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Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices

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Summary

The effects of some formulation variables on the release rates of promethazine hydrochloride from hydroxypropylmethylcellulose (HPMC) tablet matrices have been investigated. The major controlling factor appeared to be the promethazine: HPMC ratio and a straight-line relationship existed between the Higuchi-type release rate and the reciprocal of the tablet content of HPMC. Increasing the particle size range of promethazine from 45–63 to 500–700 μm only produced a 12% increase in the drug release rate. Variation in compaction pressure from 93 to 1395 MNm^{-2} and the absence or presence of 0.75% magnesium stearate as lubricant appeared not to modify release rates. The lowest viscosity grade of HPMC used (HPMC K100) gave the highest release rates at constant HPMC: drug ratio. The other three grades (HPMC K4M, K15M and K100M) showed similar release rates despite the variation in their molecular size.

Introduction

Cellulose ethers have been used in a variety of formulations including topical and ophthalmic preparations, enteric polymer film coats, microcapsules and matrix

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systems. 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 released. 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.

The aqueous solubility of a drug will affect the release mechanism from polymer matrices and therefore allows difficult mathematical interpretations of dissolution rate (Higuchi 1963, Higuchi, 1962, Lapidus and Lordi 1968). Water penetration may be visualized as a front moving into the tablet, hydrating the polymer and dissolving the active material which then diffuses out through the swollen matrix. If the drug has limited water solubility so that it has not completely dissolved when the polymer is hydrated then diffusion will commence from a saturated solution. The expression describing drug release from the single face of a tablet is (Higuchi, 1963):

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

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 = solubility of the drug in release medium, ϵ = porosity of the hydrated matrix, D′ = apparent diffusion coefficient of the drug in the hydrated matrix.

If the drug has a high aqueous solubility and has completely dissolved when the matrix is hydrated, then the following expression applies (Higuchi, 1962):

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

Generally for Eqns. 1 and 2 to hold, drug release should be examined under near perfect sink conditions and the amount dissolved should be less than 30% of the initial dose. S and V are larger than the corresponding values of the tablet prior to immersion in the solvent due to swelling of the matrix when hydrated. Eqns. 1 and 2 predict a zero intercept but inevitably small negative intercepts will be obtained due to failure of the systems to attain immediately the state of diffusion described by Eqns. 1 and 2. Generally, however, a soluble drug is released by diffusion from the gel layer and by tablet erosion whereas an insoluble drug is released by exposure through tablet erosion.

There are, therefore, other factors, not immediately apparent from Eqns. 1 and 2, which control the release of a drug. For instance the rate of hydration of the hydrophilic matrix compared to the rate of wetting and dissolution of the remainder of the tablet. Using constant tablet weights but different chlorpheniramine hydro-

chloride : hydroxypropylmethylcellulose ratios, Lapidus and Lordi (1966) noted that the Higuchian dissolution rates, plotted as a function of the dose within the tablet were linear for up to a 25% concentration of drug. The positive change in linearity above this level resulted from a change in the tortuosity of the hydrated polymer. Tortuosity τ can be related to D′ and the actual diffusion coefficient D of the drug in the release media by

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

and hence tortuosity may influence drug release. Similar positive deviations occurred at a lower drug level (16.6%) when the dissolution media was replaced by 0.1 M HCl (Lapidus and Lordi, 1968). The term $(S/V)(D'/\pi)^{1/2}$ in Eqn. 2 is therefore subject to variation as the drug : polymer ratio is varied and also as the solvent is altered (Lapidus and Lordi, 1968). The non-active moiety of a drug molecule may further modify the release rate by altering tortuosity of the gel, since sodium ions for instance, compared to chlorpheniramine ions, possess a greater ability to dehydrate the polymer and therefore decrease tortuosity (Lapidus and Lordi 1968).

Formulation additives further modify release rates. Daly et al. (1984) considered that the addition of surfactants may modify release from HPMC matrices by binding to the polymer and increasing the viscosity. More simple molecules, for example insoluble diluents such as tribasic calcium phosphate or water soluble diluents such as lactose may modify release rates. Lapidus and Lordi (1968) showed that the addition of lactose increased the release rate of chlorpheniramine more than the equivalent amount of calcium phosphate, due to the former reducing the tortuosity of the diffusion pattern of the drug whereas the latter merely reduces the hydroxypropylmethylcellulose (HPMC) concentration.

