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Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets

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Summary

The dissolution of 7 drugs from hydroxypropylmethylcellulose (HPMC) matrices have been examined to determine the time exponent (t^n) required to produce linear dissolution profiles. A value of $n = \sim 0.67$ was obtained for time-dependent release for soluble drugs, the precise values being 0.71, 0.65, 0.67 and 0.64 for promethazine hydrochloride, aminophylline, propranolol hydrochloride and theophylline, respectively. The insoluble drugs, indomethacin and diazepam, displayed values of $n = 0.90$ and 0.82 indicating a near zero-order release. Matrices containing tetracycline hydrochloride, however, showed a value of $n = 0.45$ and displayed complex release patterns and lower release rates than anticipated on the basis of solubility. Replacement of HPMC by calcium phosphate or lactose increased the dissolution rates of promethazine hydrochloride although the values of n were unchanged. Differences in release rates between lactose and calcium phosphate replacement occurred only when matrices contained high levels of the diluents. A straight line relationship existed between release rates and tablet surface area for HPMC tablets containing promethazine hydrochloride.

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 polyvinylpyrrolidone may be used to increase the dissolution rates of poorly soluble drugs (Ford, 1985) and slowly soluble, biodegradable polymers such as polylactic acid may be used for controlled release implants (Rak et al., 1985). Hydrogels provide the basis for implantation, transdermal and oral-controlled release systems. Hydroxypropylmethylcelluloses (HPMC) are cellulose ethers which may be used as the basis for hydrophilic matrices for controlled release oral delivery. Alderman (1984) described the prolonged release from HPMC matrices and concluded that a gelatinous layer, formed when the polymer hydrated on contact with water, controlled the release of drugs by two mechanisms.

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Water-soluble drugs were released by diffusion out of the gelatinous layer and by erosion of the gel, whereas poorly soluble drugs were released solely by erosion.

The kinetics of drug release from matrices were examined for both freely soluble (Higuchi, 1962) and poorly water-soluble drugs (Higuchi, 1963) and mathematical models have been developed to allow for the influences of hydration, swelling and glass transition temperatures on release (Peppas, 1984; Lee, 1985). Korsmeyer et al. (1983) derived a simple relationship (Eqn. 1) 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.

$$\frac{M_t}{M_\infty} = k \cdot t^n \quad (1)$$

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 $\sqrt{\text{time}}$ kinetics and $n = 1.0$ for zero-order release.

Ford et al. (1985a, b and c) have examined the influence of formulation factors on drug release from HPMC matrix tablets. Dissolution rates were derived using Higuchi-type plots (Higuchi, 1962, 1963) which gave straight-line plots for promethazine hydrochloride (Ford et al, 1985a), aminophylline and propranolol hydrochloride (Ford et al., 1985b), but were sigmoidal for the poorly soluble drug, indomethacin (Ford et al., 1985c). The major factor controlling drug release was the drug : HPMC ratio and for each of the drugs a straight line relationship existed between the release rates and the reciprocal of the weight of HPMC in the matrices. Variation in compaction pressure appeared not to modify release rates and drug particle size only modified the release of the insoluble indomethacin.

This paper re-examines the previously published data (Ford et al., 1985a, b and c) to determine the value of the release exponent n. The influence of drug type is further explored using additional data for theophylline, tetracycline hydrochloride and diazepam. Additionally our previous studies have included into the matrix formulation only magnesium stearate as lubricant. This paper examines the effect of replacing some of the HPMC in the matrix, by either the soluble diluent lactose or the insoluble diluent calcium phosphate, on the dissolution rates of promethazine hydrochloride and further studies the influence of tablet shape on promethazine release.

Materials and Methods

All drugs were B.P. grade. Hydroxypropylmethylcellulose K15M viscosity grade (Dow Chemicals, 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): 25 mg, HPMC K15M: 20, 25, 40, 50, 80, 120 or 160 mg, magnesium stearate: 0.75%. Compaction pressure was 1395 $MN \cdot m^{-2}$ (as Ford et al., 1985a).

(ii) Aminophylline (125–180 μm): 225 mg, HPMC K15M: 45, 60, 90, 180 or 270 mg, magnesium stearate: 0.85%. Compaction pressure was 455 $MN \cdot m^{-2}$ (as Ford et al., 1985b).

(iii) Propranolol hydrochloride (125–180 μm): 160 mg, HPMC K15M: 57, 71, 95, 140 or 285 mg, magnesium stearate: 0.75%. Compaction pressure was 348.5 $MN \cdot m^{-2}$ (as Ford et al., 1985b).

