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The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrix tablets

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Summary

The ability of a salt to lower the cloud point of hydroxypropylmethylcellulose (HPMC) gels was found to follow their order in the lyotropic series, i.e. chloride < tartrate < phosphates and potassium < sodium. Anions were more important than cations in lowering the cloud point. The dissolution of propranolol hydrochloride from HPMC matrix tablets into dissolution media containing a number of different phosphate and chloride salts was investigated. As the ionic strength increased the dissolution rates decreased to a minimum before rising to give a 'burst' release. Disintegration times of HPMC matrices, without active, also varied to the ionic strength of the disintegration medium. By determining the cloud points it proved possible to predict if a matrix will show burst release in a given solution of electrolytes. Propranolol hydrochloride, promethazine hydrochloride, aminophylline and tetracycline hydrochloride increased the cloud point but theophylline and quinine bisulphate had little effect on the cloud point.

Introduction

Hydroxypropylmethylcellulose (HPMC) is frequently used in dosage forms to provide a sustained-release of drugs. The ability of HPMC to hydrate rapidly when in contact with water and thus form a protective gel around the tablet contents is an essential property for this role (Alderman, 1984).

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Relationships between drug release rates and formulation factors such as drug: HPMC ratio (Ford et al., 1985a,b), viscosity grade of HPMC (Ford et al., 1985a), particle size of drug (Ford et al., 1985a,b), added lubricant (Ford et al., 1985a), added excipients (Ford et al., 1987), drug solubility (Ford et al., 1987) and tablet shape (Ford et al., 1987) have been evaluated using water as the dissolution media. Although release rates could be usually described by root-time plots (Higuchi, W., 1962; Higuchi, T., 1963) more sophisticated data treatments differentiated release mechanisms (Ford et al., 1987).

Attempts have been made to quantify the in-

fluences of variation media on dissolution rates. Thus the effect of pH on the dissolution rates from HPMC matrices (Ford et al., 1985c) and the disintegration of matrices based on some cellulose derivatives into solutions containing phosphate and chloride ions at different ionic strengths (Fagan et al., 1989) were examined.

The hydration of HPMC is affected by temperature (Lapidus and Lordi, 1968; Sarkar, 1979). As the temperature of the gel increases HPMC loses its water of hydration: this is accompanied by a drop in relative viscosity. As the polymer loses more water of hydration a polymer-polymer interaction takes place, primarily caused by the methoxy-substituents which are hydrophobic (Sarkar, 1979), giving a dramatic increase in relative viscosity. This is known as the gel point. Another phenomenon observed in HPMC gels with increase in their temperature is a precipitation of the polymer molecules, a property which can be measured by light transmission (Sarkar, 1979). The temperatures at which light transmission reaches 97.5 and 50% are called incipient precipitation temperature and cloud point, respectively (Sarkar, 1979). However the latter is often measured subjectively as the lowest temperature at which turbidity develops (Klug, 1971; Fagan et al., 1989). There seems to be no relationship between the thermal gelation temperature and the cloud point. At low concentrations of HPMC it is possible to produce a turbid solution before gelation occurs whilst at higher concentrations a gel is produced before turbidity is apparant. However, both properties are affected by electrolytes in a similar manner i.e. an electrolyte that reduces the cloud point will reduce the thermal gelation temperature. The effects of electrolytes on the thermal gelation temperature and the cloud point of methylcellulose (Levy and Schwarz, 1958; Touitou and Donbrow, 1982) and hydroxyethylcellulose and hydroxypropylcellulose (Klug, 1971) have been investigated but such data for HPMC is limited (Fagan et al., 1989).

This paper reports the effect of pH, electrolytes, and drugs on the cloud points of HPMC gels and the effect of these electrolytes on the dissolution of propranolol hydrochloride from HPMC matrices, and on the disintegration of HPMC matrices containing no drug.

Materials and Methods

Materials

The hydroxypropylmethylcellulose was manufactured by Dow Chemicals (U.S.A.) as Methocel K15M and Methocel K100 grades. Sodium dihydrogen orthophosphate, disodium hydrogen orthophosphate, trisodium orthophosphate, tetrasodium pyrophosphate, sodium chloride, sodium sulphate, dipotassium hydrogen orthophosphate, potassium dihydrogen orthophosphate, potassium chloride, potassium tartrate, aluminium chloride, magnesium stearate, hydrochloric acid, and sodium hydroxide were all of laboratory reagent standard from British Drug Houses (Poole, U.K.). Propranolol hydrochloride, tetracycline hydrochloride, promethazine hydrochloride, aminophylline, theophylline and quinine bisulphate were all of B.P. standard.