Polymer viscosity further modifies release rate. Nakano et al. (1983) indicated that the release of theophylline from hydroxypropylcellulose (HPC) matrices decreased as the viscosity grate of the HPC increased. However, earlier work by Salomen et al. (1979) indicated that the viscosity grade of HPMC only affected the lag time for potassium chloride diffusion to become quasi-stationary but did not affect the rate of release. Huber and Christenson (1968) indicated that although increased compaction pressure increased the apparent density of HPMC tablets the release characteristics were not markedly affected.

The formulator of HPMC matrix tablets is therefore confronted with a large number of variables which can alter the release rate of drug, not least of which is that much of the published data is restricted to only the single face of a tablet and that, for instance, the influence of drug : HPMC ratio has only been examined without keeping the drug quantity constant and only varying the HPMC level. This paper evaluates the release of promethazine hydrochloride from HPMC matrix tablets containing 25 mg drug and a constant lubricant level of 0.75% magnesium stearate.

The influences on release rate of drug particle size, drug : HPMC ratio, HPMC viscosity grade, compaction pressure and absence or presence of lubricant have been examined.

Materials and Methods

Materials

Promethazine hydrochloride B.P. (May and Baker, Dagenham U.K.) was sieved to produce size fractions of 43–63, 63–90, 125–180, 180–250, 250–500 and 500–750 μm. Four viscosity grades of hydroxypropylmethylcellulose, (Dow Chemicals, U.S.A.) were used. They were Methocel K100, Methocel K4M, Methocel K15M and Methocel K100M and the viscosities of their 2% aqueous solutions were 106, 3850, 12,450 and 93,000 cps, respectively. Magnesium stearate (BDH, UK) was used as lubricant.

Tablet formulae

All tablets contained 25 mg promethazine hydrochloride and, except for those used to test release rate in the absence of lubricant, 0.75% magnesium stearate. Compression was accomplished with 0.25 inch flat-faced punches on a Manesty F3 single punch tableting machine. The compaction pressure, except for the studies on the effect of pressure on release rate, was 1395 MNm^{-2}. Compaction was accomplished using direct compression of promethazine hydrochloride—HPMC-magnesium stearate blends that had been thoroughly mixed for 15 min using a mixer. The following variations in tablet formulae were utilized.

(a) Effect of viscosity grade of HPMC and promethazine hydrochloride : HPMC ratio: using the four viscosity grades of HPMC, tablets were made containing 20, 25, 40, 50, 80, 120 or 160 mg HPMC. The 250–500 μm fraction of promethazine was used.

(b) Effect of particle size of promethazine: tablets were compressed using 80 mg HPMC.K15M using each of the promethazine particle size fractions.

(c) Effect of compaction pressure: tablets contained 25 mg promethazine hydrochloride (250–500 μm fraction) and 80 mg HPMC.K15M, and were compressed at 93, 403, 775 and 1395 MNm^{-2}.

(d) Effect of magnesium stearate: 80 mg of HPMC.K15M per tablet was used containing 63–90 or 250–500 μm promethazine. Tablets were compressed in the absence or presence of magnesium stearate (0.75%).

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 dissolution method was used at a rotation speed of 100 rpm. Dissolution was continuously recorded using a spectrophotometer (Kontron, model Uvikon 810) at 250 nm connected to a Commodore Model 8032 microprocessor. Dissolution studies were performed in triplicate for each batch of tablets. The dissolution data were plotted as the percent promethazine dissolved against the square-root of time to give typical straight-line Higuchi-type plots (Higuchi, 1962; Higuchi, 1963). The dissolution rates of these plots were usually determined by linear regression of the data from 5 to 70% promethazine released.

