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# Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose

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## Summary

The effect of aminophylline and propranolol hydrochloride release from sustained release tablets containing four grades of hydroxypropylmethylcellulose (HPMC) has been examined. The effect of drug : HPMC ratio and drug particle size on drug release has also been investigated. In all cases a plot of % drug dissolved against $\sqrt{\text{time}}$ produced a straight line. Similar release rates were obtained from HPMC K4M, HPMC K15M, and HPMC K100M matrices at similar drug : HPMC ratios, although HPMC K100 matrices gave consistently higher rates at identical drug : HPMC levels. It was found that the major factor controlling drug release was the drug : HPMC ratio; increasing the polymer content decreased the dissolution rate of the drug. A straight line relationship was established between the logarithm of the tablet HPMC content and the logarithm of the release rates ($mg \cdot min^{-1/2}$), enabling release rates to be predicted for a variety of different drug substances. It has been suggested that this relationship is accounted for by considering that the weight of HPMC directly influences the surface area of the matrix which in turn controls the release rate. Changes in drug particle size insignificantly affected drug release.

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## Introduction

Hydroxypropylmethylcelluloses have often been used in controlled release tablet formulations. Successful controlled release has been reported with quinidine sulphate and drotaverine (Ventouras and Buri, 1978), chlorpheniramine maleate (Lapidus and Lordi, 1966; Daly et al., 1984), sodium salicylate, benzoic acid and benzocaine (Lapidus and Lordi, 1968), potassium chloride (Salomen et al., 1979a and b) and promethazine hydrochloride (Ford et al., 1985).

Hydroxypropylmethylcellulose (HPMC) offers the advantage that, although wet-massing may be used to conventionally granulate the material, direct compression of the dry blended drug with HPMC is easily accomplished. It would, however, be of benefit to have mathematical principles by which to formulate drugs with HPMC.

The fundamental equations describing drug release from matrices are either:

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

which describes the release of poorly water soluble drugs (Higuchi, 1963) or

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

which describes the release of freely water-soluble drugs (Higuchi, 1962), where $W_r$ = the amount of drug released in time t, $W_0$ = the dose of the drug, S = the effective diffusional area, V = effective volume of the hydrated matrix, $C_s$ = solubility of the drug in the release medium, $\epsilon$ = porosity of the hydrated matrix, and $D'$ = the apparent diffusion coefficient of the drug in the hydrated matrix. Eqns. 1 and 2 describe the release of drugs only from a planar surface. However, Lapidus and Lordi (1968) used the equations to show that a straight-line plot may be achieved by plotting $W_r/t^{1/2}$ against $W_0$, the dose of a soluble drug (e.g. chlorpheniramine maleate) whereas for poorly water soluble drugs (e.g. benzocaine) linearity was obtained by $W_r/t^{1/2}$ against $W_0^{1/2}$. Deviations from such linearity occurred when the tortuosity of the hydrated gels was reduced by high drug levels since the term $D'$ in Eqns. 1 and 2 is linked to tortuosity $\tau$ by the relationship

$$D' = \frac{D}{\tau} \tag{3}$$

where D is the actual diffusion coefficient of the drug in the release media. Both Eqns. 1 and 2 predict a zero intercept when $W_r$ is plotted against $t^{1/2}$. However, lag times, due to hydration of the polymer, result in small negative intercepts (Ford et al., 1985). The actual mechanism of release from HPMC matrices is modified by drug solubility. For water-soluble drugs, release is effected by both diffusion of the drug through the HPMC and by slow dissolution of the matrix itself following hydration, a process known as attrition. For drugs of low solubility, however, release is generally regarded as being an attrition process.

Recently, Ford et al. (1985) considered the effects of some formulation variables on the release of promethazine hydrochloride from HPMC matrices. The release rate was not modified by the presence of magnesium stearate (as lubricant) or by variation in compaction pressure. Increasing the drug particle size from a range of 45–63 $\mu$m to 500–750 $\mu$m only increased the release rate of promethazine by 12%. The predominant factor in controlling the release rate appeared to be the promethazine hydrochloride : HPMC ratio and the following relationship was derived from experimental results.

$$R = M\left(\frac{1}{W}\right) + C \tag{4}$$

where R = Higuchi-type release rate (% $min^{-1/2}$), M = slope of the derived line, W = weight of HPMC (mg) in tablet, C = constant. Thus a plot of the promethazine release rate against the reciprocal HPMC content within the tablet produced a straight line.