Cloud point studies

Quantities of gel (50 g) were prepared to contain 2% w/v HPMC by dispersing the pre-weighed polymer into approximately one third of the total amount of distilled water previously heated to 80°C, adding distilled water containing the required amount of dissolved electrolyte or drug and making up to weight with distilled water. When cool the weights were checked and more cool water added if necessary. The gels were stored overnight in a refrigerator to hydrate fully. Samples were transferred to disposable 1 cm^2 cuvettes (Elkay). Any air bubbles entrapped in the gels were removed by centrifugation. The samples were then placed in a water bath with a temperature regulator and their temperature gradually increased. Initially readings were taken at 5°C intervals which were reduced to 1°C increments near the cloud points. The samples were measured spectrophotometrically at 800 nm against a 2% aqueous solution of the gel maintained at room temperature. The cloud point was taken to be the temperature at which the light transmission was 50% of the reference.

For studies on the effect of pH on the cloud point of gels containing 2% HPMC K100, the gels were prepared as above but without the added electrolyte. After storing the samples overnight to

hydrate their pH was adjusted with 1 M HCl or 1 M NaOH to that required.

Disintegration studies

Tablets (1/4 inch, shallow convex) containing 300 mg HPMC K15M and 1% magnesium stearate were prepared by direct compression to a tablet crushing strength of approx. 11 kPa (Schleuniger). Tests were performed in triplicate using the British Pharmacopoeia (1988) disintegration apparatus in 800 ml of media at 37°C using discs. The test was stopped after 2 h if the tablets had not disintegrated.

Dissolution studies

Tablets (1/4 inch, shallow convex) containing 160 mg propranolol hydrochloride, 140 mg HPMC K15M, and 1% magnesium stearate were prepared by direct compression to a tablet crushing strength of approx. 8 kPa (Schleuniger). Three tablets were tested using a Copley Series 8000 automatic Dissolution Tester into 1 l of dissolution fluid buffer maintained at 37°C. The British Pharmacopoeia (1988) basket method was utilized, rotating at 100 rpm and monitoring the release of propranolol hydrochloride at 288 nm. All media were prepared in molar concentrations and contained only the electrolyte stated. When the pH of the media was adjusted to pH 6 ± 0.2 either 1 M HCl or 1 M NaOH was used. Their quantities added did not significantly increase the ionic strength of the media.

The ionic strength, I, of the solutions used for cloud point, disintegration and dissolution fluids were calculated according to Eqn 1 (Neibergall, 1975):

$$I = 0.5 \Sigma (mz^2) \quad (1)$$

where m is the molarity and z is the valency of each ion in the solution. In the calculation of ionic strength the difference between molarity and molality for the dissolution fluids was so slight that they were taken to be the same, the difference between the values being less than 1%.

Results and Discussion

Effect of pH on cloud points

Although HPMC is not thought itself to be affected by changes in pH (Alderman, 1984) the pH of a dissolution fluid is known to affect release rates of drugs from HPMC matrices. Ford et al. (1985c) showed that the dissolution rates of promethazine hydrochloride from matrices composed of HPMC were high at a pH of 1 or 3 but dropped considerably in media of pH of 7 or above. This was attributed to the formation of the insoluble, unionized form of promethazine which has a pK_a of 9.1, rather than to a specific pH effect on HPMC. This was confirmed by the effect of pH on the cloud points of 2% K100 gels (Table 1) which indicated that the cloud point was only affected by pH at low pH. On the basis of these results it was considered unnecessary to modify the pH of electrolyte solutions used to determine cloud points.