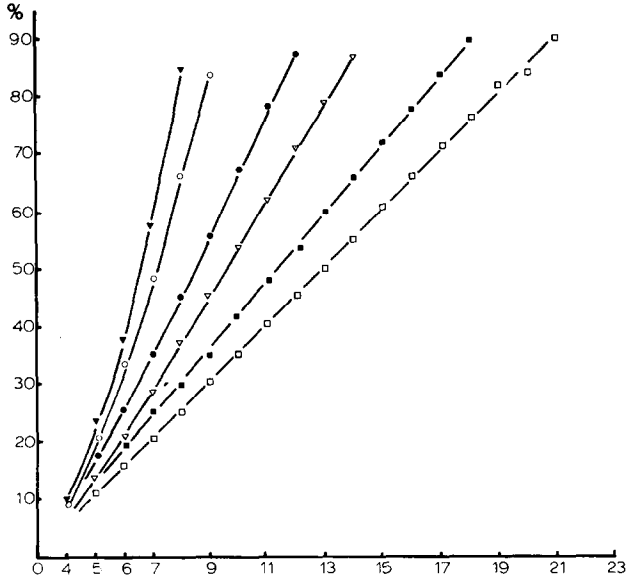

Fig. 1. The effect of promethazine hydrochloride: hydroxypropyl methylcellulose K100 variation on the release of 25 mg promethazine into 1000 ml water at 37°C from tablets containing (mg of HPMC.K100): ▼, 20; ○, 25; ●, 40; ▽, 50; ■, 120; □, 160. Ordinate: % promethazine hydrochloride dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).

Results and Discussion

Promethazine hydrochloride has a high aqueous solubility of 1 in 0.6 parts water. Consequently both diffusion and attrition should contribute to its release rate from HPMC matrix tablets. Similarly Eqn. 2 should describe its release from these formulations through the planar face of a tablet. There is, however, an obvious need to evaluate dissolution from the whole product. Lapidus and Lordi (1968) following chlorpheniramine maleate release from HPMC matrices found linearity of release when measuring dissolution from the plane surface of a tablet. This indicated that an intact hydrated layer was established over the period of study and therefore diffusion was the most important factor controlling the rate of drug release from the system. However, linearity was not maintained when dissolution was studied from the whole tablet and a positive deviation from linearity occurred within 100 min. Tablet attrition accounted for this positive deviation and although the contribution to release rate was difficult to determine (Lapidus and Lordi, 1968), HPMC 25 cps was twice as susceptible to attrition than HPMC 15,000 cps.

These findings can be extended to Figs. 1–4 which depict the influence of drug : HPMC ratio on the release rates of promethazine hydrochloride from matrices of the four HPMC grades. Only the curves obtained from matrices containing 20 or 25 mg HPMC K100 or 20 mg HPMC K4M displayed positive deviation from

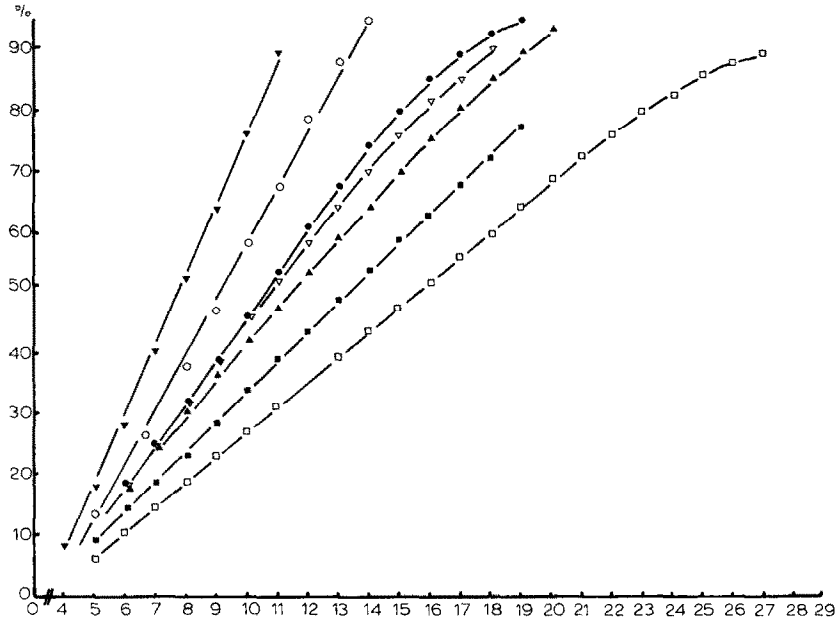

Fig. 2. The effect of promethazine hydrochloride: hydroxypropylmethylcellulose K4M variation on the release of 25 mg promethazine into 1000 ml water at 37°C from tablets containing (mg of HPMC.K4M): ▼, 20; ○, 25; ●, 40; ▽, 50; ▲, 80; ■, 120; □, 160. Ordinate: % promethazine hydrochloride dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).

