Pharmaceutical Research, Vol. 12, No. 7, 1995

Research Article

Diffusion in HPMC Gels. II. Prediction of Drug Release Rates from Hydrophilic Matrix Extended-Release Dosage Forms

Ping Gao,[1] Phillip R. Nixon,[2] and John W. Skoug[1,3]

Received October 6, 1994; accepted February 21, 1995

Purpose. A mathematical model is described for the prediction of the relative change in drug release rate as a function of formulation composition for HPMC-based extended-release (ER) tablets of adinazolam mesylate and alprazolam. ***Methods.*** The model is based on the equation derived by Higuchi for the diffusional release of soluble drugs from polymeric matrices and on our recent measurements of the concentration dependency of adinazolam diffusivity in dilute HPMC gels and solutions. The assumptions made in applying the model include (i) that diffusion is the sole mechanism of drug release (i.e. swelling kinetics are ignored), and (ii) that the surface area-to-volume ratio and concentrations of adinazolam, lactose and HPMC in the gel layer are proportional to that of the dry tablet. ***Results.*** Reasonable correlations were obtained between the experimental drug release rate ratios and the predicted drug release rate ratios for ER adinazolam mesylate (R^2 = 0.82) and low-dose (0.5 mg) ER alprazolam tablets (R^2 = 0.87). The predictive power for a 6-fold higher dose of ER alprazolam tablets was not as good (R^2 = 0.52). ***Conclusions.*** These results are consistent with previous knowledge of the release mechanisms of these formulations. ER adinazolam mesylate and ER alprazolam 0.5 mg exhibit primarily a diffusion controlled release mechanism, while ER alprazolam 3 mg deviates from pure diffusional release. The limitations of the model are discussed and point to the need for continued study of the swelling kinetics of matrix ER systems.

KEY WORDS: dissolution; diffusion coefficient; HPMC; extended-release formulation; mathematical model; prediction.

INTRODUCTION

Our previous studies of HPMC-based extended-release (ER) tablets of adinazolam mesylate and alprazolam qualitatively indicate that diffusion is a predominant release mechanism (1,2). Our long-term interest lies in a more fundamental understanding of these dosage forms so that ultimately predictions of the drug release rate can be made from first principles, thus speeding up formulation development. Empirical relationships between drug release rate and HPMC concentration have been commonly used for predicting drug release, but these must be established for each drug and formulation (3,4). More recently, Shah et al. (5) reported a method for the prediction of drug release rate as a function of HPMC concentration utilizing the Higuchi theory for soluble drugs. In that work, the authors hypothesized that HPMC concentration modulates the effective diffusion coefficient of the drug, thus providing a basis in theory for the observed effect of this important formulation variable and the empirical relationships mentioned above. It was demonstrated that predictions of drug release rate as a function of HPMC concentration could be made on the basis of only a few experiments, although the approach is somewhat convoluted by the fitting of regression parameters to develop a working equation.

In a companion paper (6), we described the use of pulsed field gradient spin-echo (PFGSE) NMR to measure drug/water self-diffusion coefficients in HPMC gels and related solutions. We demonstrated that the diffusion coefficient of adinazolam (D_A) depends exponentially on HPMC concentration and is independent of HPMC 2208 USP viscosity grade for materials with a 2% solution viscosity of 100 cps (HPMC K100LV) to 15000 cps (HPMC K15M). Measurements of D_A in mixtures containing HPMC, lactose and adinazolam itself indicate that the retardation effects from all three components are independent and quantitatively additive. We developed an empirical equation to describe the adinazolam diffusivity in dilute and moderately concentrated multicomponent HPMC gels (6).

Here we investigate whether the concentration dependency of drug diffusion coefficients can be used to predict the relative drug release rate in extended release tablets which vary in formation composition. Although our approach is similar to that of Shah et. al., that is the Higuchi equation is used as the basis for the predictive method, our method relies on fundamental measurements of drug diffusion coefficients as a function of gel composition. We show that the relationship between the drug diffusivity and solu-

[1] Analytical Research and Specifications Development, The Upjohn Company, 7000 Portage Road, Kalamazoo, Michigan 49001.

[2] Drug Delivery Research and Development, The Upjohn Company, Kalamazoo, Michigan.

[3] To whom correspondence should be addressed.

