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HYDROXYPROPYLMETHYLCELLULOSE SUSTAINED RELEASE TECHNOLOGY

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ABSTRACT

The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceuticals. Watersoluble polymers such as polyethylene glycol and polyvinylpyrrolidone may be used to increase the dissolution rates of poorly soluble drugs (Ford)[1] and slowly soluble, biodegradable polymers such as polylactic acid may be used for controlled release implants (Rak et al.[2]). Hydrogels provide the basis for implantation, transdermal and oral-controlled release systems. Hydroxypropylmethylcellulose (HPMC) are cellulose ethers which may be used as the basic for hydrophilic matrices for controlled release oral delivery.

In tablet matrix systems the tablet is in the form of compressed compact containing an active ingredient,

lubricant, excipient, filler or binder. The matrix may be tabletted from wet-massed granules or by direct compression.

This review article examines a previously published series of work and concentrates on the following aspects of the subject; the relationship between release rate and quantity of polymers, such consideration allow a certain predicability in release rates to be made. Also the effect of drug particle size, tablet shape and the presence of additional diluents in the formula are examined.

INTRODUCTION

The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceuticals. Water-soluble polymers such as polyethylene glycol and polyvinylprrolidone may be used to increase the dissolution rates of poorly soluble drugs (Ford[1]) and slowly soluble, biodegradable polymers such as polylactic acid may be used for controlled release implants (Rak et al.[2]). Hydrogels provide the basis for implantation, transdermal and oral-controlled release systems. Hydroxypropylmethylcellulose (HPMC) are cellulose ethers which may be used as the basis for hydrophilic matrices for controlled release oral delivery.

In tablet matrix systems the tablet is in the form of a compressed compact containing an active ingredient,

lubricant, excipient, filler or binder. The matrix may be tabletted from wet-massed granules or by direct compression.

The operative principle controlling drug release in matrix tablets is that on exposure to aqueous fluids the tablet surface becomes wet and the polymer starts to partially hydrate to form a gel layer. An initial burst of soluble drug from the external layer may be relased. There follows an expansion of the gel layer when water permeates into the tablet increasing the thickness of the gel layer and soluble drug diffuses through the gel barrier. Concomitantly the outer layers become fully hydrated and dissolve, a process generally referred to as erosion. Water continues to penetrate towards the tablet core until it has dissolved.

This review article examines a previously published series of work and concentrates on the following aspects of the subject; the relationship between release rate and quantity of polymer, such considerations allow a certain predictability in release rates to me made. Also the effect of drug particle size, tablet shape and the presence of additional diluents in the formula are examined.

MATERIALS AND METHODS

All drugs were B.P. grade. Hydroxypropylmethylcellulose, Methocel (Dow Chemical, U.S.A.) was used without further preparation. Magnesium

stearate (B.D.H., U.K.) was used as lubricant. Calcium phosphate (B.D.H.) or spray-dried lactose were used as required as diluents. Compaction was accomplished using direct compression of the blends that had been thoroughly mixed for 15 min using a tumbler mixer. The following variables were examined.

Influence of Drug:HPMC Ratios

Blends were compressed to the following formulae.

(i) Promethazine hydrochloride (250-500 μm): 25mg, HPMC K15M: 20, 25, 40, 50, 80, 120 or 160mg, magnesium stearate: 0.75%. Compaction pressure was 1395 $MN.m^{-2}$ (as Ford[3]).

(ii) Aminophylline (125-180 μm): 225mg, HPMC K15M: 45, 60, 90, 180 or 270mg, magnesium stearate: 0.85%. Compaction pressure was 455 $MN.m^{-2}$ (as Ford et al.[4]).

(iii) Propranolol hydrochloride (125-180 μm): 160 mg, HPMC K15M: 57, 71, 95, 140 or 285mg, magnesium stearate: 0.75%. Compaction pressure was 348.5 $MN.m^{-2}$ (as Ford et al.[4]).

(iv) Indomethacin (90-125 μm): 25mg, HPMC K15M: 25.8, 36, 61.5 or 200mg, magnesium stearate: 0.75%. Compaction pressure was 1395 $MN.m^{-2}$ (as Ford et al.[5]).

(v) Tetracycline hydrochloride (125-180 μm): 250mg, HPMC K15M: 45, 60, 90, 180 or 270mg,

magnesium stearate: 0.75%. Compaction pressure was 455 $MN.m^{-2}$.