linearity indicating a marked contribution to release rates by attrition and consequently dissolution rates were determined only from the linear portions of the profile. Coincidentally all the curves (Figs. 1–4) displayed negative deviations from linearity once approximately 70% of the drug had been dissolved and probably represents depletion of the drug in the matrix and hence deviation from the Higuchi ideal. Attrition therefore occurred predominantly in the tablets containing the low viscosity grades of HPMC only and at high drug content. Dissolution of the promethazine would leave a matrix of HPMC of high porosity and low tortuosity which would presumably possess a low gel strength and allow rapid diffusion of the drug and would be subject to rapid erosion. These findings concur with the results of Lapidus and Lordi (1968).

Simple examination of Figs. 1–4 indicates that as the polymer fraction increased, the dissolution of the drug decreased. However, a prospective formulator would require a more quantitative rationalization of these trends. The slopes (% $\text{min}^{-1/2}$) of the linear portions of the graphs (Figs. 1–4) are given in Table 1. When plotted as a function of the reciprocal of the HPMC concentration at which they were obtained, straight line plots were obtained (Fig. 5) for each of the HPMC fractions. The general relationship for each of these lines can be expressed by the equation:

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

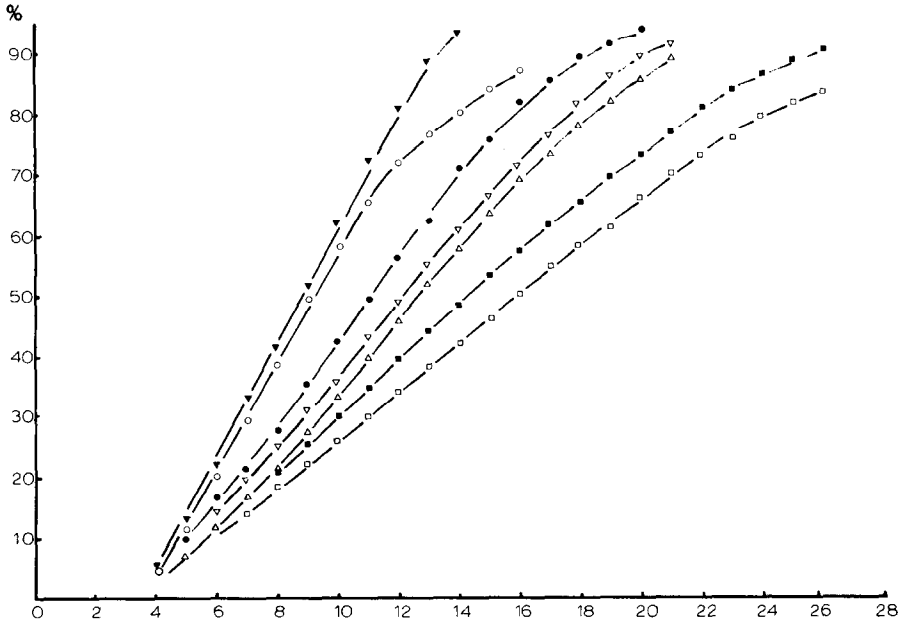

Fig. 3. The effect of promethazine hydrochloride: hydroxypropylmethylcellulose K15M variation on the release of 25 mg promethazine into 1000 ml water at 37°C from tablets containing (mg of HPMC.K15M): ▼, 20; ○, 25; ●, 40; ▽, 50; △, 80; ■, 120; □, 160. Ordinate: % promethazine hydrochloride dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).

where R = Higuchian release rate (% $\text{min}^{-1/2}$), M = slope of derived line, W = weight of HPMC (mg), C = constant.