0724-8741/95/0700-0965$07.50/0

tion concentrations of key formulation components (HPMC, lactose and adinazolam) can be related using Higuchi's equation to the change in drug release rate caused by the variation of the initial formulation composition. The mathematical relationships and the correlation between predicted drug release rates based on solution diffusion data and experimentally measured drug release rates from ER tablets of adinazolam mesylate and alprazolam are the subjects of this report.

MATHEMATICAL FRAMEWORK

Using a steady-state approximation to Fick's Laws, Higuchi derived an equation for the release of drugs from solid matrices (7). Equation 1 lists the so-called Higuchi equation, as adapted by Lapidus and Lordi (8), describing the release of soluble drugs from matrix sustained release tablets,

$$M_t = M_o \cdot S/V \cdot \left(\frac{D't}{\pi}\right)^{1/2} \quad (1)$$

where M_t is the amount of drug released at time t, M_o is the initial amount of drug in the tablet, S is the surface area and V is the volume available for release, and D' is the effective diffusion coefficient. The effective diffusion coefficient is defined by Equation 2,

$$D' = D/\tau \quad (2)$$

in which D is the true self-diffusion coefficient of the drug in the release medium alone and τ is the tortuosity of the diffusing matrix. Equation 1 shows that drug release is proportional to the initial amount of drug in the tablet, the surface area-to-volume ratio (S/V) available for release, and the square-roots of both the effective diffusion coefficient and time. In applying Equation 1, drug release data (mass or percent of label dissolved) are plotted as a function of the square-root-of-time; if a straight line relationship over a given time interval is obtained then it is inferred that diffusion is the mechanism of drug release.[4] The slope of a plot of percent dissolved vs. the square-root of time (Equation 3) has units of $t^{-1/2}$; this quantity is hereafter referred to as the drug release rate (DRR),

$$DRR = M_t/M_o/t^{1/2} = S/V\, D'^{1/2}/\pi \quad (3)$$

Thus, for a purely diffusional release mechanism and for a formulation in which the drug solubility exceeds that of the initial tablet dose, Equation 3 predicts that drug release rate can be computed by knowing the surface area-to-volume ratio of the dry tablet, and the effective drug diffusion coefficient in the hydrated tablet matrix.

Direct measurement of drug diffusion in hydrating HPMC tablets is of interest. In principle, it can be done by using NMR imaging methods, however, we propose that the measurement of diffusion coefficients of drug in equilibrium swollen gels can be used to approximate the composition of the tablet gel layer. Thus, the diffusivity data obtained in equilibrium swollen gels can be used to predict drug release rates according to Equation 3. We have shown (6) that the dependence of the drug diffusivity of adinazolam on the concentration of viscosity increasing agents (VIA) is fit well by a simple exponential function as shown in Equation 4:

$$D_A = D_A^o \exp(-K_i C_i) \quad (4)$$

where the subscript i denotes the VIA in which drug diffusivity measurements were made, K is a constant indicative of the retarding effect of each VIA, and C is the weight concentration in solution; D_A^o is the diffusion coefficient of adinazolam extrapolated to infinite dilution. We also showed (6) that the retarding effects of adinazolam, lactose and HPMC concentration on adinazolam diffusivity are independent of each other. Thus, the relationships between drug diffusion coefficient and concentration developed for each VIA can be applied to quaternary mixtures of drug, lactose, HPMC and water. Equation 5 expresses this statement mathematically,

$$D_A = D_A^o \exp-(K_A C_A + K_L C_L + K_H C_H)$$
$$= D_A^o \exp-\left(\sum_i K_i C_i\right) \quad (5)$$

where the subscripts A, L and H refer to adinazolam, lactose and HPMC, respectively. Equations 3 and 5 provide the framework for relating drug diffusion coefficients measured in equilibrium swollen gels to drug release rate in tablets. We assume that the formulations exhibit identical swelling kinetics (medium penetration rate, matrix swelling and erosion) and that the concentrations of adinazolam, lactose and HPMC in the gel layer are proportional to their respective weight concentration in the dry tablet. Substitution of Eqn. 5 for D' in Eqn. 3 and expressing the result relative to an arbitrarily chosen reference formulation yields Equation 6,

$$\frac{DRR_1}{DRR_2} = \frac{\left(\frac{M_t/M_o}{t^{1/2}}\right)_1}{\left(\frac{M_t/M_o}{t^{1/2}}\right)_2} = \frac{\left(\sqrt{\exp\left(\sum_i - K_i C_i\right)}\right)_1}{\left(\sqrt{\exp\left(\sum_i - K_i C_i\right)}\right)_2} \frac{\left(\frac{S}{V}\right)_1}{\left(\frac{S}{V}\right)_2} \quad (6)$$