(iv) Indomethacin (90–125 μm): 25 mg, HPMC K15M: 25.8, 36, 61.5 or 200 mg, magnesium stearate: 0.75%. Compaction pressure was 1395 $MN \cdot m^{-2}$ (as Ford et al., 1985c).

(v) Tetracycline hydrochloride (125–180 μm): 250 mg, HPMC K15M: 45, 60, 90, 180 or 270 mg, magnesium stearate: 0.75%. Compaction pressure was 455 $MN \cdot m^{-2}$.

(vi) Theophylline hydrochloride (125–180 μm): 225

mg, HPMC K15M: 60, 90, 180 or 270 mg, magnesium stearate; 0.75% Compaction pressure was 455 $MN \cdot m^{-2}$.

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

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.

Effect of tablet shape

Promethazine hydrochloride (180–250 μm): 25 mg, HPMC K15M: 120 mg, magnesium stearate: 0.75%.

Compaction was accomplished using 0.5 inch flat-faced punches at 392 $MN \cdot m^{-2}$, 0.375 inch flat-faced punches at 890 $MN \cdot m^{-2}$, 0.25 inch flat-faced punches at 1580 $MN \cdot m^{-2}$ or 0.375 inch concave punches at 890 $MN \cdot m^{-2}$ on a Manesty E single-punch tableting machine.

The dimensions of the tablets were measured prior to dissolution studies using a screw-gauge micrometer (Moore and Wright, Sheffield) and used to calculate average tablet surface areas. The surface areas (A) of the flat-faced tablets were given by Eqn. 2:

$$A = 2\pi r(r + h) \tag{2}$$

where r = tablet radius and h = tablet thickness. The surface areas (A) of the convex-shaped tablets were given by Eqn. 3:

$$A = 2\pi r h_1 + 2\pi\left(r^2 + \left(\frac{h_2 - h_1}{2}\right)^2\right) \tag{3}$$

where h_1 = the height of the wall of the tablets and h_2 = maximum tablet thickness at the centre of the convex faces.

Effect of HPMC replacement by diluents

Promethazine hydrochloride (90–125 μm): 25 mg; HPMC K15M and diluents: 40 or 160 mg; and magnesium stearate: 0.75%. HPMC : diluent ratios of 1 : 0, 3 : 1, 1 : 1 or 1 : 3 were used utilizing 90–125 μm spray-dried lactose or calcium phosphate. Additionally diluent particle size influences were examined using the 1 : 1 HPMC : diluent ratio at each tablet weight using 45–63 μm or 180–250 μm spray-dried lactose and 45–63 μm or 125–180 μm calcium phosphate. The lower weight tablets were compressed using 0.2188 inch diameter concave punches at 134 $MN \cdot m^{-2}$ and the higher weight tablets at 66 $MN \cdot m^{-2}$ using 0.625 inch diameter concave punches on a Manesty E tableting machine.

Dissolution studies

The dissolution rates of the tablets were monitored using a Copley Series 8000 dissolution tester (Copley Instruments, Nottingham, U.K.). 1000 ml of distilled water was used as dissolution media and maintained at 37 °C. The USP I basket dissolution method was used at a rotation speed of 100 rpm. Dissolution was continuously recorded using a spectrophotometer (Kontron, model Uvikon 810) connected to a Commodore Model 8032 microprocessor. The wavelengths used to monitor each drug were: promethazine hydrochloride, 250 nm; propanolol hydrochloride, 288 nm; aminophylline, 243 nm; indomethacin, 266 nm; diazepam, 230 nm; tetracycline hydrochloride, 390 nm; and theophylline, 243 nm. Dissolution studies were performed in triplicate for each batch of tablets.

Results and Discussion

Influence of drug type

Figs. 1–3 show the $\sqrt{\text{time}}$ dissolution profiles of HPMC matrix tablets containing theophylline, tetracycline hydrochloride and diazepam. The theophylline profiles (Fig. 1) were linear in the time period 4–15 $min^{1/2}$ but thereafter showed positive deviations. Such phenomena were reported in chlorpheniramine maleate–HPMC matrices (Lapidus and Lordi, 1968) and attributed to tablet attrition and in promethazine hydrochloride–HPMC matrices (Ford et al., 1985a) where deviation occurred only in tablets containing low levels of HPMC.