The effect of inorganic salts and drugs on the cloud point of 2% HPMC gels

Fig. 1 gives typical data used in the determination of the cloud point of HPMC gels. As the molality of a particular electrolyte increased the cloud point decreased (Figs 2 and 3). The ability of an electrolyte to salt out a polymer from its solution generally follows the salts order in the lyotropic series (Heyman et al., 1938). Univalent cations follow the order $Li^+ > Na^+ > K^+$, and more common anions follow the order $CNS^- < I^- < Br^- < NO_3^- < Cl^- <$ tartrate $< SO_4^{2-} < PO_4^{3-}$. Cloud point reduction is explained by ions (which have a greater affinity for water than HPMC) removing water of hydration from the polymer and

TABLE 1

The effect of pH on the cloud point of 2% K100 gels

Gel pH	Cloud point (°C)
1	64.5
3	68.8
5	70.5
7	70.5
9	70.5
12.23	69.7
K100 unadjusted	70.4

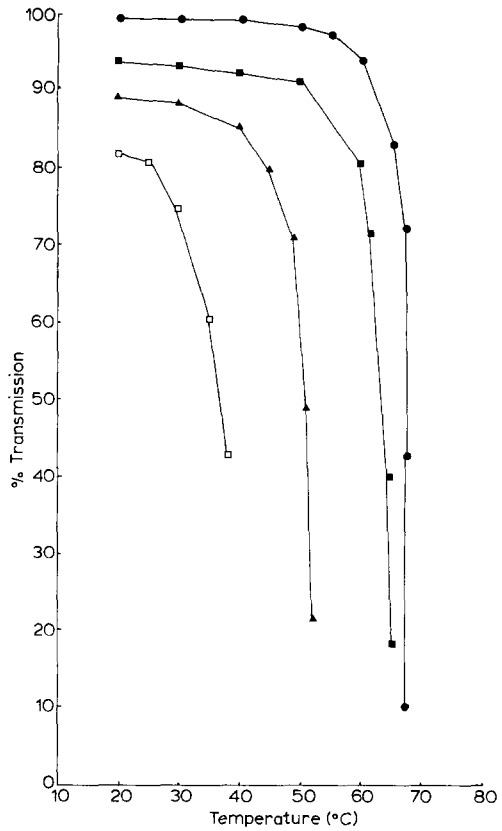

Fig. 1. The effect of temperature on the light transmission of some 2% HPMC K15M gels. The cloud point is taken as the temperature at which light transmission = 50%. (Solute) (•) Distilled water, (■) 0.02 M disodium hydrogen orthophosphate, (▲) 0.1 M disodium hydrogen orthophosphate; (□) 0.2 M disodium hydrogen orthophosphate.

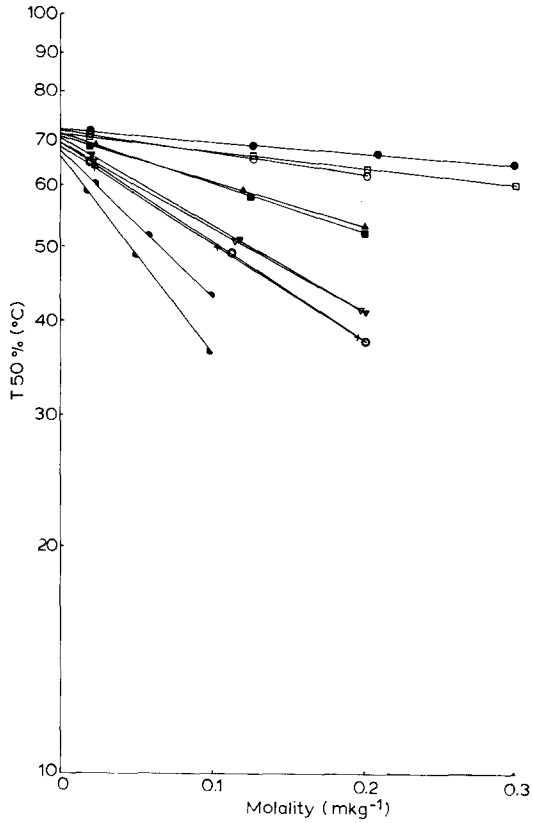

Fig. 2. The effect of solute and solute concentration on the cloud point (log scale) of some 2% HPMC K100 gels. (•) Potassium chloride, (○) aluminium chloride, (□) sodium chloride, (■) potassium dihydrogen orthophosphate, (▲) sodium dihydrogen orthophosphate, (▼) dipotassium hydrogen orthophosphate, (▽) potassium tartrate, (⊙) disodium hydrogen orthophosphate, (○) sodium sulphate, (◓) trisodium orthophosphate, (◒) tetrasodium pyrophosphate.