where the subscripts 1 and 2 denote the two formulations being compared. Equation 6 represents a semiquantitative relationship for predicting the *relative* change in drug release rate caused by a change in formulation composition. Thus, the change in drug release rate of formulation 1 relative to that of formulation 2 can be predicted knowing the weight concentration of drug, lactose and HPMC in the two formulations and the constants K_A, K_L and K_H, determined from the solution diffusion data. To test the utility of equation 6, we report a comparison between the experimentally determined drug release rate ratio (the left hand side of equation 6) and the predicted drug release rate ratio (computed using the right hand side of equation 6) for a large number of adi-

[4] Assumptions made in the derivation of Equation 1 that are clearly violated when applying it to drug release from HPMC matrix tablets include a pseudo steady-state approximation to Fick's Laws, one-dimensional diffusion and that no alteration of the tablet matrix occurs. Even with these limitations, it is well documented that drug release behavior from such tablets are in general agreement with so-called square-root time kinetics described by Equation 1.

nazolam mesylate and alprazolam ER tablets. Details of the calculation procedure are presented below.

MATERIALS AND METHODS

ER adinazolam mesylate tablets were manufactured by direct compression to contain variable amounts of a high viscosity grade of hydroxypropylmethylcellulose (HPMC), lactose and adinazolam mesylate. The composition of HPMC and lactose varied by ±50% about a "target" concentration, while that of the drug ranged between 1–7% by weight. Total tablet mass (and thus surface to volume ratio) varied between 400 to 680 mg among the various formulations. ER alprazolam tablets were manufactured in a similar fashion, except a blend of a high and low viscosity grade HPMC polymer was used. Separate studies using two different drug loadings (≈0.15% and 1.0%) were conducted. Total tablet mass among these studies varied between 260 to 430 mg.

All drug release experiments were conducted using test conditions previously described (1); briefly, the USP apparatus I (rotating basket) at 100 rpm and 500 ml of dissolution media were used. For ER adinazolam mesylate, the medium was 0.05 M phosphate, pH 7.0, while for ER alprazolam tablets, the medium was 0.07 M phosphate, pH 6.0. Samples were acquired at discrete time intervals between 1 and 20 hrs. The experimental drug release rates for each formulation were determined by computing the least-squares slopes of the linear portion of Higuchi plots (percent dissolved vs. $t^{1/2}$) of the drug release data. For ER adinazolam mesylate tablets, the Higuchi plots were fit through 5 hr, while for ER alprazolam tablets 0.5 and 3 mg the data were fit through 4 hr. The fitting ranges correspond to roughly 50–60% dissolved for each formulation, in accordance with the assumptions made in the derivation of Higuchi's equation (7).

The predicted drug release rates were computed using the right hand side of equation 6. Values for K_A, K_L and K_H of 5.22, 3.48 and 7.85, respectively, were obtained from the slope of the plot of $\ln(D_A/D_A^o)$ vs C_i as described previously (6). The weight concentrations of drug, lactose and HPMC obtained from the formulation composition of the dry tablet were used in the calculations. Results were computed both with and without incorporating the surface-to-volume ratio of the dry tablet (see Equation 6). The surface-to-volume ratios were computed for each tablet based on the tooling geometry and measured tablet thicknesses.

All calculations were performed with EXCEL 4.0a; data were plotted using SigmaPlot for WINDOWS v 1.02.

RESULTS AND DISCUSSION

ER Adinazolam Mesylate Tablets

Figure 1 presents correlation plots of the experimental DRR ratio vs. the predicted DRR ratio for a series of ER adinazolam mesylate formulations. The reference formulation was arbitrarily selected as the formulation with the highest HPMC content, so that ratios would be greater than unity. Note that the predicted DRR ratios were computed using three different approaches, by considering the retarding effects for adinazolam diffusion from (i) HPMC alone, (ii) both HPMC and lactose, and (iii) HPMC, lactose and adinazolam. For example, the upper frame in Figure 1 corresponds to the predicted DRR ratios computed using only the HPMC term (i.e. from equation 5, the diffusivity for each formulation was computed using the equation $D_A = D_A^o \exp(-K_H C_H)$). The middle frame in Figure 1 shows the predicted DRR ratios obtained by incorporating both HPMC and lactose terms into the model; and the lower frame shows the predicted release rate ratios computed using the terms for HPMC, lactose and adinazolam. This allowed a comparison of the improvement in the predictive power of the model by incorporating additional terms. In Figure 1, the predicted DRR ratios were computed by correcting for the tablet surface-to-volume ratio (computed from the measured thicknesses and known geometry of the dry tablet). The effect of incorporating this term in the calculations is shown in Table 1, which presents the regression statistics for each of the relationships shown in Figure 1 both with and without correction for S/V ratio. For a perfect theoretical description, the slope and intercept of the correlation plots should equal 1.0 and 0.0, respectively, with $R^2 = 1.0$ and a small value for the standard deviation of the residuals (sdres), the latter being a measure of the scatter in the data about the fitted regression line. Comparison of the statistics listed in Table 1 reveals the following conclusions:

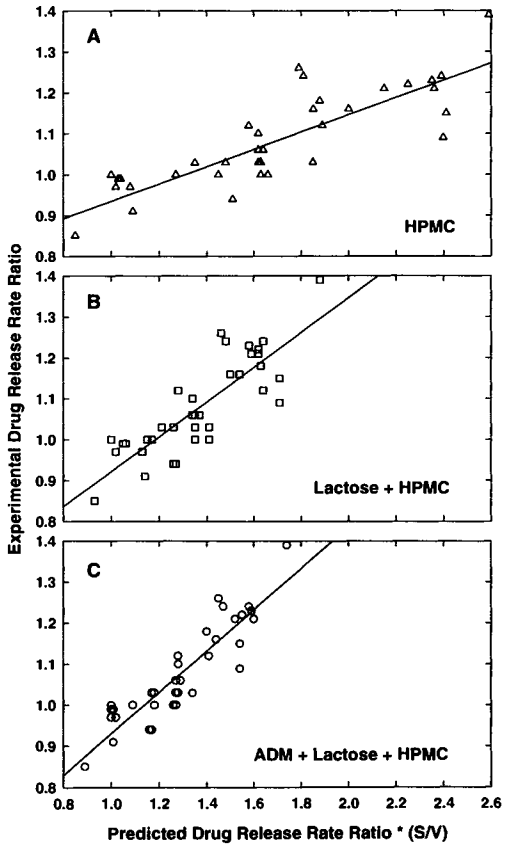

Figure 1. Correlation between the experimental and the predicted drug release rate ratios for 40 formulations of ER adinazolam mesylate tablets which vary in formulation composition. The predicted release rates were calculated using diffusion data for (A) HPMC, (B) lactose plus HPMC, and (C) adinazolam, lactose and HPMC. The predicted release rates have been multiplied by the S/V ratio (see equation 6).

Table 1. Regression Statistics for Plots of Experimental Drug Release Rate Ratio (y) vs Predicted Drug Release Rate Ratio or Reciprocal HPMC Concentration (x) for ER Adinazolam Mesylate Tablets

Independent variable[a]	Slope (±s.d.)	Intercept (±s.d.)	R^2	sdres	Figure reference
	Predicted drug release rate ratio				
H	0.18 (0.03)	0.77 (0.06)	0.4792	0.084	—
L + H	0.36 (0.07)	0.58 (0.10)	0.4331	0.088	—
A + L + H	0.42 (0.07)	0.52 (0.10)	0.5036	0.082	—
H * S/V	0.21 (0.03)	0.72 (0.04)	0.6784	0.066	1A
(L + H)*S/V	0.43 (0.05)	0.49 (0.07)	0.6951	0.064	1B
(A + L + H)*S/V	0.51 (0.04)	0.41 (0.05)	0.8158	0.050	1C
	Empirical relationships				
(1/HPMC)	0.27 (0.05)	0.69 (0.07)	0.4693	0.085	—
(1/HPMC)*S/V	0.33 (0.04)	0.62 (0.05)	0.7093	0.063	2
(Lactose/HPMC)*S/V	0.17 (0.02)	0.78 (0.04)	0.6549	0.068	—

[a] For each regression, the experimental drug release rate ratio is the dependent (y) variable. Abbreviations correspond to the terms included in the model (H = HPMC, L = lactose, A = adinazolam mesylate, S/V = surface-to-volume ratio).
s.d. = standard deviation, sdres = standard deviation of the residuals.

(i) The predictive power is markedly improved by incorporating the S/V ratio into the model. This is reflected as a significant increase in the coefficient of determination and corresponding decrease in the standard deviation of the residuals. The coefficient of determination (R^2) ranges from 0.48 to 0.50 for data not corrected for the S/V ratio, while R^2 ranges from 0.68 to 0.82 for data that are corrected. Accordingly, further discussion will focus on the data that have been corrected for the S/V ratio (Fig. 1).