(vi) Theophylline hydrochloride (125-180 μm): 225mg, HPMC K15M: 60, 90, 180 or 270mg, magnesium stearate: 0.75%. Compaction pressure was 455 $MN.m^{-2}$.

(vii) Diazepam (125-180 um): 10mg, HPMC K15M: 50, 61.5, 80, 114.3 or 200mg, magnesium stearate: 0.75%. Compaction pressure was 1395 $MN.m^{-2}$.

Compaction was accomplished using flat-faced punches on a Manesty F3 single-punch tableting machine. Propranolol tablets were 0.5 inch diameter, promethazine, indomethacin and diazepam tablets were 0.25 inch diameter, the remainder were 0.4375 inch diameter.

Dissolution Studies

The dissolution rates of the tablets were monitored using a Copley-Series 8000 dissolution tester (Copley Instruments, Nottingham, U.K.). 1000ml of distilled water was used as dissolution media and maintained at 37°C. The USP 1 dissolution method was used at a rotation speed of 100 rpm. Dissolution was continuously recorded using a spectrophotometer (Kontrol, model Uvikon 810) at 250 nm connected to a Commodore Model 8032 microprocessor. Dissolution studies were performed in triplicate for each batch of tablets.

TABLE 1

Statistical Data Giving the Slope M (|% Promethazine HCL||min|$^{-1/2}$|mg HPMC|) and Intercept C (|%Promethazine HCL||min|$^{-1/2}$) and Pression Coefficients of the Plots of Promethazine HCL Release Rate (%min$^{-1/2}$) Against Reciprocal Hydroxypropylmethylcellulose concentration (mg^{-1})

HPMC grade	Slope M (%min$^{-1/2}$.mg)	Intercept C (%min^{-1})	Regression coefficient * (r)
K100	209.7	4.19	0.993
K4M	146.8	3.54	0.992
K15M	132.0	3.33	0.995
K100M	168.3	2.98	0.997

*All significant $P < 0.001$.

RESULTS AND DISCUSSION

Relationship Between Release Rate and Polymer Quantity

Examination of dissolution curves of the drug promethazine hydrochloride with differing polymer quantity shows that as the polymer fraction increases, the dissolution of the drug decreases.This is shown in Table 1.

The generalised relationship for each of these lines can be expressed by the relationship:

$$R = M.\left(\frac{1}{W}\right) + C \qquad \text{Equation 1}$$

Where R = Higuchian release rate (% min $^{-\frac{1}{2}}$)

M = Slope of the derived line

W = Weight of HPMC (mg)

C = Constant

TABLE 2

Statistical Data Giving the Slopes m (| % Drug ||$min^{-1/2}$ ||mg HPMC |) and Intercepts C (| % Drug ||$min^{-1/2}$ |) and Regression Coefficients of the Plots of Drug Release Rate (% $min^{-1/2}$) Againts the Reciprocal Hydroxypropylmethylcellulose Concentration (mg^{-1}) for Propranolol Hydrochloride and Aminophylline

Drug	HPMC grade	Slope M (% min^{-1}·mg)	Intercept C (% min^{-1})	Regression coefficient (V)	Degree of significance
Aminophylline	K100	764.5	2.68	0.996	$P < 0.001$
	K4M	288.6	3.24	0.994	$P < 0.01$
	K15M	258.9	3.29	0.987	$P < 0.01$
	K100M	247.1	3.47	0.986	$P < 0.01$
Propranolol hydrochloride	K100	724.4	2.37	0.998	$P < 0.001$
	K4M	321.5	3.06	0.992	$P < 0.001$
	K15M	207.9	2.97	0.996	$P < 0.001$
	K100M	251.0	3.21	0.936	$P < 0.02$

A similar treatment with the drugs aminophylline and propranolol hydrochloride provides the data in Table 2

The compositions of the blends of drug and HPMC being given in the materials and methods section.