thus dehydrating or 'salting out' the polymer (Heyman et al., 1938). The relation between cloud point reduction and concentration of salt was generally linear (Figs 2 and 3). The cloud point may be regarded as a limit of solubility, since the turbidity produced is due to HPMC precipitating from solution. Eqn 2 (Niebergall, 1975) predicts the effect of electrolyte on polymer solubility.

$$\log S = \log S_0 \pm K_s \cdot m \qquad (2)$$

where $\log S$ is the solubility of polymer in an electrolyte solution, $\log S_0$ is the solubility of the polymer in water, K_s is a salting out constant empirically chosen for each salt and m is its molal concentration of the electrolyte. This equation does not predict the influences of temperature on polymer solubility in the presence of electrolytes. Consequently Eqn 3 was used to determine the effect of salt concentration on the cloud point, from the linear portions of Figs 2 and 3.

$$\log CP = \log CP_0 \pm K_{cp} m \qquad (3)$$

where $\log CP$ is the observed cloud point of HPMC in the solution of the electrolyte, $\log CP_0$ is a theoretical cloud point based on the intercept at zero solute concentration, K_{CP} is a salting out constant analogous to that in Eqn 2 and m is the molal

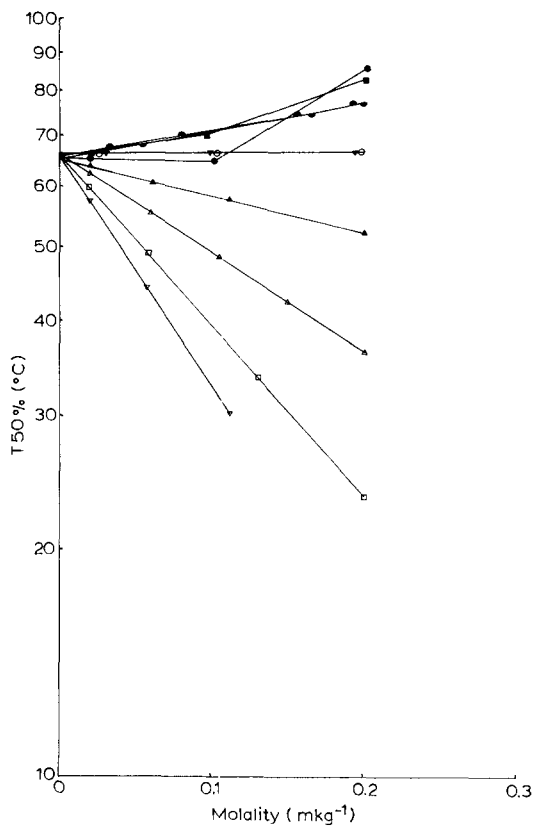

Fig. 3. The effect of drug and drug concentration on the cloud point (log scale) of some 2% HPMC K15M gels. (●) Promethazine hydrochloride, (■) propranolol hydrochloride, (◓) aminophylline, (▬) tetracycline hydrochloride, (○) theophylline, (▼) quinine bisulphate, (▲) sodium dihydrogen orthophosphate, (△) disodium hydrogen orthophosphate, (□) trisodium orthophosphate, (▽) tetrasodium pyrophosphate.

concentration. The gradient of the straight line portion, K_{cp}, is positive for salting in and negative for salting out. Values calculated by linear regression and using the straight line portions in Figs 2 and 3 are given in Table 2. It can readily be determined that the various sodium phosphate salts rank as tetrasodium pyrophosphate > trisodium orthophosphate > disodium hydrogen orthophosphate > sodium dihydrogen orthophosphate in order of their salting out ability. Thus, the decrease in cloud point escalated as the valency of the phosphate ion increased. Additionally the sodium salts (dihydrogen orthophosphate, monohydrogen orthophosphate and chloride) more readily caused salting out than the corresponding potassium salts and that tartrate and sulphate ions rank somewhat below hydrogen orthophosphate in their salting out abilities. It would suggest that the nature of the anion plays a more significant role than the cation in determining cloud point reduction since aluminium chloride reduces the cloud point of K100 to a similar extent as sodium chloride.