The lag times of the Higuchi-plots were not generally affected by the viscosity grade of the four HPMCs examined. The K100 grade gave consistently higher releases than the K4M, K15M and K100M grades at similar drug : HPMC ratios. This paper extends the findings of that previous paper (Ford et al., 1985) and examines the effects of drug : HPMC ratio and drug particle size on drug release from HPMC tablets containing aminophylline and propranolol hydrochloride.

## Materials and Methods

### *Materials*

Propranolol hydrochloride B.P. (Berk Pharmaceuticals) was sieved to produce size fractions of 63–90, 90–125, 125–180, 180–250 and 250–500 $\mu$m. Similarly aminophylline B.P. (Boehringer Ingelheim) was sieved to produce 63–90, 125–180 and 180–250 $\mu$m.

Four viscosity grades of HPMC (Methocel; Dow Chemicals, U.S.A.) were used. These were HPMC K100, HPMC K4M, HPMC K15M and HPMC K100M, and the viscosities of their 2% aqueous solutions were 106, 3850, 12449 and 93000 cps. Magnesium stearate (British Drug Houses, U.K.) was used as lubricant.

### *Tableting*

Flat-faced tablets, 7/16 inch diameter for aminophylline and 0.5 inch for propranolol hydrochloride were compressed on a Manesty F3 single-punch tableting machine at 455 $MNm^{-2}$ and 348.5 $MNm^{-2}$, respectively. Compaction was accomplished by direct compression of drug–HPMC–magnesium stearate blends that had been mixed for 15 min using a tumbler mixer.

### *Aminophylline*

All tablets contained 225 mg aminophylline and 0.85% magnesium stearate. The effects of the following variations in tablet formulae on dissolution rates were examined:

*(a) Viscosity grade of HPMC and aminophylline: HPMC ratio.* Using each of the four viscosity grades of HPMC, tablets were made containing 45, 60, 90, 180 or 270 mg HPMC. The 125–180 $\mu$m fraction of aminophylline was used.

*(b) Aminophylline particle size.* Tablets were made containing either 45 or 180 mg HPMC K15M, using each of the particle size fractions of aminophylline.

*Propranolol hydrochloride*

All tablets contained 160 mg propranolol and 0.75% magnesium stearate. The effects of the following variations in tablet formulae on dissolution rates were examined:

*(a) Viscosity grade of HPMC and propranolol: HPMC ratio.* Using each of the four viscosity grades of HPMC, tablets were made containing 57, 71, 95, 140 and 285 mg HPMC. The 125–180 $\mu$m fraction of propranolol was used.

*(b) Propranolol hydrochloride particle size.* Tablets were made containing either 57 or 285 mg HPMC K15M, using each of the particle size fractions of propranolol.

*Dissolution studies*

Dissolution was measured by the Copley Series 8000 dissolution tester (Copley Instruments, Nottingham, U.K.) and continuously recorded by a spectrophotometer (Kontron model Uvikon 810). The USP I basket method was used, rotating at 100 rpm in 1000 ml distilled water maintained at 37°C. Aminophylline and propranolol hydrochloride levels were monitored at 243 and 288 nm, respectively. Studies were performed in triplicate for each batch of tablets. Data were plotted as the % drug dissolved against $\sqrt{\text{time}}$ to give the typical straight-line Higuchi-type plots (W.I. Higuchi, 1962; T. Higuchi, 1963). The slopes of these lines were generally determined by linear regression of the data corresponding to 5–70% drug dissolved.

## Results and Discussion

The release rates of each drug decreased as the tablet content of HPMC increased. Typical plots are given in Figs. 1 and 2. All the data could be presented as Higuchi-type plots and Tables 1 and 2 summarize the release rates and intercepts for aminophylline and propranolol hydrochloride. No positive deviation occurred from the curves indicating that attrition did not contribute to drug release (Lapidus and Lordi, 1968). Similar dependence of release rates on the drug : HPMC ratio have been observed for HPMC matrices of potassium chloride (Salomen et al., 1979) and promethazine hydrochloride (Ford et al., 1985).

Substitution of the release rates given in Tables 1 and 2 into Eqn. 4 gives the derived values of M and C, presented in Table 3, which in turn were used to produce Figs. 3 and 4. These figures, together with the coefficients of linear regression presented in Table 3 confirm that such data treatment may be used to predict the release rates from HPMC matrices.

