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Mathematical modelling of drug release from hydroxypropylmethylcellulose matrices: Effect of temperature

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Summary

A number of mathematical models have been used to describe the release of promethazine hydrochloride from matrices containing hydroxypropylmethylcellulose. Relationships, such as predicted by the Korsmeyer equation ($M_t/M_\infty = kt^n$), were considered inappropriate since the introduction of a lag period was essential to describe accurately the quantity of drug released. An equation ($M_t/M_\infty = k(t-l)^n + k'(t-l)^{2n}$) incorporating a lag period (l), kinetic constants (k and k') for diffusion and erosion controlled release and a diffusional component (n) produced the best fit of the data as evaluated by information criteria and unweighted sums of squares. The kinetic constants were not normally additive, k' becoming increasingly negative with increase in temperature. Values of n were in the range 0.563–0.764 indicating that release was controlled by both diffusion and erosion. Increasing the temperature increased the root time release rate constants from the matrices but its effect on the overall contribution to mechanisms controlling release was difficult to interpret.

Introduction

Hydroxypropylmethylcellulose (HPMC) is a polymer which is frequently used in sustained release matrices. The mechanisms by which it retards drug release centre on its abiltiy to form rapidly a gel layer around the surface of a matrix exposed to aqueous fluids (Alderman, 1984). The passage of drugs, via diffusion, through this gel layer controls the dissolution of water-soluble drugs giving release rates which are approximately dependent on the square root of time (Ford et al., 1985a,b, 1987) and follow Eqn 1 (Higuchi, 1962).

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

where W_r = amount of drug dissolved in time t, W_0 = dose of drug, S = the effective diffusional

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area, V = effective volume of the hydrated matrix and D' = apparent diffusion coefficient of the drug in the hydrated matrix. Diffusion is not, however, the only mechanism by which solutes are released from HPMC matrices and erosion, the dissolution of the matrix itself following hydration of the HPMC, will contribute to the overall release. To account for these dual release mechanisms, Korsmeyer et al. (1983) used a simple empirical equation, Eqn 2, to describe general solute release behaviour from controlled release polymeric matrices.

$$M_t/M_\infty = kt^n \quad (2)$$

where M_t/M_∞ = fraction of drug released, k = a kinetic constant, t = release time and n = the diffusional exponent for drug release. Peppas (1985) claimed that Eqn 2 could adequately describe the release of solutes from slabs, spheres, cylinders and discs (tablets), regardless of the release mechanism. The value of n gives an indication of the release mechanism. Peppas (1985) stated that n is 0.5 for Fickian diffusion, $0.5 < n > 1.0$ for non-Fickian transport and 1.0 for case II transport. When $n > 1.0$ super case II transport is apparent (Peppas, 1985). Case II transport involves polymer dissolution and chain disentanglement (Harland et al, 1988).

Ritger and Peppas (1987) applied Eqn 2 to swellable matrices and considered that the equation is only suitable for matrices which swell moderately, i.e. an equilibrium swelling ratio of not greater than 1.33 equivalent to 25% of the original value. Values of $n = 0.432 \pm 0.007$ and 0.85 ± 0.02 for swellable spheres were reported for case I and case II mechanisms, respectively, although n is dependent on the shape of the matrix (Ritger and Peppas, 1987).

Eqn 2 is based on the assumption that release occurs as soon as the matrix is placed in contact with fluid and thus predicts an intercept at the origin. Indeed, several studies (e.g., Baveja and Ranga Rao, 1986) have ignored the presence of a lag period in calculating values of n in Eqn 2 despite acknowledging that lag periods of the order of 5 min were apparent. The lag periods are thought to be equivalent to the time required for the matrix edges to hydrate and reach equilibrium before erosion and the advance of solvent front through the matrix occur. Ford et al. (1987) corrected for lag times by estimating their values by linear regression of the square root time data. The values were subtracted from the actual sampling times to produce corrected sampling times. Using this adjustment, Ford et al. (1987) determined the release exponent n for various soluble and poorly soluble drugs and found that for water-soluble drugs $n \simeq 0.7$. For insoluble drugs (indomethacin and diazepam) n was ~ 0.85 and was indicative of near zero-order release where erosion of the gel controls release rather than diffusion (Peppas and Sahlin, 1989). Other values of n include 0.713 for centperazine from matrices containing sodium carboxymethylcellulose and HPMC (Baveja and Ranga Rao, 1986) and 0.58 for alprenolol release from HPMC K4M matrices. Values of n of 0.6314 (Ranga Rao et al., 1990) and 0.64 (Ford et al., 1987) were found for propranolol hydrochloride release from HPMC K4M and HPMC K15M matrices, respectively, and of 0.71 for promethazine hydrochloride from HPMC K15M matrices (Ford et al., 1987).