The cloud points involving HPMC K15M gels were lower than those of HPMC K100 gels, a difference of approx. 2°C being noted. Sarkar (1979) also found differences between the cloud points of different molecular weight K grades, e.g., HPMC K100 and HPMC K4M gave cloud points at 76 and 70°C, respectively. The pattern the electrolytes produced was otherwise similar for the two grades. For direct comparison to be made between the dissolution data cited here and by Ford et al. (1985c, 1987) the cloud points from HPMC K15M must be used. The drugs chosen (not quinine bisulphate) were utilized previously (Ford et al., 1987) when differences in their release rates from HPMC matrices were explained on the basis of their aqueous solubilities.

Touitou and Donbrow (1982) noted that large ions, e.g. tetracaine hydrochloride, sodium salicylate, and sodium benzoate each with low affinities for water, raised the gelation temperature, and presumably the cloud point, of HPMC. The effect was explained on the basis that a large ion is adsorbed onto the macromolecule, carrying with it water molecules raising the degree of hydration of the colloid. Quinine bisulphate was anomalous since, in spite of being water soluble (1 in 8 parts of water; British Pharmacopoeia, 1988) and containing sulphate ions, it did not affect the cloud point. One explanation could be that the hydrating effect of the quinine molecule was counteracted by the dehydrating effect of the sulphate ions. Theophylline, which is slightly soluble in water (British Pharmacopoeia, 1988), did not affect the cloud point.

Aminophylline and tetracycline hydrochloride gave straight line relationships between their concentration in gels and the observed cloud points (Fig. 3). In the case of tetracycline this did not explain a complex, non-Higuchian release pattern

TABLE 2

Salting out constants [k_{cp}] of additives derived from the cloud points of 2% HPMC K100 or 2% HPMC K15M gels

Additive	Concentration range (molal unless otherwise stated)	K_{cp}	
		HPMC K100	HPMC K15M
NaH_2PO_4	0.02 - 0.2	−0.63	−0.53
KH_2PO_4	0.02 - 0.2	−0.57	
Na_2HPO_4	0.02 - 0.2	−1.30	−1.32
Na_3PO_4	0.02 - 0.2	−2.20	−2.32
$Na_4P_2O_7$	0.02 - 0.15	−2.68	−2.52
K_2HPO_4	0.02 - 0.2	−1.20	
$AlCl_3$	0.02 - 0.2	−0.30	
NaCl	0.1 - 1.0	−0.22	
KCl	0.2 - 0.6	−0.10	
Potassium tartrate	0.02 - 0.2	−1.16	
Na_2SO_4	0.02 - 0.2	−1.28	
Theophylline	0.02 - 0.1		0.00
Aminophylline	0.02 - 0.2		0.32
Tetracycline HCl	0.02 - 0.2		0.35
Quinine bisulphate	0.02 - 0.2		0.00

previously found during dissolution from tetracycline-HPMC matrix tablets which was thought to be caused by a complex drug-HPMC gel interaction (Ford et al., 1987). Propranolol hydrochloride and promethazine hydrochloride increased the gel points and no straight line relationship existed (Fig. 3). This indicated that at higher concentrations these drugs enable the polymer to hydrate to a much larger extent than at lower concentrations.

Most electrolytes, as well as sorbitol, sucrose and glycerol, depress the gel point by dehydrating the polymer thus promoting polymer-polymer interactions (Levy and Schwarz, 1958). Other compounds including ethanol, polyethylene glycol and potassium thiocyanate increase the gel point by what is thought to be adsorption of the large ion of relatively low water affinity onto the macromolecule (Levy and Schwarz, 1958) carrying with it water molecules and raising the degree of hydration (Katz and Muschter, 1933).

The effect of salts on the disintegration of tablets

Since the cloud points represent the precipitation of HPMC due to dehydration, the effects of varying the concentration of electrolyte, and hence the ionic strength (Eqn 1) of the disintegration media on the integrity of HPMC tablets were studied (Table 3). Touitou and Donbrow (1982) have previously described three different kinds of response when matrices were exposed to fluids containing solutes, namely (a) rapid disintegration, (b) gradual attrition or (c) maintenance of integrity. In these studies (Table 3) three different responses occurred when HPMC K15M matrices, without drug, were exposed to disintegration fluids of varying concentration of solute.