The derived values of M and C are given in Table 2. The units of M are % $\text{min}^{-1/2}$ mg (% $\text{min}^{-1/2}$ being the release rate of promethazine hydrochloride and mg is the weight of HPMC in the tablet) and C is % $\text{min}^{-1/2}$ representing the promethazine release rate at a theoretical infinitely high HPMC level. The coefficients of linear regression of the lines and their level of significance are also given in Table 2.

The release rate $W_r/t^{1/2}$ derived from the Higuchi equations (Eqns. 1 and 2) predict a zero intercept. However, it is obvious that all the release rate curves of Figs. 1–4 possess negative intercepts. These obviously represent a failure of the systems to immediately attain the state of equilibrium diffusion described by Eqns. 1 and 2 and hence the use of R rather than $W_r/t^{1/2}$ in Eqn. 4. Interception on the $t^{1/2}$ axis gave values which ranged from 2.76 to 3.99 $\text{min}^{-1/2}$ (equivalent to 7.6 and 15.9 min) although no relationship was found between these values and either the HPMC level or HPMC viscosity type.

The data summarized in Table 2 permit calculated dissolution rates to be estimated from a limited number of data points. The results were surprisingly similar for the matrices containing the K4M, K15M and K100M grades of HPMC despite the difference in molecular sizes of the polymers (Tables 1, 2 and Fig. 5). Previous

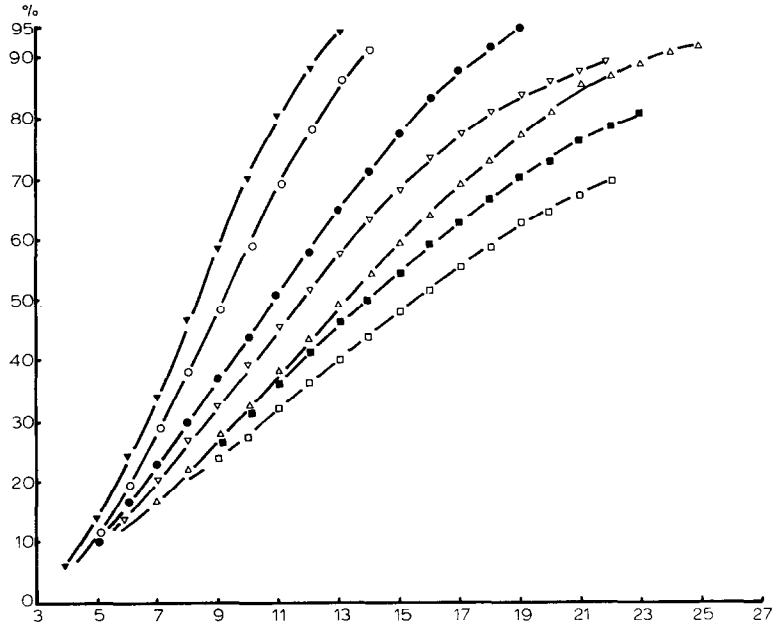

Fig. 4. The effect of promethazine hydrochloride: hydroxypropylmethylcellulose K100M variation on the release of 25 mg promethazine into 1000 ml water at 37°C from tablets containing (mg of HPMC.K100M): ▼, 20; ○, 25; ●, 40; ▽, 50; △, 80; ■, 120; □, 160. Ordinate: % promethazine hydrochloride dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).

workers, e.g. Lapidus and Lordi (1968) and Daly et al. (1984) have intimated that as the viscosity grade of HPMC increased the release rate of drugs formulated within them decreased. A limited comparison of the data obtained from HPMC.K100 data

TABLE 1

THE EFFECT OF HYDROXYPROPYLMETHYLCELLULOSE VISCOSITY GRADE AND PROMETHAZINE: HYDROXYPROPYLMETHYLCELLULOSE RATIO ON THE RELEASE RATE (% $\text{min}^{-1/2}$) OF PROMETHAZINE HYDROCHLORIDE FROM TABLETS CONTAINING 25 mg PROMETHAZINE AND 0.75% MAGNESIUM STEARATE (DERIVED FROM FIGS. 1–4)

Mg HPMC	Hydroxypropylmethylcellulose viscosity grade			
	K100	K4M	K15M	K100M
20	14.12	11.24	9.63	11.65
25	13.20	8.94	8.96	9.63
40	9.77	7.06	6.80	6.86
50	8.16	6.52	5.85	6.09
80	–	5.68	4.99	5.22
120	5.83	4.97	4.51	4.53
160	5.41	4.16	3.99	4.15