The purposes of this paper are to examine the relevance and accuracy of a number of equations that have been used to describe drug release from matrices to HPMC matrix tablets containing promethazine hydrochloride as a model drug. Additionally, the influence of temperature on release rates was examined using these models in an attempt to interpret the mechanisms of drug release and specifically the role of erosion in controlling the release of a water-soluble drug.

Other models

Although models relating matrix swelling and dissolution are often complex and involve estimates of the gel layer thickness (Harland et al., 1988), Eqn 2 provides a simple approach for determining the mechanisms of release from matrices. For the purposes of this study it has been simplified and rewritten as Eqn 3,

$$Q = kt^n \quad (3)$$

where Q is the percentage of promethazine released at time t. Eqn 3 may be modified to account for a lag period (l) prior to release giving Eqn 4.

$$Q = k(t-1)^n \quad (4)$$

where l is the lag time.

Cattelani et al. (1988) and Harland et al. (1988) additionally used Eqn 5 to describe release from matrices when both diffusion and polymer relaxation contribute to the mechanisms of transport.

$$M_t/M_\infty = k_1 t^{0.5} + k_2 t \quad (5)$$

Catellani et al. (1988) considered that the right side of the equation contained the two limiting cases involved in release from matrices, i.e., Fickian diffusion by which the first 60% is linearly related to the square root of time and the polymer relaxation transport which, if solvent uptake is linearly related to time and is slower than drug diffusion, will lead to zero-order drug release. Thus, k_1 and k_2 in Eqn 5 express the relative contributions of Fickian and relaxation mechanisms. Eqn 5 was modified to Eqn 6.

$$Q = k_1 t^{0.5} + k_2 t \quad (6)$$

Peppas and Sahlin (1989) derived Eqn 7 by introducing a second term to represent case II transport into Eqn 2.

$$M_t/M_\infty = kt^n + k't^{2n} \quad (7)$$

The constants k and k' represent, in a manner analogous to Eqn 5, the relative contributions of Fickian and relaxation mechanisms, respectively. Peppas and Sahlin (1989) considered that the two phenomena controlling release were additive. Regardless of the geometric device used the value of the exponent for case II transport mechanism is twice that of the pure Fickian diffusional mechanism (Peppas and Sahlin, 1989). Taking into account the lag times introduced in Eqn 4, Eqn 7 can similarly be rewritten as Eqn 8.

$$Q = k(t-1)^n + k'(t-1)^{2n} \quad (8)$$

For comparison purposes, the data in this study was subjected to Eqn 9, which may be considered a simple, Higuchi-type equation.

$$Q = At^{0.5} + c \quad (9)$$

Eqn 9, for release data dependent on the square root of time, would give a straight line release profile, with A presented as a root time dissolution rate constant and c as a constant. The lag period, prior to the commencement of release, is defined as $-c/A$.

Materials and Methods

Materials

Promethazine hydrochloride B.P., hydroxypropylmethylcellulose (HPMC K15M: Methocel®, Dow Chemicals, U.S.A.) and magnesium stearate (British Drug Houses, U.K.) were used as supplied.

Tabletting

Tablets (6.35 mm flat face or 7.93 mm shallow concave) containing 25 mg promethazine hydrochloride, 50, 75, 100 or 150 mg HPMC K15M and 0.75% w/w magnesium stearate were prepared by direct compression on a Manesty F3 single-punch tableting machine.

Dissolution studies

Dissolution was studied using a Series 8000 automatic dissolution tester (Copley Instruments, Nottingham, U.K.) into 1 l of distilled water, rotating at 100 rpm, using the B.P. 1988 method 1 and monitoring promethazine hydrochloride at 250 nm. Temperatures were maintained at 25, 30, 37, 45 or 50 °C. Studies were performed in triplicate.