At low ionic strengths the matrices were unaffected by electrolytes and hydration occurred to produce an intact gel layer as is usually observed when HPMC matrix tablets are exposed to water. At intermediate ionic strengths the matrices lost shape and integrity and disintegrated rapidly. The released particles did however slowly gel indicating that hydration had not been prevented but merely retarded. This demonstrates how essential thé rapid production of a gel around a tablet is in maintaining the integrity of the matrix. At higher ionic strengths the matrices maintained their integrity, swelling slightly but not gelling. The matrix surface became porous giving it a spongy texture. The ionic strengths which caused disintegration varied to the salt used. Thus at an ionic strength of 0.9 sodium dihydrogen orthophosphate caused disintegration of the matrices within one hour but an ionic strength of 2.0 of sodium chloride was required to effect disintegration. As previously discussed, the ability of cations to depress the cloud point of HPMC is depen-

TABLE 3

The effect of solutes and ionic strength on disintegration times of HPMC K15M tablets

Additives	Concentration (M)	Ionic strength	Time (min)	Cloud point (°C)[a]	Matrix type[b]
NaH_2PO_4	0.9	0.9	52	18.9	2
	0.6	0.6	>120	29.2	1
KH_2PO_4	0.9	0.9	35	21.0	2
Na_2HPO_4	0.3	0.9	23	28.5	2
	0.8	2.4	>120	6.3	3
	0.1	0.3	>120	52.0	1
K_2HPO_4	0.3	0.9	18	31.0	2
NaCl	0.9	0.9	>120	43.7	1
	1.5	1.5	>120	32.0	1
	2.0	2.0	85	24.7	2
	2.5	2.5	>120	19.0	3
KCl	2.0	2.0	98	43.9	2
$AlCl_3$	0.35	2.1	>120	56.0	1
Na_2SO_4	0.3	0.9	35	28.5	2
K_2SO_4	0.3	0.9	24		2

[a]Cloud points based on K100 gels not K15M.

[b]1, rapid gelling, matrix intact; 2, slowly gelling, disintegration; 3, non gelling.

dent on their position in the lyotropic series. Since the disintegration of the tablets can be explained by the salt decreasing the cloud point (and hence solubility), then the effect of salts on disintegration should also follow the lyotropic series. On this basis sodium salts appear anomolous (Table 3) since they should produce lower disintegration times than potassium salts. This was not the case in three out of four of of the salts tested. In studies on the disintegration of HPMC matrices, Fagan et al. (1989) introduced a concept of threshold ionic strengths, where a matrix is not susceptible to ionic strengths below a certain point. This theory is not upheld by the results in Table 3 which show that at an ionic strength of 0.9, although resulting in disintegration of the matrices in solutions containing several of the salts failed to facilitate disintegration when sodium chloride was used. Consequently disintegration depends on the susceptibility to the dehydration effects of specific ions rather than a specific ionic strength. This may further be suggested by the results in Table 2, e.g., with 0.2 M sodium dihydrogen orthophosphate (I = 0.2) lowering the cloud point to a greater extent than 0.2 M aluminium chloride (I = 1.2).

The effect of salts on the dissolution of propranolol from HPMC K15M matrices

In view of the effects that salts have on the disintegration of HPMC K15M matrices (Table 3) and their effect on the cloud point of HPMC K15M gels (Fig. 3) dissolution from HPMC K15M matrices of a model drug, propranolol hydrochloride, was studied in order to determine salt effect on dissolution rate. Dissolution from matrices into media which had not been pH adjusted gave non-linear plots, such as obtained by using disodium hydrogen orthophosphate or trisodium orthophosphate (Fig. 4). Deviations from linearity is indicative of precipitation of propranolol at the surface of the tablet of free propranolol base. The solubility of propranolol is pH dependent, its pK_a