The relationships indicated by Tables 1 and 2 allow predictions of release rates to be made for drug:HPMC ratios not experimentally determined. It would be equally beneficial to estimate the release rates of other drugs, not experimentally determined. However, problems such as variation in the dose of drug

TABLE 3

Estimated Release Rates (%$min^{-1/2}$ or mg. $min^{-1/2}$) of Aminophylline, Propranolol Hydrochloride and Promethazine Hydrochloride from their HPMC Matrix Tablets Containing 1:1 or 1:2 Drug: HPMC for 4 Viscosity Grades of HPMC

Drug (dose)	HPMC viscosity grade	Drug:HPMC ratio	Release rates		Modified release rate ($mg \cdot min^{-1/2}$) / $W_I^{2/3}$ **
			% $min^{-1/2}$	$mg \cdot min^{-1/2}$	
Aminophylline (225 mg)	K100	1:1	6.08	13.68	36.98
		1:2	4.38	9.85	16.78
	K4M	1:1	4.52	10.18	27.52
		1:2	3.88	8.73	14.87
	K15M	1:1	4.44	9.99	27.01
		1:2	3.87	8.70	14.82
	K100M	1:1	4.57	10.28	27.79
		1:2	4.02	9.04	16.78
Propranolol hydrochloride (160 mg)	K100	1:1	6.89	11.03	37.43
		1:2	4.63	7.41	15.84
	K4M	1:1	5.07	8.11	27.52
		1:2	4.07	6.51	13.92
	K15M	1:1	4.26	6.83	23.18
		1:2	3.62	5.79	12.38
	K100M	1:1	4.78	7.64	25.92
		1:2	3.99	6.39	13.66
Promethazine hydrochloride * (25 mg)	K100	1:1	12.37	3.09	36.14
		1:2	8.13	2.03	14.96
	K4M	1:1	9.45	2.36	27.60
		1:2	6.48	1.62	11.94
	K15M	1:1	8.61	2.15	25.17
		1:2	5.97	1.49	11.00
	K100M	1:1	9.71	2.43	28.42
		1:2	6.35	1.59	11.72

* Data from Ford et al.[3]
** $W_I^{2/3}$ = (wt of HPMC)$^{2/3}$.

or possible drug-HPMC interactions may complicate such calculations. Nonetheless, as a first step to interrelate the dissolution rates of the three drugs in this study Eqn. 1 was used to predict the dissolution rates from 1:1 to 1:2 drug:HPMC matrices. These calculated rates are expressed in Table 3.

Direct comparison of the % $min^{-\frac{1}{2}}$ data is somewhat confusing since it indicates, for example, that promethazine is liberated approximately twice as fast as aminophylline from similar drug:HPMC ratio matrices. However, a similar comparison of the $mg.min^{-\frac{1}{2}}$ data indicates that as the dose of the drug and consequently as the amount of HPMC within the tablet increases, the dissolution rates increases. In fact, a straight-line relationship existed between the logarithm of the tablet HPMC content and the logarithm of the release rates ($mg.min^{-\frac{1}{2}}$) at similar drug:HPMC ratios. The eight sets of data in Table 3 (4 HPMC grades x 2 drug:HPMC ratios) can therefore be reduced to the following relationship:

$$\log R = m \log HPMC + \text{contant } A \qquad \text{Equation 2}$$

where log R = log of Higuchi-type release rate ($mg.\ min^{-\frac{1}{2}}$), and log HPMC = log of tablet content of HPMC (mg).

The data for Eqn. 2 are determined at a constant drug:HPMC ratio. Such treatment theoretically allows a potential formulator to predict the dissolution rate of a drug from its HPMC matrix provided the rates of other drugs at similar drug:HPMC ratios have previously been determined.

However, for the extension of these findings to other drugs, certain restrictions or assumptions have

to be made. The doses of drugs so far studied have been between 25 and 225mg, since this was the range over which Eqn. 2 was developed. Similarly it is valid for lubricant (or other insoluble excipient) levels of up to only 0.85%. Ford et al.[3] previously showed that the absence or presence of 0.75% lubricant did not modify dissolution rates.

Eqn. 2 was also constructed from data derived for water-soluble drugs. Promethazine hydrochloride, aminophylline and propranolol hydrochloride have aqueous solubilities of 1 in 0.6, 1 in 5 and 1 in 20 parts of water, respectively, and the application of Eqn. 2 to drugs of lower solubility is unclear. It has been assumed that the drugs used in this study alter similarly the tortuosity of HPMC matrices. Both the promethazine and propranolol salts possess chloride ions as the counterbalancing moiety to the base and aminophylline is the free base. However, Lapidus and Lordi[6] have shown that certain ions, e.g. the sodium ion, may decrease the tortuosity of the HPMC gel by dehydrating the polymer. The applicatiblity of Eqn. 2 to other drug-HPMC systems probably depends on the other drugs dehydrating the polymer to a similar extent.