Curve fitting

Fitting of curves to the data points, using Eqns 3, 4, 6, 8 and 9, was carried out using a privately produced 'Curfit' program. The program uses a non-linear least-squares fitting method to determine the optimum values for the parameters present in each equation. The curve-fitting algorithm is essentially the same as the Damped

Gauss-Newton method of Yamaoka et al. (1981). No weighting factor was applied. Information criteria were calculated based on the methods of Akaike (1974) and of Schwartz (1978). Data in the range 5–60% released were used. These correspond to the limits of applicability of applicability of Eqn 2 (Korsmeyer et al., 1983; Peppas, 1985; Peppas and Sahlin, 1989).

Results and Discussion

Many curve-fitting algorithms use a weighted least-squares method, because the data shows a tendency for the largest observed values to be associated with the greatest degree of imprecision. In such cases, it is desirable to place extra weight upon the most reliable data points. With the data presented in this paper, no correlation was detected between the magnitude of the observations and the associated error. Consequently, a simple unweighted least squares analysis was used.

Information criteria are values which can be used to determine the most appropriate model for a data set. Such criteria are calculated from two factors: (1) the sum of squares of errors, which is a measure of the discrepancies between the observed data and the values that would have been predicted by a particular model and (2) the number of parameters used by the model. The sum of squares gives an initial guide to the quality of a model; the greater the sum of the squares, the poorer the model. However, the introduction of additional parameters, even if devoid of significance, will almost always allow a better fit. It is therefore necessary to add a 'penalty factor' that reflects the number of parameters. The more the parameters there are, the greater the penalty. An information criterion is therefore based upon the sum of squares plus a suitable penalty factor. In this way, additional parameters will only reduce the overall values of the information criterion if they improve the fit to an extent great enough to counter the extra penalty incurred. The model producing the lowest value for the information criterion is considered to be the most appropriate.

Several authors have published methods for calculating information critera and use different methods to calculate the penalty factor. No one of these methods has been clearly established to be superior to all the others and therefore two different criteria are used in this paper. Both criteria differentiate clearly between the various models and in all cases the two criteria indicate the same model to be optimal. The precise choice of criterion does not appear to be crucial.

As an example of the data obtained, Fig. 1, plotting release as a function of the square root of time, shows the effect of temperature on the release from matrices containing 75 mg HPMC. Typically, the data at 45 and 50 °C showed a negative deviation from linearity whilst the remainder were acceptable straight lines. The root time dissolution rate constants, calculated according to Eqn 9, are given in Table 1 and confirm earlier findings (Ford et al., 1985a) that the dissolution rates of water-soluble drugs from HPMC matrices decreases with an increase in HPMC content and that dissolution rates increase with an increase in temperature. Interestingly, the sum of squares and each information criterion showed their lowest values consistantly at 37 °C increasing with both an increase and decrease in temperature. Whilst the deviations in linearity are apparent in Fig. 1 at 45 and 50 °C and indicate that root time is not the most suitable time basis for this data, no apparent explanation for the increase in the sums of squares and information criteria at 25 and 30 °C can be forwarded.

Table 2 gives an estimate of n based on Eqn 3 without lag time correction. The high values of the sum of squares and information criteria suggest that this empirical equation does not provide a good fit for the results. Although it appeared that the kinetic constant k increased with temperature it was not possible to identify trends in the temperature-induced changes of the n values. Values of n at any particular temperature tended to decrease with an increase in HPMC content but no definite relationship could be elucidated between either k or HPMC content with temperature.

The addition of a lag period, l, to Eqn 3 to produce Eqn 4 resulted in very good fits for the data (Table 3). Such estimates of the lag periods are considerably more accurate than those used by Ford et al. (1987) and Mitchell et al. (1990a) on

TABLE 1

Best fit parameters, sums of squares (ss) and information criteria (Akaike (1974) and Schwartz (1978)) based on Eqn 9 ($Q = Kt^{0.5} + c$)