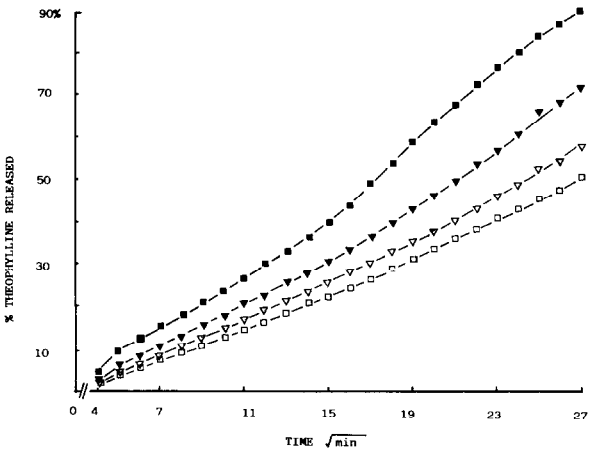

Fig. 1. The effect of theophylline : hydroxypropylmethylcellulose K15M variation on the release of 225 mg theophylline into 1000 ml water at 37 °C from tablets containing (mg of HPMC): ■, 60; ▼, 90; ▽ 180; □, 270.

The $\sqrt{\text{time}}$ profiles for tetracycline hydrochloride matrices (Fig. 2) were more complicated. Initial rapid release by 5 $min^{1/2}$ was followed by retardation in release rates and then by further increases in release rates. $\sqrt{\text{time}}$ kinetics therefore do not accurately describe the tetracycline release. The diazepam profiles (Fig. 3) displayed gradual increases in release rates in the time period up to ~ 19 $min^{1/2}$ before linearity occurred. These findings resemble observations with indomethacin–HPMC matrices (Ford et al., 1985c) when sigmoidal profiles were obtained and confirm that, for drugs of low aqueous solubility, a considerable lag-time may occur (equivalent to an excess of 2 h) before $\sqrt{\text{time}}$ kinetics were obeyed. The lag times are probably due to poor wetting of these drugs with low aqueous solubility.

Higuchi (1963) derived Eqn. 4 which describes the release of a poorly water-soluble drug from the single face of a tablet:

$$\frac{W_r}{t^{1/2}} = S\left[D'\epsilon C_s\left(\frac{2W_0}{V} - \epsilon C_s\right)\right]^{1/2} \quad (4)$$

where W_r = amount of drug dissolved in time t, W_0 = 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. 5 applies (Higuchi, 1962):

$$\frac{W_r}{t^{1/2}} = 2W_0\left(\frac{S}{V}\right)\left(\frac{D'}{\pi}\right)^{1/2} \quad (5)$$

Both Eqns. 4 and 5 therefore predict a $\sqrt{\text{time}}$-dependent dissolution rate which assumes Fickian

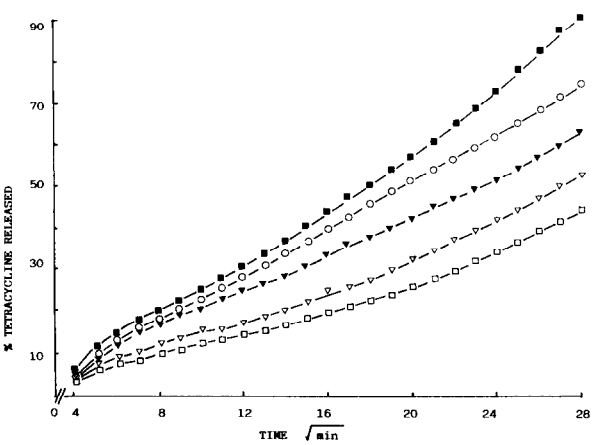

Fig. 2. The effect of tetracycline hydrochloride : hydroxypropylmethylcellulose K15M variation on the release of 250 mg tetracycline into 1000 ml water at 37 °C from tablets containing (mg of HPMC): ■, 45; ○, 60; ▼, 90; ▽, 180; □, 270.

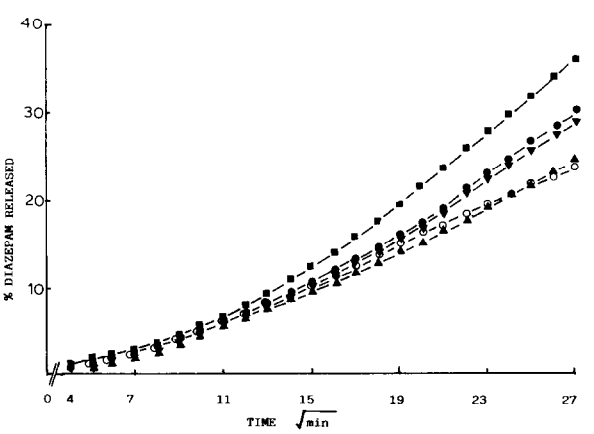

Fig. 3. The effect of diazepam : hydroxypropylmethylcellulose K15M variation on the release of 10 mg diazepam into 1000 ml water at 37 °C from tablets containing (mg of HPMC): ■, 50; ●, 61.5; ▼, 80; ▲, 114.3; ○, 200.