The explanation of the relationship described by Eqn. 2 is probably through a surface area relationship. The tablets, on exposure to water, swelled due to

hydration of the HPMC but did not maintain their typical form and became biconvex, somewhat analogous to a sphere. For all regular-shaped objects, a linear relationship can be obtained between the log weight and log surface area. Assuming that the drug dissolves to leave the HPMC which swells to an approximate spherical shape, i.e. the drug does not contribute to the overall size of the hydrated matrix, then the surface area A can be related to HPMC weight by the relationships:

$$V \propto W \propto r^3 \qquad \text{Equation 3}$$

where V = volume of sphere, W = weight of sphere, r = radius of the sphere, and therefore:

$$S \propto r^2 \propto W^{2/3} \qquad \text{Equation 4}$$

Consequently the surface area S varies to $W^{2/3}$. Assuming that all the HPMC viscosity grades swell to the same extent when hydrated, and that the hydrated matrices have the same density, then the effective surface area presented by the tablets should be proportional to $W^{2/3}$. Dividing the release rates given in Table 3 by $W_1^{2/3}$, where W_1 is the weight of HPMC, gives the modified release rates. It is apparent in Table 3 that these modified rates are similar when derived from HPMC K4M, HPMC K15M and HPMC K100M matrices thereby explaining the relationships outlined by Eqn. 2. The higher values of HPMC K100 matrices (Table 3) indicate that either this matrix is less tortuous than matrices of the other HPMCs,

or that the assumption that the matrices of the polymers, when hydrated, swell to a similar extent is incorrect. Should the latter be the correct assumption then an over-allowance was made for the swelling capacity of this polymer when hydrated and HPMC K100 does not swell to the same extent as the other grades. Certainly, however, there is evidence within the literature that the higher molecular weight HPMCs form gels possessing the same gel strengths whereas the lower molecular weight polymers possess lower gel strengths (Sarkar[7]). It is probable that other physicochemical properties show the same discontinuity with molecular weight and are responsible for the apparent effects of molecular weight on release rate observed here.

Effect of Drug Particle Size

The particle size range of a drug over which Eqn. 2 applies also needs elucidating. Ford et al.[3] previously indicated that as the particle size of promethazine hydrochloride was increased from 45-63 μm to 500-750 μm, only a corresponding 12% increase in dissolution rate was achieved from 4.62 to 5.18% min^{-1}. The data used for Table 3 were taken from the 250-500 μm range of promethazine but from the 125-180 μm range of both aminophylline and propranolol. However, the difference in results between the 125-180 and 250-500 μm ranges for promethazine was only 3.5% and therefore these

TABLE 4

The Influence of Aminophylline Particle Size on the Release Rates of Aminophylline from Tablets Containing 225 mg Aminophylline and 45 or 180 mg HPMC K15M

Aminophylline Particle Size (μm)	Wt. of HPMC K15M	
	45mg Release$_{\frac{1}{2}}$ Rates (% min$^{-\frac{1}{2}}$)	180 mg
63-90	8.88	5.26
125-180	9.12	4.93
180-250	9.75	5.05

TABLE 5

The Influence of Propranolol Hydrochloride Particle Size on the Release Rates of Propranolol from Tablets Containing 160mg Propranolol Hydrochloride and 57 or 285mg HPMC K15M

Propranolol Hydrochloride Particle Size (μm)	Wt. of HPMC K15M	
	57 mg Release$_{\frac{1}{2}}$ Rates (% min$^{-\frac{1}{2}}$)	285 mg
63-90	7.83	3.63
90-125	7.52	3.77
125-180	6.49	3.64
180-250	7.98	3.80
250-500	28.30	3.98

differences have been considered as marginal and would not affect Table 3 or Eqn. 2.

The influence of particle size on the drug release rate is indicated by Tables 4 and 5. It is evident that for both aminophylline and propranolol, an increase in particle size alters little the release rate of drug. In fact it is only at the low drug:HPMC ratio, and at the

largest particle size that any noticeable effect is seen. This is only because the matrix was presumably very loose and tended to disintegrate (especially for the 250-500 μm range of propranolol) during release studies. These data therefore tend to indicate that Eqn. 2 would be valid over a wide drug particle size range, i.e. 63-250 μm and only become invalid in matrices containing low levels of HPMC with a large particle size of drug. In this case, rapid solution of the water-soluble drug would leave a matrix with a low tortuosity and high porosity.