HPMC (mg)	Temp. (°C)	k	c	ss	Akaike	Schwartz	Number of data points [a]
50	25	5.03	−19.2	2.90	16.760	17.729	12
50	30	5.69	−21.4	1.13	5.372	6.168	11
50	37	6.64	−24.4	0.367	−3.021	−3.129	8
50	45	7.41	−27.0	1.51	7.305	7.464	8
50	50	7.41	−24.8	6.23	18.629	18.788	8
75	25	4.61	−17.4	6.76	26.936	27.906	12
75	30	4.90	−17.1	0.902	2.761	3.731	12
75	37	5.66	−23.0	0.302	−9.173	−8.377	11
75	45	5.75	−18.3	3.20	15.626	16.231	10
75	50	5.77	−17.7	14.8	30.937	31.542	10
100	25	3.59	−14.2	8.16	39.678	41.344	17
100	30	3.94	−15.0	3.72	23.719	25.136	15
100	37	4.23	−14.6	1.20	6.537	7.815	14
100	45	4.91	−17.3	1.77	10.850	11.819	12
100	50	5.07	−16.6	4.60	22.322	23.292	12
150	25	3.32	−13.8	5.79	35.608	37.389	18
150	30	3.40	−13.2	4.44	30.850	32.630	18
150	37	4.03	−15.5	2.19	14.200	15.330	13
150	45	3.92	−13.7	9.75	35.886	37.165	14
150	50	4.15	−11.4	11.4	35.665	36.795	13

[a] Used for Tables 2–6.

TABLE 2

Best fit parameters, sums of squares (ss) and information criteria (Akaike (1974)) and Schwartz (1978)) based on Eqn 3 ($Q = kt^n$)

HPMC (mg)	Temp. (°C)	k	n	ss	Akaike	Schwartz
50	25	0.703	0.812	18.6	39.084	40.054
50	30	0.765	0.823	22.9	38.466	39.262
50	37	0.794	0.851	26.1	30.105	30.264
50	45	0.789	0.883	32.2	31.773	31.932
50	50	1.080	0.825	39.7	33.447	33.606
75	25	0.653	0.810	15.3	36.770	37.740
75	30	0.898	0.766	18.5	38.985	39.995
75	37	0.619	0.857	43.0	45.362	46.158
75	45	1.150	0.759	29.0	37.675	38.280
75	50	1.330	0.733	53.6	43.808	44.413
100	25	0.663	0.749	15.1	50.148	51.814
100	30	0.712	0.758	17.0	46.466	47.882
100	37	0.952	0.725	30.1	51.679	52.957
100	45	0.903	0.765	29.6	44.647	45.617
100	50	1.050	0.749	35.5	46.847	47.817
150	25	0.599	0.749	21.9	59.573	61.354
150	30	0.714	0.727	19.8	57.717	59.498
150	37	0.709	0.762	20.1	42.978	44.108
150	45	1.030	0.696	40.7	55.901	57.179
150	50	1.520	0.647	33.0	49.463	50.593