diffusion of the drug molecules through the matrix. Previous studies have reported that the soluble drugs, promethazine hydrochloride, aminophylline and propranolol hydrochloride (Ford et al., 1985a and b), are released by $\sqrt{\text{time}}$ kinetics from HPMC matrices in the range 5–70% drug released and it appeared that for soluble drugs therefore, $\sqrt{\text{time}}$ plots present a good approximation of release kinetics. For indomethacin–HPMC matrices $\sqrt{\text{time}}$ kinetics allowed rate determinations in the approximate range 14–26 $\text{min}^{1/2}$, depending on indomethacin : HPMC ratio (Ford et al., 1985c). The linear portions of Fig. 1 (equivalent to ~ 4–16 $\text{min}^{1/2}$) and Fig. 3 (equivalent to ~ 19–28 $\text{min}^{1/2}$) were used to estimate $\sqrt{\text{time}}$ release. The tetracycline profiles (Fig. 2) were treated as linear throughout the whole of the data (5–28 $\text{min}^{1/2}$) to provide an approximation of release rates. The data therefore for theophylline, tetracycline hydrochloride and diazepam is included in Table 1 following regression analysis.

Ford et al. (1985a) derived the general relationship, Eqn. 6, between drug release and matrix HPMC content:

$$R = M\left(\frac{1}{W}\right) + C \qquad (6)$$

where R = Higuchian release rate ($\% \cdot \text{min}^{-1/2}$), M = derived slope of line, W = weight (mg) of HPMC and C = contant. Insertion of the values in Table 1 gave values of M and C which are presented in Table 2 with previously derived data. Table 2 indicates that Eqn. 6 is valid when applied to drugs of diverse aqueous solubility, provided that $\sqrt{\text{time}}$ release kinetics are approximately followed. However, since the dose of the drugs in Table 2 varies considerably (10–250 mg) further allowance for variations in the size of the tablets needs to be made before comparison of the influences of different drugs may be made. Ford et al. (1985b) suggested that conversion to $\text{mg} \cdot \text{min}^{-1/2}$ release rates at a constant drug : HPMC ratio and division by $W^{2/3}$ (W = weight of HPMC, mg) allowed comparison of different drugs. Indeed on this basis, promethazine hydrochloride, propranolol hydrochloride and aminophylline performed equivalently. Similar treatment for the drugs used in this study allowed the determination of the modified release rates, given in Table 3, at a 1 : 1 drug:HPMC level. The drugs are arranged in order of decreasing solubility and indicate that for soluble drugs the values of the release rates are in the range $23\text{–}27 \times 10^{-2}$ mg (drug) $\cdot \text{min}^{-1/2} \cdot \text{mg}^{-2/3}$ (HPMC) but tend to decrease thereafter with reduction in solubility. The anomalous system would appear to be the tetracycline hydrochloride matrices where the value of the predicted release is considerably lower than predicted on the basis of solubility. It is possible also that the rate for theophylline is lower than anticipated or that of diazepam is higher than predicted on the basis of solubility alone. The latter is more likely due to the low dosage (10 mg) used for the diazepam study leading to a false prediction of release rate.

Two data treatments may provide rationalization for the influences of drug solubility on release rates. Lapidus and Lordi (1968) showed that for soluble drugs Eqn. 5 predicts a linear relationship between the $\sqrt{\text{time}}$ release rate ($W_r/t^{1/2}$) and the drug dose (W_0) whereas for poorly soluble drugs Eqn. 4 predicts a linear relationship between

TABLE 1

The effect of drug : hydroxypropylmethylcellulose ratio on the release rates ($\% \cdot \text{min}^{-1/2}$) of theophylline, tetracycline hydrochloride and diazepam from matrix tablets containing 225, 250 and 10 mg drug, respectively

Theophylline		Tetracycline hydrochloride		Diazepam	
mg HPMC	release rate	mg HPMC	release rate	mg HPMC	release rate
–	–	45	3.37	50	2.05
60	3.00	60	2.75	61.5	1.75
90	2.46	90	2.20	80	1.63
180	2.07	180	1.91	114.3	1.21
270	1.87	270	1.57	200	1.12

TABLE 2

Statistical data from Table 1 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 (% min$^{-1/2}$) against the reciprocal HPMC concentration (mg^{-1}) as given in Eqn 6. For comparison previously published data are included