Further Investigations into the Kinetics of Drug Release

The kinetics of drug release from matrices were examined for both freely soluble (Higuchi[8]) and poorly water-soluble drugs (Higuchi[9]) and mathematical models have been developed to allow for the influences of hydration, swelling and glass transition temperatures on release (Peppas[10]; Lee[11]). Korsmeyer et al.[12] derived a simple relationship (Eqn. 5) which may be used to describe drug release from polymeric systems in which release deviates from Fickian diffusion and follows a non-Fickian (anomalous) behaviour.

$$\frac{M_t}{M_\infty} = k.t^n \qquad \text{Equation 5}$$

where M_t/M_∞ is the fractional release of the drug, t is

the release time, k is a constant incorporating structural and geometric characteristic of the release device and n is the release exponent indicative of the mechanism of release. For instance n = 0.5 for $\sqrt{time}$ kinetics and n = 1.0 for zero-order release.

Alternatively:

$$\log \frac{M_t}{M_\infty} = \log k + n.\log t \qquad \text{Equation 6}$$

Table 6 gives the values of n obtained by regression analysis for each of the tablet formulations. Peppas[13] used values of M_t/M_∞ of $\leqslant 0.6$ for data analysis whilst Korsmeyer et al.[12] showed that data of M_t/M_∞ of $\leqslant 0.15$ were non-linear. Data with range M_t/M_∞ = 0.05-0.70 were found to be generally linear (with the exception of tetracycline) and therefore acceptable for determination of the exponent n of Eqns. 3 and 4 by linear regression. Two values for each indomethacin:HPMC ratio are included corresponding to the range of linearity previously used in $\sqrt{time}$ determinations (Ford et al. [3 and 4]). Because the $\sqrt{time}$ data for tetracycline were not linear, values of n were determined throughout the data range.

The derived values of n (Table 6) were relatively invariant for each particular drug system, although for promethazine and diazepam matrices they appeared slightly higher at low HPMC content. The values of n were similar (0.65-0.71) for the highly soluble drugs

TABLE 6

The Effect of Drug: Hydroxypropylmethylcellulose Ratio on the Exponent n Derived from Dissolution Data for 7 Drugs

Promethazine hydrochloride 25 mg			Aminophylline 225 mg			Propranolol hydrochloride 160 mg			Indomethacin 25 mg				
mg HPMC	$\sqrt{t}$	n	mg HPMC	$\sqrt{t}$	n	mg HPMC	$\sqrt{t}$	n	mg HPMC	$\sqrt{t}$	n	$\sqrt{t}$ *	n *
20	4–11	0.75	45	5–11	0.69	57	4–13	0.69	25.8	14–21	0.93	5–20	0.92
25	4–11	0.76	60	5–12	0.63	71	4–14	0.68	36	13–23	0.82	5–22	0.83
40	5–14	0.72	90	5–13	0.64	95	4–16	0.67	61.5	15–25	1.07	6–24	1.03
50	5–16	0.68	180	5–16	0.63	140	4–19	0.66	200	17–26	0.90	6–30	0.82
120	5–18	0.68	270	5–20	0.66	285	4–25	0.63					
160	5–18	0.67											

Tetracycline hydrochloride 250 mg					Diazepam 10 mg					Theophylline 225 mg		
mg HPMC	$\sqrt{t}$	n	$\sqrt{t}$ *	n*	mg HPMC	$\sqrt{t}$	n	$\sqrt{t}$ *	n *	mg HPMC	$\sqrt{t}$	n
45	5–28	0.53	5–13	0.46	50	19–27	0.85	9–27	0.91	60	5–16	0.61
60	5–28	0.51	5–13	0.46	61.5	19–27	0.86	8–27	0.90	90	5–16	0.65
90	5–28	0.47	5–13	0.45	80	20–28	0.81	6–28	0.83	180	5–16	0.64
180	5–28	0.52	5–13	0.46	114.3	20–28	0.76	5–28	0.77	270	5–16	0.67
270	5–28	0.51	5–13	0.42	200	19–28	0.64	6–28	0.70			

promethazine hydrochloride, aminophylline and propranolol hydrochloride and additionally theophylline (0.64).