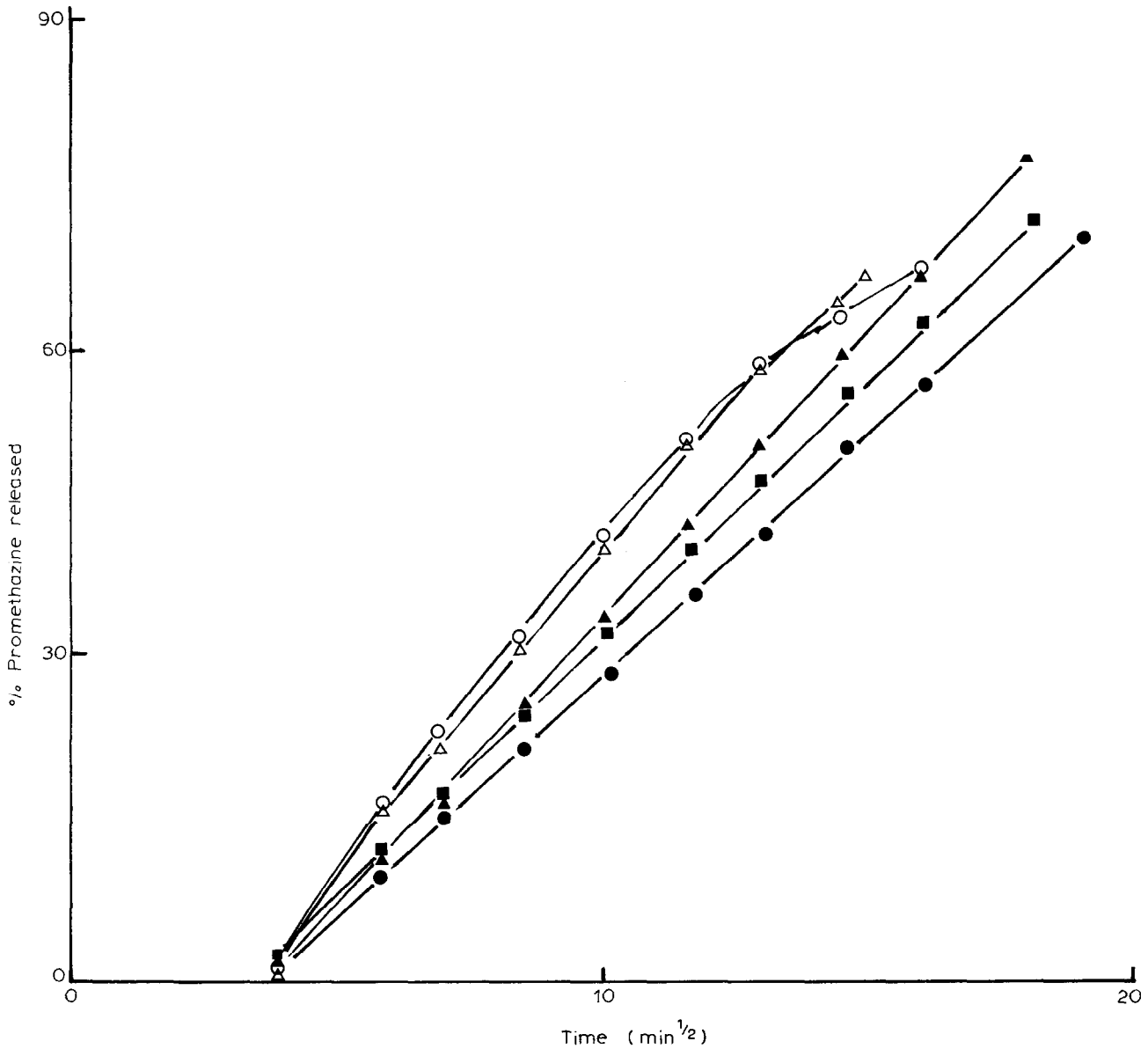

Fig. 1. The effect of temperature on the release of 25 mg promethazine hydrochloride from matrices containing 75 mg HPMC K15M. (●) 25 °C, (■) 30 °C, (▲) 37 °C, (△) 45 °C and (○) 50 °C.

the basis of root time plots. Other authors have ignored the problems caused by lag periods in determining n and k (Ranga Rao et al., 1987; Baveja et al., 1987) and, in view of the improvement in data fitting shown in Table 3 compared to Table 2, doubts must be cast on the accuracy of their data treatment. The reductions in the values of the sum of squares and the information criteria justify the inclusion of lag periods, despite their being relatively constant, into the calculations. The values of n were lower than those in Table 2. By including the lag period definite trends could

TABLE 4

Effect of temperature on first order dissolution rate constants ($min^{-1} \times 10^4$) for promethazine hydrochloride release from HPMC K15M matrices (from Mitchell et al, 1990a)

HPMC (mg)	25 °C	30 °C	37 °C	45 °C	50 °C
50	37.4	45.9	62.2	75.8	89.1
75	31.3	37.0	44.6	59.3	64.7
100	21.3	25.1	28.5	38.1	40.9
150	18.8	21.6	24.9	28.0	34.8

be identified for both k and n. Values of k increased with increase in temperature and values of n simultaneously decreased indicating an increased role for diffusion as the temperature increased and n approached 0.5.

The data described in this paper have previously been briefly described (Mitchell et al., 1990a) using first-order release rate constants (from plots of log remaining to be dissolved vs time) to derive activation energies and are reproduced in Table 4. The energies decreased with an increase in HPMC being 27.5, 23.8, 21.3 and 18.2 kJ mol^{-1} for the matrices containing 50, 75, 100 and 150 mg HPMC, respectively. This decrease confirms that diffusion was not the sole controller of release rates from the matrices otherwise the obtained energies would be independent of drug : HPMC ratio used in the matrices.