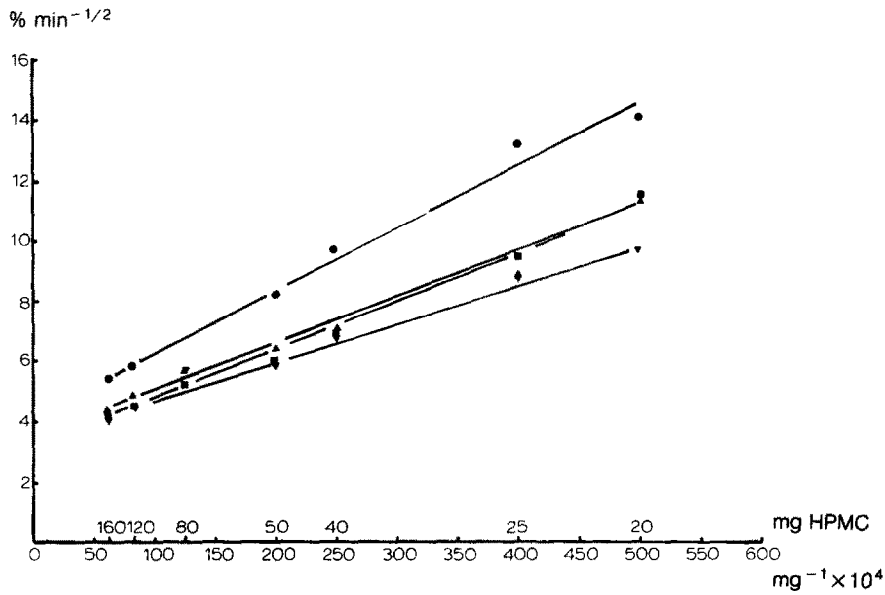

Fig. 5. Graphs showing the relationship between release rates (% $min^{-1/2}$) of promethazine hydrochloride and the reciprocal tablet content ($mg^{-1} \times 10^4$) of hydroxypropylmethylcellulose for tablets containing 25 mg promethazine hydrochloride and: ●, HPMC K100; ▲, HPMC K4M; ▼, HPMC K15M; ■, HPMC K100M. (Release rates determined from Figs. 1–4.)

with those obtained from the other matrices concur with their findings. However, the relative lack of difference in data from the other matrices supports the findings of Salomen et al. (1979) that the viscosity of HPMC only affects the lag time before quasi-stationary diffusion but not the rate of release. As previously mentioned,

TABLE 2

STATISTICAL DATA FROM FIG. 5 GIVING THE SLOPE M ([% PROMETHAZINE HCl][min]$^{-1/2}$ [mg HPMC]) AND INTERCEPT C ([% PROMETHAZINE HCl] [min]$^{-1/2}$) AND REGRESSION 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 at $P < 0.001$.

TABLE 3

THE INFLUENCE OF COMPACTION PRESSURE ON THE RELEASE RATES OF PROMETHAZINE HCl FROM TABLETS CONTAINING 25 mg PROMETHAZINE HYDROCHLORIDE, 80 mg HPMC.K15M AND 0.75% MAGNESIUM STEARATE

Compaction pressure (MNm^{-2})	Release rate ($\%\ min^{-1/2}$)
93	4.87
403	4.44
775	5.04
1395	4.99

however, no relationship was found between the lag times and the viscosity grades of the polymer used.

Several theories may account for these differences. The K100 matrices may, with reference to Eqn. 2 possess a higher apparent diffusion coefficient for promethazine hydrochloride or present a higher S/V ratio, or lower tortuosity (Eqn. 3). Conversely these must be equivalent for the matrices of the other grades of HPMC. This may also imply that the viscosities of the hydrated higher molecular weight matrices may be identical, despite the apparent differences in their viscosity grades.