Drug	Slope M (% min^{-2} · drug)	Intercept C (% min$^{-1/2}$)	Regression coefficient (r)	Degree of significance
Promethazine hydrochloride [1]	132.0	3.33	0.995	$P < 0.001$
Aminophylline [2]	258.9	3.29	0.987	$P < 0.01$
Propranolol hydrochloride [2]	207.9	2.97	0.996	$P < 0.001$
Indomethacin [3]	32.2	0.970	0.975	$P < 0.05$
Theophylline	85.1	1.56	0.997	$P < 0.01$
Tetracycline hydrochloride	91.2	1.28	0.992	$P < 0.001$
Diazepam	64.1	0.75	0.982	$P < 0.01$

Key: [1] Ford et al., 1985a; [2] Ford et al., 1985b; [3]Ford et al., 1985c.

$W_r/t^{1/2}$ and $W_0^{1/2}$. Positive deviations from linearity for either of the plots indicates a large increase in diffusivity of the drug due either to a decrease in tortuosity or an increase in porosity. The value of the exponent of W_0 may be determined simply from log–log plots of $\sqrt{\text{time}}$ dissolution rates against drug dosage. However, Lapidus and Lordi (1985) indicated that such plots should be linear in the drug content range 0–40% and consequently only the data for promethazine hydrochloride, indomethacin (Ford et al., 1985a and c) and diazepam are suitable for this treatment. Additionally Eqns. 4 and 5 predict release rates from planar equal surface areas. Consequently the release data requires adjustment for surface area influences.

Modified release rates, obtained by division of the release rates by (mg HPMC)$^{2/3}$, were used to eliminate surface area differences (Ford et al., 1985b). The results are summarized in Table 4 for release rates. The logarithmic plots of modified release rates against drug dose expressed as % gave exponent values of 1.35, 1.23 and 1.12 for the data for promethazine hydrochloride, diazepam and indomethacin, respectively. Given that release from matrix tablets might not give the precise relationship-dependence predicted by Eqns. 4 and 5, it would appear that the dependence of release rate on drug dosage is independent of solubility.

The closeness of these derived values indicates that although $\sqrt{\text{time}}$ kinetics may be a good approximation of release kinetics from matrix tablets, equations such as 4 or 5, even allowing for adjustment to make them applicable for matrix tablets, do not differentiate between drugs of varying solubility. A further explanation is that tablet erosion may play a far more important role in the release of water soluble drugs than was previously thought (Alderman, 1984). Thus drug release may be via other mechanisms than simple Fickian diffusion. Eqn. 1 (Korsmeyer et al., 1983) may be used to examine drug release from matrix tablets but predicts however a zero intercept. Figs. 1–3 and previous data (Ford et al., 1985a, b and c) indicated that release does not pass through the origin but showed the existence of lag times. These

TABLE 3

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])$^{-2/3}$ × 100 at 1 : 1 drug : HPMC ratio.

TABLE 4

Release rates of promethazine hydrochloride, diazepam and indomethacin, and adjusted for HPMC content, from HPMC matrices

Drug (dose)	% Drug	mg HPMC	Release rates	
			Obtained $mg \cdot min^{-1/2}$	Modified $mg \cdot min^{-1/2}$ $(mg : HPMC)^{-2/3}$
Promethazine hydrochloride (25 mg)	38.5	40	6.80	0.581
	33.3	50	5.85	0.431
	23.8	80	4.99	0.269
	17.2	120	4.56	0.187
	13.5	160	4.00	0.136
Diazepam (10 mg)	16.7	50	2.05	0.151
	14.0	61.5	1.75	0.113
	11.1	80	1.63	0.088
	8.0	114.3	1.21	0.051
	4.8	200	1.12	0.033
Indomethacin (25 mg)	41.0	36	1.74	0.160
	28.9	61.5	1.42	0.091
	11.1	200	1.21	0.035

are thought to be equivalent to the time required for the matrix edges to hydrate and reach equilibrium between erosion and the advance of solvent front through the matrix. To adjust the data to remove the lag times, estimates for each drug: HPMC ratio were made using linear regression of the $\sqrt{\text{time}}$ release data. The values, reconverted to minutes were subtracted from the actual sampling times to produce corrected sampling times which possessed a zero intercept. This allowed substitution into Eqn. 7, the logarithmic form of Eqn. 1:

$$\log \frac{M_t}{M_\infty} = \log k + n \cdot \log t \qquad (7)$$

from which values of n were determined. Prior to lag time adjustment the data, plotted in the logarithmic form, produced a curved relationship, e.g. Fig. 4 shows the uncorrected data for promethazine hydrochloride taken from Ford et al. (1985a) which showed acceptable $\sqrt{\text{time}}$ release. The corrected data showed a linear relationship between $\log(M_t/M_\infty)$ and $\log t$. Similar treatment for aminophylline and propranolol hydrochloride data (Ford et al., 1985b) also produced straight lines. The logarithmic treatment for theophylline (Fig. 5) displayed generally straight lines although the data for tablets containing 60 mg HPMC showed a positive deviation from linearity (as Fig. 1).