Extrapolation of all the release curves, such as Figs. 1 and 2, to a zero %-released intercept gave estimates of between 8 and 14 min. There was no substantiation to the claim of Salomen et al. (1979) that increasing the viscosity grade increased the lag

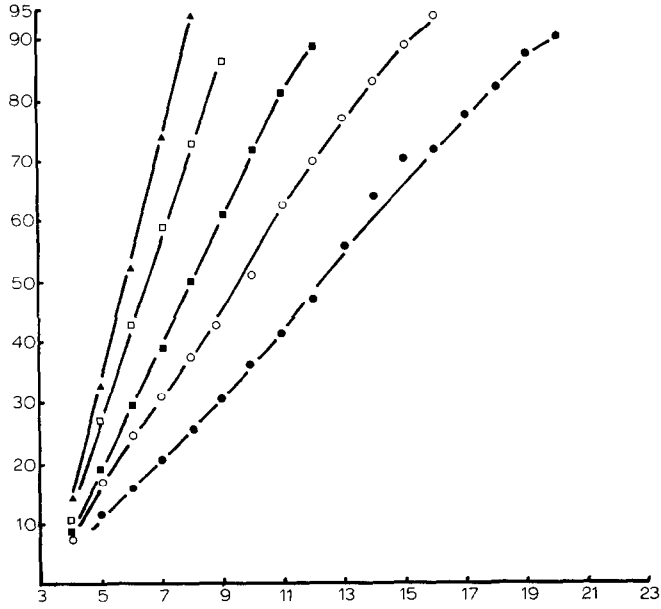


Fig. 1. The effect of aminophylline: hydroxypropylmethylcellulose K100 variation on the release of 225 mg aminophylline into 1000 ml water at 37°C from tablets containing (mg of HPMC K100): ▲, 45; □, 60; ■, 90; ○, 180; ●, 225.Ordinate: % aminophylline dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).

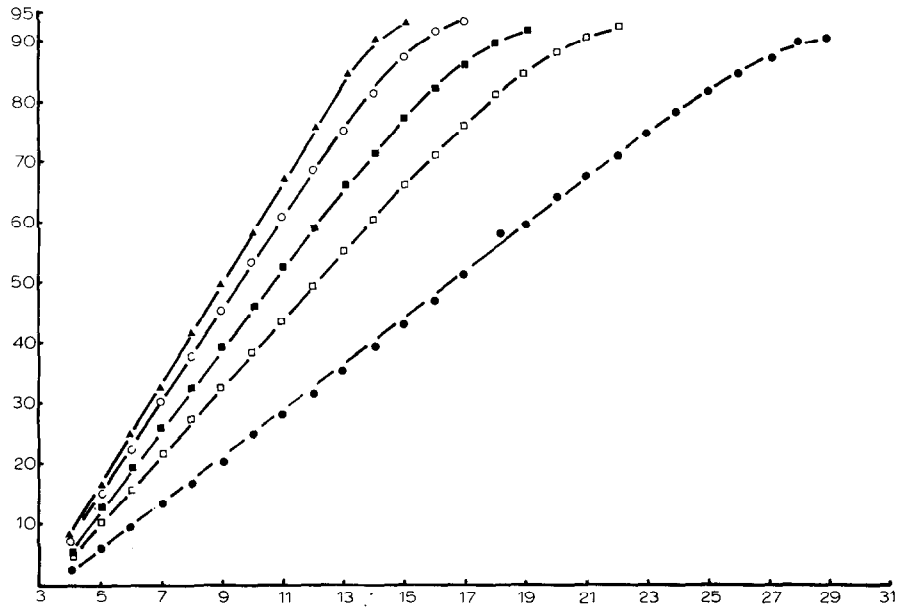


Fig. 2. The effect of propranolol: hydroxypropylmethylcellulose K4M variation on the release of 160 mg propranolol hydrochloride into 1000 ml water at 37°C from tablets containing (mg of HPMC K4M): ▲, 57; ○, 71; ■, 95; □, 140; ●, 285. Ordinate: % propranolol hydrochloride dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).

