

TABLE 4

The effect of drug loading dose on the apparent diffusion coefficients of tetracycline hydrochloride and propranolol hydrochloride in hydroxypropylmethylcellulose gels

Gel type	Release rate (% $min^{-1/2}$)	Apparent diffusion coefficient ($\times 10^6$) ($cm^2\ s^{-1}$)
5% HPMC K15M 5% THCl	2.08	2.4
10% HPMC K15M 5% THCl	1.79	1.8
15% HPMC K15M 5% THCl	1.45	1.2
5% HPMC K15M 10% THCl	2.11	2.5
10% HPMC K15M 10% THCl	1.37	1.0
15% HPMC K15M 10% THCl	1.44	1.1
5% HPMC K15M 20% THCl	1.17	0.8
10% HPMC K15M 20% THCl	1.08	0.6
15% HPMC K15M 20% THCl	0.93	0.5
5% HPMC K15M 3.2% PHCl	3.18	5.6
10% HPMC K15M 3.2% PHCl	2.66	3.9
15% HPMC K15M 3.2% PHCl	2.20	2.7
5% HPMC K15M 6.4% PHCl	3.21	5.7
10% HPMC K15M 6.4% PHCl	2.54	3.6
15% HPMC K15M 6.4% PHCl	2.40	3.2

PHCl, propranolol hydrochloride; THCl, tetracycline hydrochloride.

was plotted. Fig. 5 shows that a straight line relationship existed when the diffusion data were plotted in a similar manner to treatment of re-

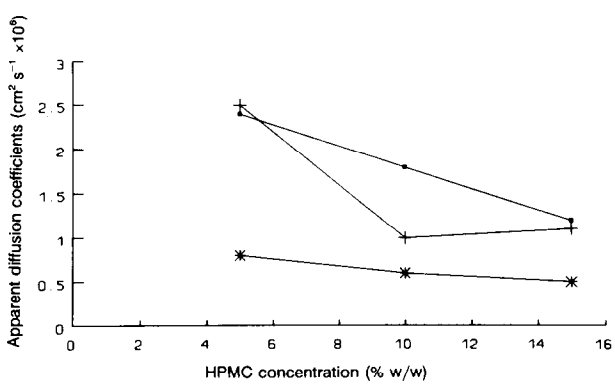

Fig. 5. The effect of drug concentration on the apparent diffusion coefficients of tetracycline hydrochloride in hydroxypropyl methylcellulose K15M gels. Gels containing: (■) 5% tetracycline HCl; (+) 10% tetracycline HCl; (*) 20% tetracycline.

sults by Ford et al. (1987). However, there are some fundamental differences between the method to test diffusion through a gel and release from a hydrating matrix. The first was that prehydrated gels were used, whereas Ford et al. (1987) used matrices which had to hydrate during the test. The second difference was that erosion of the samples was made impossible, since they were fully enclosed. These differences probably account for the, differences seen in release patterns. The sigmoidal release patterns seen by Ford et al. (1987) could be accounted for by the conversion of tetracycline hydrochloride to the less soluble tetracycline free base, during gelation.

The apparent diffusion coefficients for propranolol hydrochloride were greater than those of tetracycline hydrochloride (Table 4). This was probably due to the smaller molecular size of propranolol compared with tetracycline, the molecular weight for propranolol hydrochloride being 295, and that of tetracycline hydrochloride is 481. The tetracycline molecule would have a relatively greater spatial size than the propranolol molecule, and therefore would find it more difficult to diffuse through the gel.

According to Higuchi (1963), the true and apparent diffusion coefficients are related by the tortuosity of the gel by Eqn 4.

$$D' = D/\tau \qquad (4)$$

where D' is the apparent diffusion coefficient ($cm^2\ s^{-1}$), D denotes the true diffusion coefficient ($cm^2\ s^{-1}$) and τ is gel tortuosity.

At the lowest drug concentrations (3.2% propranolol hydrochloride and 5% tetracycline hydrochloride), a plot of apparent diffusion coefficient against polymer concentration gave a straight line (Figs 4 and 5).

Extrapolation of this straight line to zero polymer concentration should give values for the true diffusion coefficient, which is the diffusion coefficient of the drug in the absence of polymer. The extrapolated value of the apparent diffusion coefficient of propranolol hydrochloride was $6.99 \times 10^{-6}\ cm^2\ s^{-1}$ and for tetracycline hydrochloride was $3.01 \times 10^{-6}\ cm^2\ s^{-1}$. Inserting these values into Eqn 1 produced the estimated values for gel tortuosity (Table 5). The tortuosity of the gels was found to be similar at each gel concentration. The tortuosity increased as the gel concentration increased. This indicates that chain entanglement does in fact increase as the concentration increased. Even though the spatial size of the two drugs used to estimate gel tortuosity varied, they both gave similar estimations of gel tortuosity.