Tetracycline hydrochloride matrices, however, gave sigmoidal curves (Fig. 6) confirming the complex nature of release for this particular drug. This

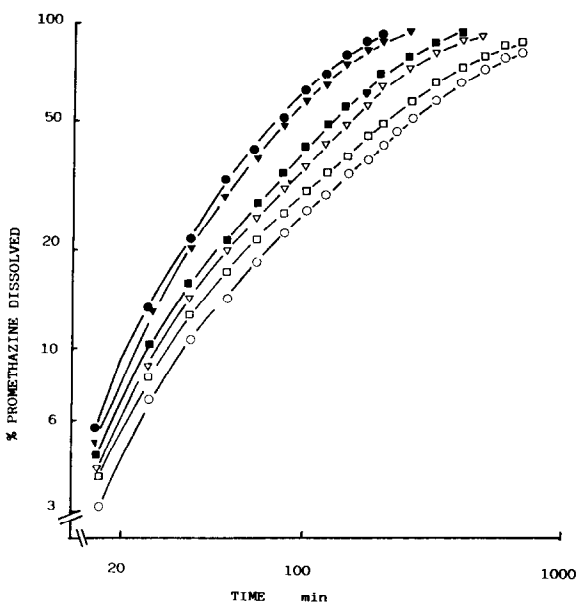

Fig. 4. The effect of promethazine hydrochloride : hydroxypropylmethylcellulose K15M variation on the release of 25 mg promethazine into 1000 ml water at 37 °C from tablets containing (mg of HPMC): ●, 20; ▼, 25; ■, 40; ▽, 50; □, 120; ○, 160.

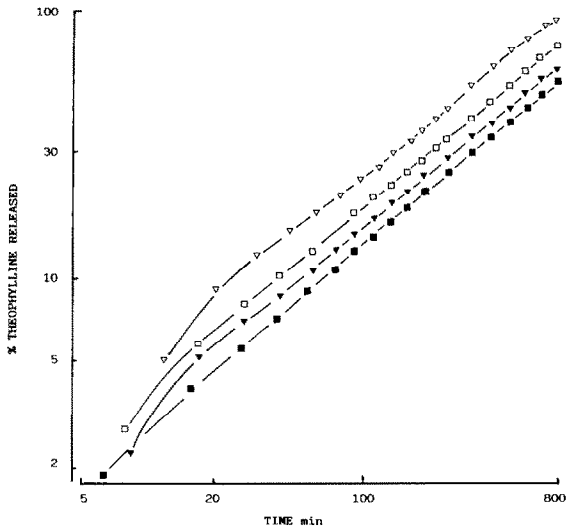

Fig. 5. The effect of theophylline : hydroxypropylmethylcellulose K15M variation on the release of 225 mg theophylline into 1000 ml water at 37 ° C from tablets containing (mg of HPMC): ▽, 60; □, 90; ▼, 180; ■, 270. Lag time corrected.

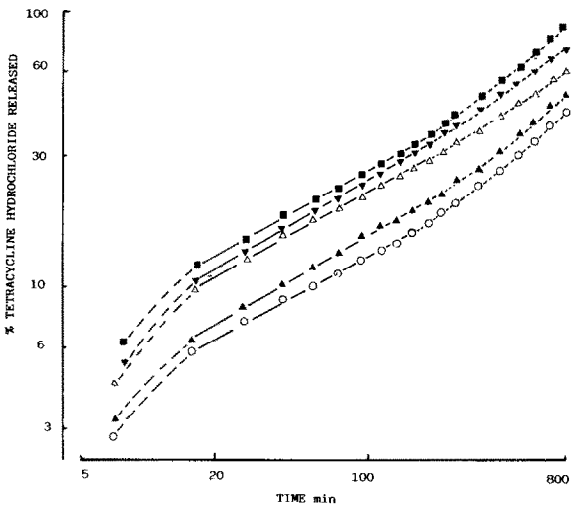

Fig. 6. The effect of tetracycline hydrochloride : hydroxypropylmethylcellulose K15M variation on the release of 250 mg tetracycline hydrochloride in 1000 ml water at 37 ° C from tablets containing (mg of HPMC): ■, 45, ▼, 60; △, 90; ▼, 180; ○, 270. Lag time corrected.

data treatment also gave straight line plots for the insoluble drugs diazepam and indomethacin (Fig. 7) the latter data being that used by Ford et al. (1985c).