Peppas[13] stated that diffusional controlled (Fickian) release from planar surfaces gave a value of n=0.5, giving the time dependent release of Eqns. 5 and 6. Higuchi[9] derived equation 7 which describes the release of poorly water soluble drug from the single face of a tablet.

$$\frac{W_r}{t^{1/2}} = S\left[D'\epsilon C_s\left(\frac{2W_0}{V} - \epsilon C_s\right)\right]^{1/2} \qquad \text{Equation 7}$$

where W_r= amount of drug dissolved in time t, W_o=dose of the drug, S=effective diffusional area, V=effective volume of the hydrated matrix, C_s is the solubility of the drug in the release medium, ϵ=porosity of the hydrated matrix and D =apparent diffusion coefficient of the drug in the hydrated matrix. However, if the drug has high aqueous solubility and has dissolved when the matrix is hydrated then Eqn. 8 applies (Higuchi[8]).

$$\frac{W_r}{t^{1/2}} = 2W_0\left(\frac{S}{V}\right)\left(\frac{D'}{\pi}\right)^{1/2} \qquad \text{Equation 8}$$

Eqn. 5 was derived for release from a planar surface and not from an erodible matrix. Nonetheless the values in Table 7 for these drugs are close to the values predicted for diffusional release.

TABLE 7

Mean Exponent n Values (Eqn.7) and Predicted Release Rates from Tablets Containing HPMC

Drug	Exponent n value (number of HPMC : drug ranges)	Predicted release [a]
Promethazine-HCl	0.71 ± 0.04 (7)	25.2
Aminophylline	0.65 ± 0.03 (5)	27.0
Tetracycline-HCl	0.45 ± 0.02 (5)	10.4
Propranolol-HCl	0.67 ± 0.02 (5)	23.2
Theophylline	0.64 ± 0.03 (4)	11.8
Diazepam	0.82 ± 0.09 (5)	15.4
Indomethacin	0.90 ± 0.10 (4)	6.6

[a] $(mg[drug])min^{-1/2}$ $(mg[HPMC])^{-2/3} \times 100$ at 1 : 1 drug : HPMC ratio.

The values for the two poorly soluble drugs were 0.82 and 0.9 for diazepam and indomethacin, respectively. A value of n=1 would indicate zero-order release from a planar surface (Peppas[13]) but for spheres and cylinders a value of~1 may not correspond to zero-order release due to geometric factors involved in the mathematical analysis. Thus the values of n obtained for indomethacin and diazepam merely emphasise that release for these drugs is not Fickian-controlled and may indicate large contributions by tablet erosion to drug release.

The anomalous behaviour for tetracycline matrices with a value of n=0.45 emphasises the complexity of release of this drug. Peppas[13] did not interpret n values of <0.5 but stated that such occurrences were an

indication of statistical analysis problems or were due to diffusion through a polymeric network where diffusion occurred partially through a swollen matrix and partly through water-filled pores. It is possible that tetracycline hydrochloride undergoes a complexation reaction with HPMC in the gel state in the hydrating matrix, retarding its release.

Effect of Tablet Shape

Table 8 summarises the influences of tablet shape and size on the time release rates of promethazine hydrochloride tablets compressed to the same weight and formula. Ford et al.[3] demonstrated that compaction pressure variations little affected the dissolution rate from promethazine-HPMC matrix tablets and also that surface area of the tablet is related to HPMC content and may influence release rates. Table 8 confirms that the $\sqrt{\text{time}}$ release rate is proportional to the surface area of the tablet prior to compression since release rates decreased as the tablet surface area decreased. In fact a linear relationship existed between release rate and surface area. Consequently the results indicate that for maximum maintenance of controlled release, tablet matrices should be as near spherical as possible to produce minimum release rates.