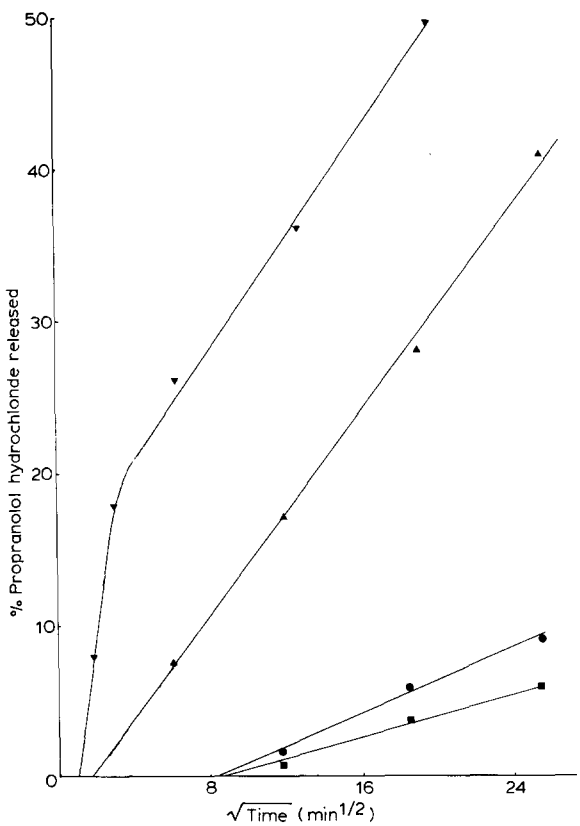

Fig. 4. Dissolution profiles of propranolol hydrochloride from matrix tablets containing 160 mg propranolol hydrochloride and 140 mg HPMC K15M into: (▼) 0.2 M disodium hydrogen orthophosphate (pH 9.16), (▲) 0.1 M disodium hydrogen orthophosphate (pH 9.23), (●) 0.1 M trisodium orthophosphate (pH 12.01), (■) 0.2 M trisodium orthophosphate (pH 12.2).

is 9.5 (Martindale: The Extra-Pharmacopoeia, 1989) influencing dissolution rates when significant amounts of the drug are unionized. The effects are similar to those reported for promethazine hydrochloride (Ford et al., 1985c). Subsequently the remaining dissolution studies were performed in solutions whose pH was adjusted to pH 6.0 ± 0.2.

Drug release data from the tablets in various dissolution media are summarised in Table 4. In all cases the release rates decreased initially from the control (distilled water) with an increase in concentration of electrolyte, until a minimum release rate was obtained. As the concentration increased further the release rates increased until a 'burst' release (100% drug dissolved within 15 min occurred. These initial decreases in release rates were probably coincident with thermal gelation, in that as the concentration of the dissolution media is increased the cloud point is lowered towards 37°C. It may be seen from Table 4 that minimum release rates occurred when the cloud point was approx. 37°C. At this point the pore tortuosity, τ, within the matrix structure should also be at a maximum. Tortuosity is related to release rate since it is related to the apparent diffusion coefficient in the hydrated matrix, D', and the actual diffusion coefficient, D, of the drug in the release media by Eqn 4.

$$D' = D/\tau \tag{4}$$

which in turn may be related to the dissolution rate, $W_r/t^{1/2}$, by Eqn 5

$$W_r/t^{1/2} = 2w_0(S/V)\,(D'/\pi)^{1/2} \tag{5}$$

Eqn 5 describes the release of freely water soluble drugs (Higuchi, 1962), where W_r is the amount of drug released in time t, W_0, is the dose of drug, S is the effective diffusional area and V is the effective volume of the hydrated matrix. It is unlikely to be an increase in viscosity that retards release rates since Ford et al. (1985a) showed that viscosity has little effect on release rates. Any reduction in hydration, such as that caused by increasing the concentration of solute in the dissolution media or increasing the temperature of the dissolution media, will start to prevent gelation and therefore the tablet will cease to act as a sustained release matrix.

The data produced here explain the results of Fassihi and Mundy (1989) who noted that phosphate buffers retarded the release of theophylline. This was attributed to a possible interaction between the phosphate ions and theophylline molecules. Whilst this cannot be discounted, in view of the results reported here with propranolol this would seem unlikely since retardation can be achieved by not only phosphate ions but also by varying the ionic strength of sodium chloride in the dissolution medium (see Table 4).