Table 5 gives the values of n obtained by regression analysis for each of the tablet formulations. Peppas (1985) used values of M_t/M_∞ of $\leqslant 0.6$ for data analysis whilst Korsmeyer et al. (1983) showed that data of M_t/M_∞ of $\leqslant 0.15$ were non-linear. Data with range $M_t/M_\infty = 0.05–0.70$ were found to be generally linear (with the exception of tetracycline) and therefore acceptable for determination of the exponent n of Eqns. 1 and 7 by linear regression. For consistency, the data used for promethazine, aminophylline and propranolol determinations were identical to that used for previous $\sqrt{\text{time}}$ determinations (Ford et al., 1985a and b). Two values for each indomethacin : HPMC ratio are included corresponding to the range of linearity previously used in $\sqrt{\text{time}}$ determinations (Ford et al., 1985c) and to the range of linearity of Fig. 7. Similar treatment was used for diazepam (Fig. 3). Because the $\sqrt{\text{time}}$ data for tetracycline (Fig. 2) were not linear, values of n were determined throughout the data range (corresponding to values used to determine the release rate in Table 1) and over the narrower linear portion of Fig. 6. The values used

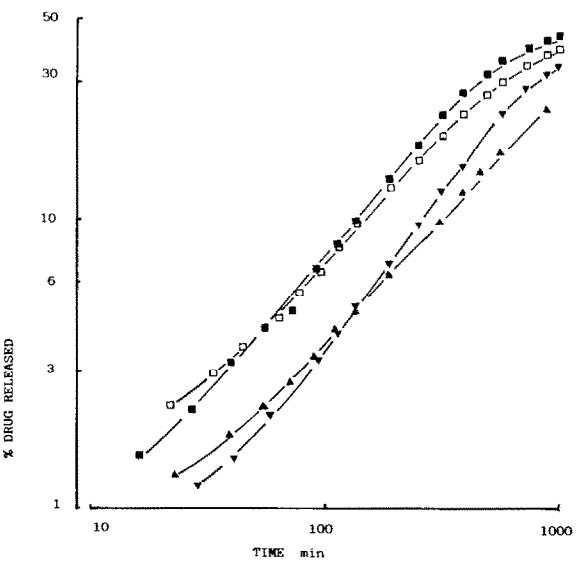

Fig. 7. The effect of indomethacin : hydroxypropylmethylcellulose K15M variation on the release of 25 mg indomethacin in 1000 ml water at 37 ° C from tablets containing (mg of HPMC): ■, 25.8; □, 36; ▼, 61.5; ▲, 200. Lag time corrected.

TABLE 5

The effect of drug : hydroxypropylmethylcellulose ratio on the exponent n (Eqn. 7) derived from dissolution data for 7 drugs

Promethazine hydrochloride [1] 25 mg			Aminophylline 225 mg			Propranolol hydrochloride [2] 160 mg			Indomethacin [3] 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			

Key: [1] after Ford et al., 1985a; [2] after Ford et al., 1985b; [3] after Ford et al., 1985c.
* Values used for Table 4.

for theophylline corresponded to the range used for rate determinations in Table 1, the linear portion of Fig. 3.

The derived values of n (Table 5) were relatively invariant for each particular drug system, although for promethazine and diazepam matrices they appeared slightly higher at low HPMC content. Table 3 gives the mean values for n, irrespective of the HPMC : drug ratio used. The values were similar (0.65–0.71) for the highly soluble drugs promethazine hydrochloride, aminophylline and propranolol hydrochloride and additionally theophylline (0.64). Peppas (1985) stated that diffusional controlled (Fickian) release from planar surfaces gave a value of $n = 0.5$, giving the $\sqrt{\text{time}}$ dependent release of Eqns. 4 and 5. The slightly higher values may be explained on the basis that Eqn. 1 was derived for release from a planar surface and not from an erodible matrix. Nonetheless the values in Table 3 for these drugs are close to the values predicted for diffusional release.