TABLE 1

THE EFFECT OF HYDROXYPROPYLMETHYLCELLULOSE VISCOSITY GRADE AND AMINOPHYLLINE : HYDROXYPROPYLMETHYLCELLULOSE RATIO ON THE RELEASE RATES (% $min^{-1/2}$) OF AMINOPHYLLINE FROM TABLETS CONTAINING 225 mg AMINOPHYLLINE AND 0.85% magnesium stearate

| | Hydroxypropyl methylcellulose viscosity grade | | | |
|---|---|---|---|---|
| mg HPMC | K100 | K4M | K15M | K100M |
| 270 | 5.66 | 4.03 | 3.95 | 4.09 |
| 180 | 7.35 | 4.94 | 4.93 | 4.48 |
| 90 | 10.42 | 6.77 | 6.54 | 6.72 |
| 60 | 15.17 | – | 7.24 | 7.66 |
| 45 | 20.10 | 9.51 | 9.12 | 8.70 |

TABLE 2

THE EFFECT OF HYDROXYPROPYLMETHYLCELLULOSE VISCOSITY GRADE AND PROPRANOLOL : HYDROXYPROPYLMETHYLCELLULOSE RATIO ON THE RELEASE RATES (% $min^{-1/2}$) OF PROPRANOLOL HYDROCHLORIDE FROM TABLETS CONTAINING 160 mg PROPRANOLOL HYDROCHLORIDE AND 0.75% MAGNESIUM STEARATE

| | Hydroxypropyl methylcellulose viscosity grade | | | |
|---|---|---|---|---|
| mg HPMC | K100 | K4M | K15M | K100M |
| 285 | 5.03 | 3.90 | 3.64 | 3.54 |
| 140 | 7.61 | 5.59 | 4.43 | 5.24 |
| 95 | 9.53 | 6.60 | 5.26 | 6.44 |
| 71 | 12.68 | 7.66 | 6.01 | 7.01 |
| 57 | 15.17 | 8.49 | 6.49 | 7.04 |

TABLE 3

STATISTICAL DATA FROM TABLES 1 AND 2 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 (% $min^{-1/2}$) AGAINST THE RECIPROCAL HYDROXYPROPYLMETHYLCELLULOSE CONCENTRATION ($mg^{-1}$) AS GIVEN IN EQN. 4 FOR PROPRANOLOL HYDROCHLORIDE AND AMINOPHYLLINE.

| Drug | HPMC grade | Slope M (% $min^{-1} \cdot mg$) | 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 | $P < 0.02$ |

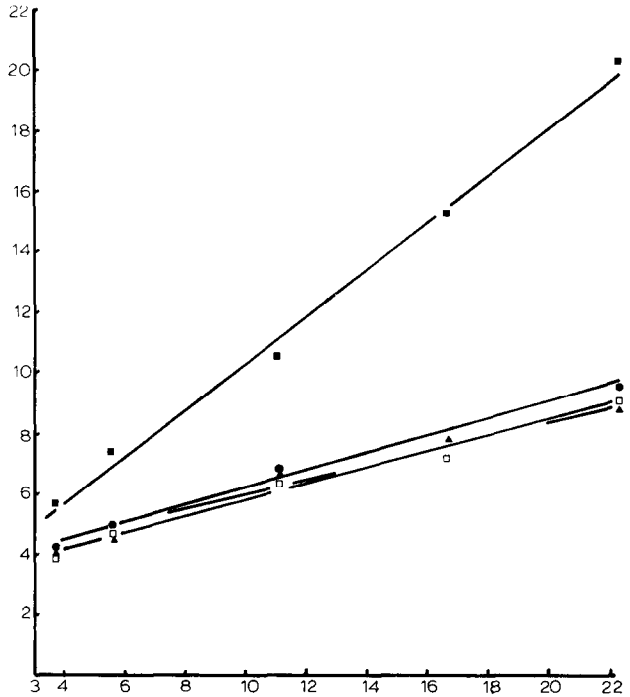


Fig. 3. Graphs showing the relationship between release rates (% $min^{-1/2}$) of aminophylline and the reciprocal tablet content ($mg^{-1} \times 10^4$) of hydroxypropylmethylcellulose for tablets containing 225 mg aminophylline and: ■, HPMC K100; ●, HPMC K4M; □, HPMC K15M; ▲, HPMC K100M. Ordinate: release rate (% $min^{-1/2}$). Abscissa: reciprocal HPMC ($mg^{-1} \times 10^4$).