Effect of HPMC Replacement by Diluents

Formulation of matrix tablets may require the addition of excipients to alter the size of the tablet

TABLE 8

The Effect of Tablet Shape on the Dissolution Rates of Promethazine from Tablets Containing Promethazine Hydrochloride 25mg. HPMC K15M 120mg. and 0.75% Magnesium Stearate

Shape	Diameter (inches)	Compaction pressure ($MN \cdot m^{-2}$)	Surface area (mm^2)	Release rates (% $min^{-1/2}$)
Flat-face	0.5	392	295.8 ± 4.3	5.99
Flat-face	0.375	890	197.9 ± 0.1	4.61
Flat-face	0.25	1580	162.4 ± 0.8	4.13
Concave	0.375	890	179.1 ± 0.6	4.23

or to replace a portion of the HPMC to modify drug release rate. Therefore the effects of partial replacement of the HPMC by either lactose or calcium phosphate were examined on release rates. The dissolution profiles, plotted on a $\sqrt{time}$ basis were acceptably linear for up to 80% drug release for either excipient at each diluent:HPMC level. The calculated $\sqrt{time}$ release rates (Table 9) for the comparative 90-125 μm excipient fractions indicate that virtually no differences in release rates were observed despite the solubility differences of the diluents. Only in tablets containing 10 mg HPMC and 30 mg of lactose or calcium phosphate were differences between the excipients apparent when the matrices containing lactose displayed higher release rates, although no positive deviations in the release profiles occurred despite the high level of soluble solids in the matrix (~85%). Interestingly the value of the exponent n (Eqn. 5) appeared not to vary from the range 0.6-0.74 indicating probably diffusion-controlled drug release. These results confirm the findings of Lapidus and Lordi that replacement of HPMC by either a soluble or insoluble diluent increased dissolution rate. Additionally they confirm that only at high diluent levels (>50%) are differences apparent between soluble and insoluble excipients (Lapidus and Lordi[6]). Indeed for chlorpheniramine maleate tablets only large differences were apparent when total soluble

TABLE 9

The Effect of Diluent Particle Size and Diluent: HPMC Ratio on the Dissolution Rate of Promethazine from Matrix Tablets Containing 25mg Promethazine Hydrochloride, 0.75% Magnesium Stearate and either 40 or 160mg HPMC: Diluent

HPMC : diluent ratio	Dissolution rates							
Diluent:	Calcium phosphate				Lactose			
HPMC : diluent weight:	40 mg	*n*	160 mg	*n*	40 mg	*n*	160 mg	*n*
1 : 0	4.99	0.63	4.00	0.64	4.99	0.63	4.00	0.64
3 : 1	6.31	0.70	4.54	0.62	6.29	0.65	4.70	0.67
1 : 1	7.73	0.73	6.07	0.63	7.70	0.74	5.97	0.64
1 : 3	9.57	0.60	7.36	0.64	10.60	0.69	7.60	0.64
1 : 1 (a)	7.22	0.68	5.66	0.60	8.66	0.68	5.63	0.74
1 : 1 (b)	–	–	–	–	7.13	0.70	6.10	0.64
1 : 1 (c)	6.95	0.64	5.76	0.64	–	–	–	–

Excipient particle size was 90–125 μm except a: 45–63, b: 180–250 and c: 125–180 μm.

solid content was 83% (Lapidus and Lordi[6]). Additionally the results contradict the statement of Alderman[14] that as little as 10% insoluble solid such as calcium phosphate may destroy the sustained release from HPMC matrices by producing non-uniformity of the gel since in the tablets containing 120 mg calcium phosphate (~65% insoluble solids) controlled release was still maintained.

Particle size variation of the diluents little influenced dissolution rates. In tablets containing 40 mg 1:1 lactose:HPMC rates appeared to decrease with increasing lactose particle size whereas in tablets containing 160mg 1:1 lactose:HPMC rates increased slightly with increase in lactose particle size (Table 9). The particle size of calcium phosphate produced no clear particle size dependent changes in release rates However, indications were that the 45-63 μm fraction of calcium phosphate produced a negative deviation from linearity in tablet containing 40 mg 1:1 calcium phosphate:HPMC at around the 65% drug released level On examination of the matrices following dissolution it appeared that calcium phosphate of this size fraction only coated the HPMC matrix surface, reducing the available surface for drug release and thereby retarding release rates. This was, however, the only size fraction and weight of calcium phosphate that produced

this phenomenon. Values of the release exponent n were unaffected by particle size.

CONCLUSION

This review has elaborated some of the relationships between rate of release from HPMC matrices and practical formulation variables within the tablet. As far as possible these relationships have been quantified and some of the exceptions to general behaviour have been explored.

Controlled release by hydrophyllic matrix remains a very versatile tool in the hands of the formulator and we can only look forward to a greater formulation predicability as more and more fundamental studies become available.

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