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, 1985) but for spheres and cylinders a value of ~ 1 may not correspond to zero-order release due to

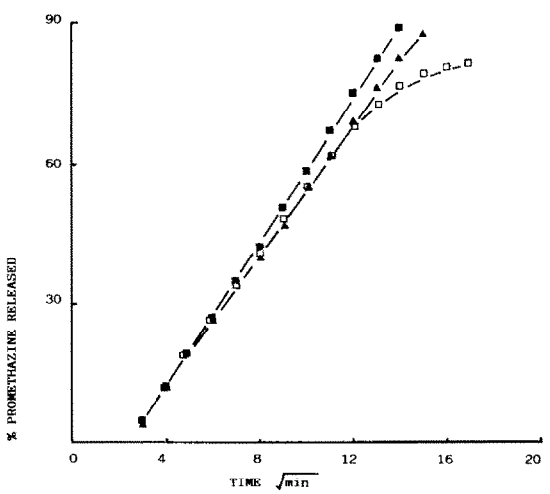

Fig. 8. Effect of calcium phosphate particle size variation on the release of 25 mg promethazine hydrochloride from tablets containing 20 mg hydroxypropylmethylcellulose K15M and 20 mg calcium phosphate of particle size: □, 45–63 μm; ■, 90–125 μm; ▲, 125–180 μm.

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 (Figs. 1 and 6; Table 3) with a value of $n = 0.45$ emphasisis the complexitiy of release of this drug. Peppas (1985) 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. This may be further emphasised by considering the data for 4 and 5 $\sqrt{\text{minutes}}$ (Fig. 2). The slopes of these initial portions of the profiles may be inserted into Eqn. 6 and converted to the modified release rates (as Table 3) which gives a value of 19.7×10^{-2} mg $\cdot$ min$^{-1/2}$ $\cdot$ mg (HPMC)$^{-2/3}$. This value is nearly double that stated in Table 3 and confirms the retardation of release of this drug as matrix hydration occurs. The mechanisms of this possible tetracycline–HPMC interaction are currently under investigation.

Effect of tablet shape

Table 6 summarises the influences of tablet shape and size on the $\sqrt{\text{time}}$ release rates of promethazine hydrochloride tablets compressed to the same weight and formula. Ford et al. (1985a) 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 6 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 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 $\sqrt{\text{time}}$ basis were acceptably linear for up to 80% drug released for either excipient at each diluent : HPMC level. The calculated $\sqrt{\text{time}}$ release rates (Table 7) 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 depite the high level of soluble solids in the matrix ($\sim$ 85%). Interestingly the value of the exponent n (Eqn. 1) appeared not to vary from the range

TABLE 6

The effect of tablet shape on the dissolution rates of promethazine from tablets containing promethazine hydrochloride 25 mg. HPMC K15M 120 mg 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 $\pm$ 4.3	5.99
Flat-face	0.375	890	197.9 $\pm$ 0.1	4.61
Flat-face	0.25	1580	162.4 $\pm$ 0.8	4.13
Concave	0.375	890	179.1 $\pm$ 0.6	4.23

TABLE 7

The effect of diluent, diluent particle size and diluent : HPMC ratio on the dissolution rate of promethazine from matrix tablets containing 25 mg promethazine hydrochloride, 0.75% magnesium stearate and either 40 or 160 mg 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.

0.6–0.74 indicating probably diffusion-controlled drug release. These results confirm the findings of Lapidus and Lordi (1966) 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, 1968). Indeed for chlorpheniramine maleate tablets only large differences were apparent when total soluble solid content was ~ 83% (Lapidus and Lordi, 1968). Additionally the results contradict the statement of Alderman (1984) 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 release rates appeared to decrease with increasing lactose particle size whereas in tablets containing 160 mg 1 : 1 lactose : HPMC rates increased slightly with increase in lactose particle size (Table 7). The particle size of calcium phosphate produced no clear particle size dependent changes in release rates. However, Fig. 7 indicates that the 45–63 μm fraction of calcium phosphate produced a negative deviation from linearity in tablets 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.

Conclusions

This study indicates that although $\sqrt{\text{time}}$ kinetics may be a close approximation which described the release of soluble drugs from matrix tablets, the true time dependency for release rate is $t^{\sim -0.65}$. Certain drugs which are freely soluble may show low exponents of time dependency, for example tetracycline hydrochloride displays a $t^{-0.45}$ dependent release. Insoluble drugs showed $t^{-0.8}$ to $t^{-0.9}$ dependent release, approximating to zero-order kinetics. Replacement of portions of HPMC within the matrices by diluents increased the release rates of promethazine hydrochloride, irrespective of whether the diluents were water soluble or water insoluble. Release rates appeared to be $t^{\sim -0.65}$ dependent. Maximum maintenance of release would occur for spherical matrices.

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