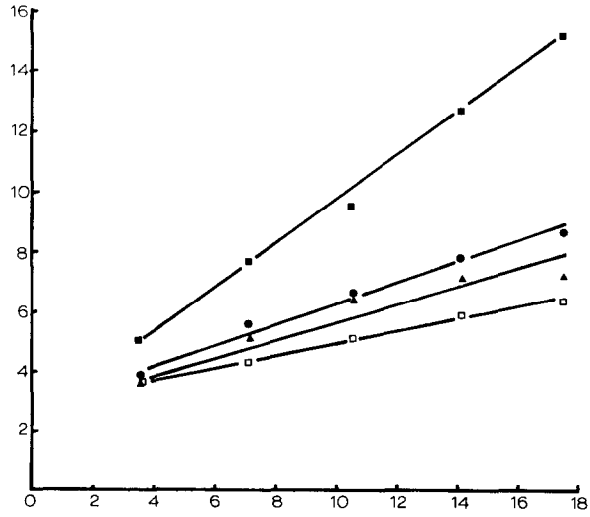


Fig. 4. Graphs showing the relationship between release rates (% $min^{-1/2}$) of propranolol hydrochloride and the reciprocal tablet content ($mg^{-1} \times 10^4$) of hydroxypropylmethylcellulose for tablets containing 160 mg propranolol hydrochloride and: ■, HPMC K100; ●, HPMC K4M; □, HPMC K15M; ▲, HPMC K100M. Ordinate: release rate (% $min^{-1/2}$). Abscissa: reciprocal HPMC ($mg^{-1} \times 10^4$).

time for quasi-stationary diffusion, since the lag times were not dependent on the HPMC grade used. Tables 1 and 2 similarly confirm that once equilibrium diffusion has been obtained the release rates from matrices containing HPMC K4M, HPMC K15M or HPMC K100M were similar but lower than from matrices containing HPMC K100 at the same drug : HPMC ratios. Both of these findings confirm the results of Ford et al. (1985).

The relationships indicated by Table 3 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 or possible drug–HPMC interactions may complicate such calculations. Nonetheless, as a first step to inter-relate the dissolution rates of the two drugs in this study and of promethazine previously reported (Ford et al., 1985), Eqn. 4 was used to predict the dissolution rates from 1 : 1 to 1 : 2 drug : HPMC matrices. These calculated rates are expressed in Table 4.

Direct comparison of the % $min^{-1/2}$ 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 $mg \cdot min^{-1/2}$ data indicates that as the dose of the drug and consequently as the amount of HPMC within the tablet increases, the dissolution rates increase. In fact, a straight-line relationship existed between the logarithm of the tablet HPMC content and the logarithm of the release rates ($mg \cdot min^{-1/2}$) at similar drug : HPMC ratios. The eight sets of data in Table 4 (4 HPMC grades $\times 2$ drug : HPMC ratios) can therefore be reduced to the following relationship:

$$\log R = m' \log \text{HPMC} + \text{constant A} \qquad (5)$$

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

The data for Eqn. 5 are determined at a constant drug : HPMC ratio. The values of the slope m′ and A for 1 : 1 and 1 : 2 ratios, together with the statistical data for this treatment are given in Table 5; 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 225 mg, since this was the range over which Eqn. 5 was developed. Similarly it is valid for lubricant (or other insoluble excipient) levels of up to only 0.85%. Ford et al. (1985) previously showed that the absence or presence of 0.75% lubricant did not modify dissolution rates. However, Lapidus and Lordi (1968) indicated that the presence of larger levels of insoluble diluents, e.g. tricalcium phosphate, reduced release rates by increasing the tortuosity of the matrix, whereas the addition of a soluble diluent, e.g. lactose, merely reduced the tortuosity of the matrix and thereby increased rates. The terms R in Eqn. 4 or log R in Eqn. 5 would probably, in the

TABLE 4

ESTIMATED RELEASE RATES (% $min^{-1/2}$ OR $mg \cdot min^{-1/2}$) 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 ($mg \cdot min^{-1/2}$) / $W_1^{2/3}$ ** |
|---|---|---|---|---|---|
| | | | % $min^{-1/2}$ | $mg \cdot min^{-1/2}$ | |
| 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. (1985).
** $W_1^{2/3}$ = (wt of HPMC)$^{2/3}$.

presence of a soluble diluent, be a summation of the dissolution rates of the diluent and the drug. The influence of an insoluble ingredient remains unclear.