Tables 5 and 6 give the curve-fitting data, respectively, for Eqns 6 and 8 which were used in an attempt to differentiate the roles of erosion and diffusion in drug release from HPMC matrices. Eqn 6, which allows no lag correction and no variation in the release exponent n, resulted in the worse fit for any of the equations examined. Although values of k_1 exceeded those of k_2 no trends could be identified for the effects of HPMC content or temperature on their values. However, by allowing the curve-fitting program to calculate values of both n and a lag period as well as values for the contributions for both Fickian (k) and relaxational (k') in Eqn 8 the best fits were obtained. Table 6 shows that the second parts of Eqns 7 and 8, generally considered to be representative of case II release were frequently negative. This indicates that instead of case II release

TABLE 3

Best fit parameters, sums of squares (ss) and information criteria (Akaike (1974) and Schwartz (1978)) based on Eqn 4 ($Q = k(t - l)^n$)

HPMC (mg)	Temp. (°C)	k	l	n	ss	Akaike	Schwartz
50	25	1.59	17.1	0.669	0.213	−12.544	−11.090
50	30	1.92	17.6	0.659	0.083	−21.417	−20.223
50	37	2.58	18.5	0.632	1.58	9.679	9.917
50	45	3.14	19.4	0.617	0.432	−0.718	−0.480
50	50	4.25	20.0	0.560	0.284	−4.068	−3.830
75	25	1.43	16.4	0.673	2.60	17.446	18.900
75	30	1.94	16.7	0.632	0.310	−8.046	−6.592
75	37	1.93	20.9	0.653	1.70	11.825	13.019
75	45	3.10	18.4	0.577	1.53	10.246	11.154
75	50	4.12	21.0	0.525	2.59	15.502	16.409
100	25	1.13	16.5	0.663	0.453	−7.479	−4.979
100	30	1.34	17.0	0.653	0.304	−11.870	−9.746
100	37	2.02	19.2	0.597	1.08	7.054	8.971
100	45	2.14	18.6	0.613	2.46	16.792	18.247
100	50	2.84	19.9	0.569	1.34	9.537	10.992
150	25	1.07	18.9	0.656	1.44	12.602	15.273
150	30	1.22	17.8	0.641	0.829	2.614	5.285
150	37	1.39	17.8	0.650	0.705	1.449	3.144
150	45	2.53	27.6	0.545	4.890	28.230	30.147
150	50	3.47	25.2	0.507	3.93	23.795	25.490

TABLE 5

Best fit parameters, sums of squares (ss) and information criteria (Akaike (1974) and Schwartz (1978)) based on Eqn 6 ($Q = k_1 t^{0.5} + k_2 t$)

HPMC (mg)	Temp. (°C)	k_1	k_2	ss	Akaike	Schwartz
50	25	1.13	0.179	28.8	44.320	45.290
50	30	1.17	0.217	33.4	42.584	43.380
50	37	0.996	0.301	30.9	28.007	27.898
50	45	0.873	0.370	38.1	33.112	33.271
50	50	1.47	0.334	48.8	35.095	35.254
75	25	1.05	0.164	22.5	41.361	42.330
75	30	1.46	0.157	30.0	44.816	45.786
75	37	0.86	0.230	54.7	48.021	48.186
75	45	1.77	0.199	40.9	41.107	41.712
75	50	2.03	0.183	69.9	46.469	47.075
100	25	1.20	0.0882	30.5	62.074	63.740
100	30	1.24	0.107	30.8	55.394	56.810
100	37	1.58	0.109	47.9	58.164	59.442
100	45	1.47	0.156	44.1	49.448	50.418
100	50	1.65	0.162	49.5	50.831	51.801
150	25	1.11	0.078	40.9	70.782	72.563
150	30	1.28	0.0748	39.1	70.005	71.786
150	37	1.23	0.111	34.6	50.070	51.200
150	45	1.69	0.0833	58.1	60.873	62.151
150	50	2.26	0.0729	46.9	54.022	55.152

TABLE 6

Best fit parameters, sums of squares (ss) and information criteria (Akaike (1974) and Schwartz (1978)) based on Eqn 9 ($Q = k(t - l)^n + k'(t - l)^{2n}$)