The influence of compaction pressure on release rate is indicated in Table 3. All the values fall within $\pm 8.2\%$ of the mean release value of 4.84% $min^{-1/2}$. No trends for the effect of compaction pressure could be detected. Although increases in pressure may alter the tortuosity or porosity of the compact the Higuchi equations relate to the hydrated matrix only. Therefore provided compaction does not modify the properties of the hydrated matrix, dissolution rates would remain unaltered.

There remains the possibility that drug particle size may control the release rate of drug from HPMC matrices by altering the matrix tortuosity. Lack of effect by increased compaction pressure tentatively indicates that release rate should be independent of particle size since stress fracture of promethazine would probably occur at the higher compaction pressures. Table 4 indicates that particle size has

TABLE 4

THE INFLUENCE OF PROMETHAZINE HYDROCHLORIDE PARTICLE SIZE ON THE RELEASE RATES OF PROMETHAZINE FROM TABLETS CONTAINING 25 mg PROMETHAZINE HYDROCHLORIDE, 80 mg HPMC K15M AND 0.75% MAGNESIUM STEARATE

Promethazine hydrochloride particle size (μm)	Release rate ($\%\ min^{-1/2}$)
500–750	5.18
250–500	4.99
180–250	4.94
125–180	4.82
63–90	4.51
45–63	4.62

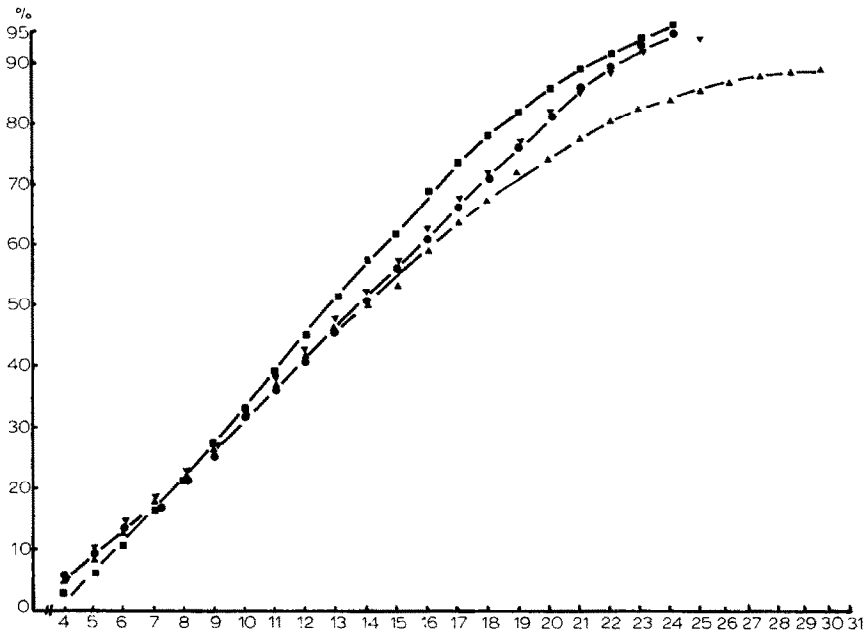

Fig. 6. The influence of magnesium stearate on the release rate of promethazine hydrochloride from tablets containing 25 mg promethazine hydrochloride and 80 mg HPMC K15M into 1000 ml water at 37°C. Ordinate: % promethazine hydrochloride dissolved. Abscissa: $\sqrt{\text{time}}$ ($\text{min}^{1/2}$).
■, promethazine hydrochloride (250–500 μm); 0.75% magnesium stearate;
●, promethazine hydrochloride (250–500 μm); 0% magnesium stearate;
▲, promethazine hydrochloride (63–90 μm); 0.75% magnesium stearate;
▼, promethazine hydrochloride (63–90 μm); 0% magnesium stearate.

little effect on release rate. All values fell within ±7.0% of a mean release value of 4.84% $\text{min}^{-1/2}$. It appeared that an increase in drug/particle size marginally increased the promethazine release rate from HPMC matrices.

Finally Fig. 6 briefly summarises the influence of lubricant on promethazine release rate. The presence or absence of magnesium stearate appeared not to affect release rate. Although Daly et al. (1984) and Lapidus and Lordi (1968) indicated that additives such as calcium phosphate, lactose or anionic surfactants may influence release rate it appears that the low level of lubricant included in this study did not significantly modify the release rate.

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