Eqn. 5 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. 5 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 (1968) have shown that certain ions, e.g. the sodium ion, may decrease the

TABLE 5

ESTIMATED VALUES OF THE SLOPE, m′, AND CONSTANT A, OF THE STRAIGHT-LINE PLOT OF LOGARITHM OF THE HPMC CONTENT OF TABLET (mg) AND THE LOGARITHM OF THE HIGUCHI RELEASE RATES DERIVED FROM THE TABLETS FOR HPMC MATRIX TABLETS OF AMINOPHYLLINE, PROPRANOLOL HYDROCHLORIDE AND PROMETHAZINE HYDROCHLORIDE

| HPMC grade | Drug : HPMC ratio | Slope m′ | Intercept A | Regression coefficient ($r$) | Degree of significance |
|---|---|---|---|---|---|
| K100 | 1 : 1 | 0.679 | −0.459 | 0.9999 | $P < 0.01$ |
| | 1 : 2 | 0.711 | −0.688 | 0.9997 | $P < 0.02$ |
| K4M | 1 : 1 | 0.665 | −0.556 | 1.000 | $P < 0.001$ |
| | 1 : 2 | 0.761 | −0.855 | 0.9998 | $P < 0.01$ |
| K15M | 1 : 1 | 0.673 | −0.6145 | 0.9954 | $P < 0.1$ |
| | 1 : 2 | 0.779 | −1.155 | 0.9970 | $P < 0.05$ |
| K100M | 1 : 1 | 0.644 | −0.517 | 0.9987 | $P < 0.05$ |
| | 1 : 2 | 0.779 | −0.890 | 0.9990 | $P < 0.05$ |

TABLE 6

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 ($\mu$m) | Wt. of HPMC K15M | |
|---|---|---|
| | 45 mg | 180 mg |
| | Release rates (% $min^{-1/2}$) | |
| 63–90 | 8.88 | 5.26 |
| 125–180 | 9.12 | 4.93 |
| 180–250 | 9.75 | 5.05 |

TABLE 7

THE INFLUENCE OF PROPRANOLOL HYDROCHLORIDE PARTICLE SIZE ON THE RELEASE RATES OF PROPRANOLOL FROM TABLETS CONTAINING 160 mg PROPRANOLOL HYDROCHLORIDE AND 57 OR 285 mg HPMC K15M

| Propranolol hydrochloride particle size ($\mu$m) | Wt. of HPMC K15M | |
|---|---|---|
| | 57 mg | 285 mg |
| | Release rates (% $min^{-1/2}$) | |
| 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 |

tortuosity of the HPMC gel by dehydrating the polymer. The applicability of Eqn. 5 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. 5 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:

$$V \propto W \propto r^3 \tag{6}$$

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

$$S \propto r^2 \propto W^{2/3} \tag{7}$$

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 4 by $W_1^{2/3}$, where $W_1$ is the weight of HPMC, gives the modified release rates. It is apparent in Table 4 that these modified rates are similar when derived from HPMC K4M, HPMC K15M and HPMC K100M matrices thereby explaining the relationships outlined by Eqn. 5. The higher values of HPMC K100 matrices (Table 4) 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, 1979). 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.

The particle size range of a drug over which Eqn. 5 applies also needs elucidating. Ford et al. (1985) previously indicated that as the particle size of promethazine hydrochloride was increased from 45–63 $\mu$m to 500–750 $\mu$m, only a corresponding 12% increase in dissolution rate was achieved from 4.62 to 5.18% $min^{-1}$. The data used for Table 4 were taken from the 250–500 $\mu$m range of promethazine but from the 125–180 $\mu$m range of both aminophylline and propranolol. However, the difference in results between the 125–180 and 250–500 $\mu$m ranges for promethazine

was only 3.5% and therefore these differences have been considered as marginal and would not affect Table 4 or Eqn. 5.

The influence of particle size on the drug release rate is indicated by Tables 6 and 7. 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 $\mu$m range of propranolol) during release studies. These data therefore tends to indicate that Eqn. 5 would be valid over a wide drug particle size range, i.e. 63–250 $\mu$m 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 which as Eqns. 1, 2 and 3 predict, would produce a rapid release rate. The applicability of Eqn. 5 to poorly water soluble drugs remains to be investigated.

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