Table 4 shows the relationship between the dissolution rates of propranolol hydrochloride from

TABLE 4

The effect of solute and ionic strength on the dissolution rate of propranolol hydrochloride from HPMC K15M matrix tablets

Dissolution media	Dissolution rate (% $min^{1/2}$	Ionic strength	Cloud point (°C)
Distilled water	3.999		
NaH_2PO_4		0.1	58.8
	3.784	0.2	52.1
	3.578	0.3	46.0
	6.013	0.5	36.0
	burst release	0.7	28.2
Na_2HPO_4	3.376	0.3	50.2
	3.200	0.36	47.3
	3.098	0.45	43.2
	3.092	0.6	37.1
	burst release	0.9	27.4
Na_3PO_4	4.052	0.13	63.7
	3.623	0.258	56.8
	3.156	0.516	45.13
	burst release	0.774	35.86
$Na_4P_2O_7$	3.155	1.193	57.8
	2.756	0.298	48.6
	2.381	0.596	34.32
	burst release	1.788	24.29
NaCl	2.476	0.500	

HPMC matrix tablets and the ionic strengths of the dissolution media. For the di-, tri- and tetravalent phosphate salts an ionic strength of approx. 0.6 produces minimum release rates from the tablets. The univalent phosphate salt produces a minimum release rates at an ionic strength of approx. 0.3. By examination of Table 4 it can be deduced that for burst release of the matrix tablet to take place the integrity need not be lost completely, e.g. using sodium dihydrogen orthophosphate as a medium an ionic strength of 0.7 is enough to produce burst release. However, the matrix did not completely disintegrate for 53 min. This emphasises the importance of the initial gelling of the HPMC is to protect tablet integrity. The data also cast doubt on the reliability of the buffers used in the quality control of such matrices. Earlier data by Ford et al. (1985c) utilized phosphate salts to produce a pH of 7. The observed reduction in release rates at this pH for promethazine from HPMC matrices, although partly due to a reduced solubility of the drug at this pH, will also be caused by the use of a phosphate buffer.

Conclusions

Cloud point studies indicated that electrolytes reduced the hydration of HPMC in gels. This was confirmed from disintegration studies using HPMC matrix tablets when, in the presence of certain salts at varying ionic strengths, the matrices started to disintegrate before the gel which normally protects the inner constituents from dissolution was formed. The dissolution rate of propranolol from HPMC K15M matrices was found to be dependent on electrolyte concentration in the dissolution medium. As the concentration increased dissolution rates decreased to a minimum before increasing dramatically. When examining the dissolution rate of drugs from HPMC matrices it would seem that electrolytes added to the dissolution medium, even in small amounts, will modify the dissolution rate.

References

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

British Pharmacopoeia, Her Majesty's Stationary Office, London, Vol. II, 1988, A143.

Fagan, P.G., Harrison, P.J. and Shankland, N., A correlation between cloud point and disintegration of hydroxy alkylcellulose controlled release matrices. *J. Pharm. Pharmacol.*, 41 (1989) 25P.

Fassihi, A.R. and Mundy, D.L., Dissolution of theophylline from film coated slow release mini tablets in various dissolution media. *J. Pharm. Pharmacol.*, 41 (1989) 369–372.

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 hydroxypropylmethyl-cellulose. *Int. J. Pharm.*, 24 (1985b) 339–350.

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

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.

Heyman, E., Bleakley, H.G. and Docking, A.R., Studies on the lyotropic series. *J. Phys. Chem.*, 42 (1938) 353–368.

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.

Katz, I.R. and Muschter, F.W., Die lyotrope reihe der quellung und ihre ausbreitung auf organische, auch nichtionisierende substanzen. *Biochem. Z.*, 257 (1933) 385–396.

Klug, E.D., Some properties of water soluble hydroxyalkyl celluloses and their derivatives. *J. Polym. Sci. C.*, 36 (1971) 419–508.

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

Levy, G. and Schwarz, T.W., The effect of certain additives on the gel point of methylcellulose. *J. Am. Pharm. Assoc. Sci. Ed.*, 47 (1958) 44–46.

Martindale: In Reynold, J.E.F. (Ed)., *The Extra Pharmacopoeia*, 29th Edn, The Pharmaceutical Press, London, 1989, p. xxvii.

Niebergall, P.J., Ionic solutions and electrolytic equilibria. In Olso, A. (Ed.), *Remington's Pharmaceutical Sciences*. Mack, Pennsylvania, 1975, pp. 255–274.

Sarkar, N., Thermal gelation Properties of Methyl· and Hydroxypropyl-methylcellulose. *J. Appl. Polym. Sci.*, 24 (1979) 1073–1087.

Touitou, E. and Donbrow, M., Influence of Additives on (hydroxyethyl) methylcellulose properties: relation between gelation temperature change, compressed matrix integrity and drug release profile. *Int. J. Pharm.*, 11 (1982) 131–14.