TABLE 5

Estimation of tortuosity values of hydroxypropylmethylcellulose K15M gels

Gel concentration	Estimation of tortuosity using	
	Propranolol hydrochloride	Tetracycline hydrochloride
5% w/w	1.250	1.258
10% w/w	1.786	1.699
15% w/w	2.636	2.588

Unfortunately, values of tortuosity could not be estimated from data produced from gels containing higher concentrations of propranolol hydrochloride or tetracycline hydrochloride, since both propranolol hydrochloride and tetracycline hydrochloride were present at concentrations above their solubility. As the concentration of the drug in the gel increased, so as to exceed its solubility in the gel, the straight line relationship seen between apparent diffusion coefficients and gel concentration at high drug concentrations ceased to exist. Hence, extrapolation of the plots could not be undertaken. Despite drugs playing a role in the water distribution with HPMC matrices and gels (Mitchell et al., 1989) it would appear that different drugs do not markedly influence gel tortuosity.

Summary

Diffusion of propranolol hydrochloride and tetracycline hydrochloride through HPMC gels was found to be dependent on the gel concentration. As the gel concentration increased, the gel tortuosity was found also to increase. Diffusion was found not to be dependent on the polymer molecular weight. Release of propranolol hydro-

chloride from matrices containing cellulose ethers was dependent on drug content. The drug appeared to be involved in maintaining the integrity of the matrix. In matrices containing methylcellulose, low contents of drug (20 mg per 150 mg methylcellulose) resulted in rapid drug release.

References

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

Ali, S.L., Tetracycline hydrochloride. In Flory, K. (Ed.), *Analytical Profiles of Drug Substances*, Vol. 13, Academic Press, New York, 1984, pp. 597–653.

Bamba, M., Pusieux, F., Marty, J.P. and Cartensen, J.T., Release mechanisms in gel-forming sustained release preparations. *Int. J. Pharm.*, 2 (1979) 307–315.

Crank, J., *Mathematics of Diffusion*, Clarendon, Oxford, 1975, pp. 9–25.

Duda, J.L. and Ventras, J.S., Syrene polymers. Physical properties – diffusion. In Mark, H.F. (Ed.), *Encylopaedia of Polymer Science and Technology*, Wiley, New York, 1970, pp. 326–342.

Ferdinando-Bain, J.C., Ganderton, D. and Soloman, H.C., Factors affecting release rate of verapamil and salbutamol from hydroxypropylmethylcellulose sustained release tablets. *Proc. 10th Pharmaceutical Technology Conference, Bologna*, 1 (1991) 337–340.

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. and Hogan, J.E., Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 24 (1985a) 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 (1985b) 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 (1985c) 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.

Higuchi, T., Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Higuchi, W.I., Analysis of data on the medicament release from ointments. *J. Pharm. Sci.*, 51 (1962) 802–804.

Huber, H.E. and Christenson, G.L., Utilization of hydrophilic gums for the control of drug substance release from tablet formulation: II. Influence of tablet hardness and density on dissolution behaviour. *J. Pharm. Sci.*, 57 (1968) 164–166.

Lapidus, H. and Lordi, N.G., Some factors affecting the release of a water-soluble drug from a compressed hydrophilic matrix. *J. Pharm. Sci.*, 55 (1966) 840–843.

Lapidus, H. and Lordi, N.G., Drug release from compressed hydrophilic matrices. *J. Pharm. Sci.*, 57 (1968) 1292–1301.

Mitchell, K., A study of factors controlling drug release from matrices containing cellulose ethers. Ph.D. Thesis, Liverpool John Moores University (1992).

Mitchell, K., Armstrong, D.J., Elliott, P.N.C., Ford, J.L., Rostron, C. and Hogan, J.E., Differential thermal analysis of hydroxypropylmethylcellulose gels: influence of water content and propranolol hydrochloride. *J. Pharm. Pharmacol.*, 42 (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., 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 up-take and dissolution of propranolol hydrochloride. *J. Pharm. Pharmacol.*, 43 (1990b) 124P.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., Swelling behaviour of cellulose ether matrix tablets. *J. Pharm. Pharmacol.*, 44 (1991) 127P.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E. and Rostron, C., The influence of substitution type on the performance of methylcellulose and hydroxypropylmethylcellulose in gels and matrices. *Int. J. Pharm.*, 100 (1993) 143–154.

Peppas, N.A., Mathematic modelling of diffusion processes in drug delivery systems. *Controlled Drug Bioavailability*, 1 (1984) 203–237.

Peppas, N.A., Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta Helv.*, 60 (1985) 110–111.

Peppas, N.A. and Franson, N.M., The swelling interface number as a criterion for prediction of diffusional solute mechanisms in swellable polymers. *J. Polym. Sci. Polym. Phys.*, 21 (1983) 983–984.

Salomen, J.L., Doelker, E. and Burl, P., Sustained release of a water soluble drug from hydrophilic compressed dosage forms. *Pharm. Ind.*, 41 (1979) 799–802.

Thomas, N.L. and Windle, A.H., A theory of case II diffusion. *Polymer*, 23 (1982) 529–542.