HPMC (mg)	Temp. (°C)	k	l	n	k'	ss	Akaike	Schwartz
50	25	1.93	18.4	0.613	0.0086	0.117	−17.738	−15.798
50	30	1.89	17.5	0.663	−0.0004	0.082	−19.485	−17.894
50	37	3.13	19.6	0.563	0.0319	1.49	11.177	11.495
50	45	2.17	17.4	0.729	−0.0108	0.068	−13.518	−13.200
50	50	3.21	18.5	0.651	−0.0214	0.003	−37.644	−37.329
75	25	2.10	19.1	0.551	0.0344	2.10	16.880	18.820
75	30	1.87	16.4	0.642	−0.0012	0.306	−6.208	−4.269
75	37	1.14	17.9	0.793	−0.0035	0.036	−28.583	−26.992
75	45	1.87	14.8	0.717	−0.0095	0.759	5.245	6.455
75	50	2.44	17.9	0.678	−0.0185	0.587	2.672	3.883
100	25	1.24	17.3	0.640	0.0013	0.415	−6.935	−3.602
100	30	1.40	17.4	0.642	0.0007	0.298	−10.181	−7.349
100	37	1.56	17.2	0.666	−0.0045	0.649	1.946	4.502
100	45	1.18	14.1	0.764	−0.0040	1.04	8.457	10.397
100	50	2.02	17.7	0.666	−0.0100	0.714	3.953	5.892
150	25	0.812	16.4	0.720	−0.0011	0.948	7.046	10.607
150	30	0.972	15.5	0.694	−0.0014	0.515	−3.933	−0.371
150	37	0.998	15.0	0.731	−0.0020	0.243	−10.406	−8.147
150	45	1.41	21.7	0.689	−0.0060	3.16	24.112	26.668
150	50	1.56	16.2	0.700	−0.0081	1.24	10.827	13.087

being an alternative additive means of release (as proposed by Ritger and Peppas (1987) and Peppas and Sahlin (1989)) the second function in Eqns 7 and 8 in fact inhibited release. The retardation probably reflects interactions of a variety of phenomena. Promethazine salts in HPMC into solution (Mitchell et al., 1990b) and probaly contributes to an increase in erosion which will be magnified by the attrition provided by the basket in the dissolution apparatus. This in turn would lead to a collapse of structure with concomitant reduction not only in diffusional path length (which should lead to an approximation of zero-order kinetics) but also to decrease in surface pore structure which would effectively retard diffusion and the overall release rate.

Values of k' (Table 6) were numerically very small in comparison to values of k. Nonetheless, they have a marked effect on their contributions to release. Using Eqns 10 and 11 (Peppas and Sahlin, 1989) it is possible to estimate the contributions of the diffusional and relaxational mechanisms at any given temperature from the parameters given in Table 6.

$$F = 1/(1 + k't^n/k) \quad (10)$$

$$R/F = k't^n/k \quad (11)$$

In Eqns 10 and 11, F is the fraction of drug release due to the Fickian mechanism and R/F is the ratio of relaxational over Fickian contributions. Considering the data for matrices containing 50 and 75 mg HPMC at 37 °C the data shows that for time periods into dissolution of 60, 120 and 180 min, 90.7, 86.9 and 84.1% of the drug would have been released by Fickian processes whereas 9.3, 13.1 and 15.9% would have been released by erosion for tablets containing 50 mg HPMC. At 75 mg HPMC the corresponding values are 108.8, 116.4 and 124.1% for release by Fickian processes and −8.8, −16.4 and −14.1 for erosion, confirming the inhibitory aspects of this second term. It must be assumed that diffusion through the gels is a rapid process for a water-soluble drug such as promethazine and that the matrix will collapse around itself.

Conclusions

Kinetic equations can be used to describe release from HPMC matrices. Although equations such as those derived by Higuchi adequately describe release better fits can be made on the assumption that release rates are not dependent on the square root of time. Therefore, when the dependence of time is allowed to be derived from the data and not given a preconceived value of root time ($n = 0.5$) better fits of data can be obtained. The treatment described in this paper suggests that lag periods in dissolution cannot be ignored when describing release using exponential functions of time and considerably alter the values of both derived kinetic constants and diffusional exponents. It is recommended therefore that all equations must include a value of l. Despite the mathematical modifications described the release patterns were a mixture of both erosion and diffusion control.

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