(ii) The predictive power of the model increases as additional VIA terms are incorporated. Comparison of the regression statistics for each correlation plot of Figure 1 support this statement. The slope of the correlation plot using HPMC diffusivity data alone in the model is about 0.2, with R^2 = 0.68 and sdres = 0.07. Incorporating HPMC plus lactose in the model results in a significant increase in the slope to about 0.4, with no change in the scatter in the data (R^2 = 0.69, sdres = 0.06). Incorporation of HPMC, lactose and adinazolam terms into the model results in a slope of about 0.5, R^2 = 0.82, and sdres = 0.05.

Thus, the best predictive model is obtained by incorporating HPMC, lactose and adinazolam terms and by correcting for the surface to volume ratio (Figure 1C). For this best case prediction, the coefficient of determination indicates that 82% of the variation in experimental release rates is accounted for by the predicted release rate ratios and the slope of 0.51 indicates that the predicted release rate ratios overestimate the experimentally observed change in release rate ratios. These results are surprisingly encouraging when one considers that (a) the predictive model simplistically assumes that diffusion is the only mechanism of drug release from matrix SR tablets, and (b) drug diffusion behavior in dilute gels/solutions has been extrapolated to the behavior in matrix ER tablets, where the actual concentrations are much higher in the gel layer, particularly near the swelling front (dry core, solvent interface). The data clearly confirm the conclusions from previous work (1,2), that diffusion is the predominant drug release mechanism for ER adinazolam mesylate tablets.

Empirical mathematical models have been used for relating drug release as a function of HPMC concentration (3–5). Typically, a series of formulations are prepared and the drug release data are fit to a linear model with the inverse of HPMC concentration (or some fractional power thereof) as the independent variable. The empirical relationship for the same formulations as shown in Figure 1 is plotted in Figure 2 as the experimental DRR ratio vs. the reciprocal HPMC concentration ratio. Note that it is not necessary to plot the release rate and inverse HPMC concentration *ratios*, but we do so in order to be consistent with the data in Figures 1 and 2. In addition, the data in Figure 2 have been

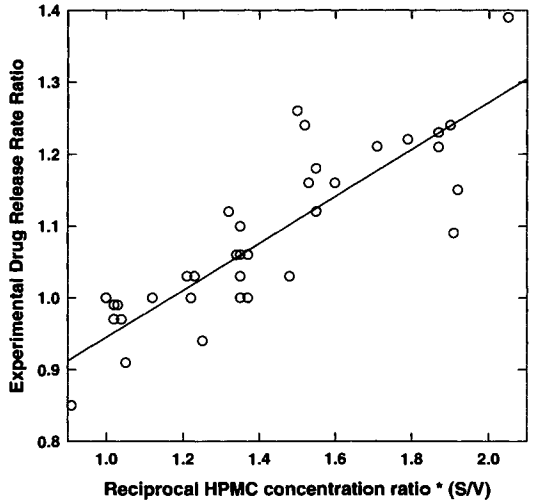

Figure 2. Empirical relationship between the experimental drug release rate and the reciprocal HPMC concentration of the dry tablet (corrected for S/V ratio) for the ER adinazolam mesylate formulations shown in Figure 1.

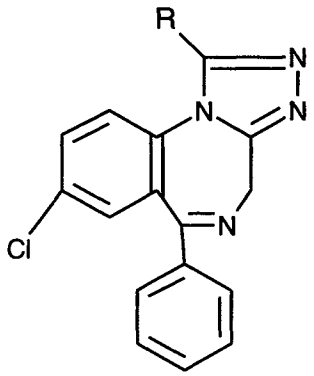

Figure 3. Chemical structures of adinazolam (R = $CH_2N(CH_3)_2$) and alprazolam (R = CH_3).

corrected for the surface-to-volume ratio of the tablet. The improvement in the results obtained by correcting for the S/V ratio of the dry tablet is evident from the regression results listed in Table 1. It can also be seen that the relationship obtained by using the lactose/HPMC ratio as the independent variable results in no improvement over that obtained using 1/HPMC alone. The R^2 for the best empirical relationship corrected for the S/V ratio indicates that 71% of the variation in the experimental release rates is explained by the empirical model. Thus, based on the value of R^2, the best theoretical model (HPMC, lactose, adinazolam) is slightly better than the best empirical model.

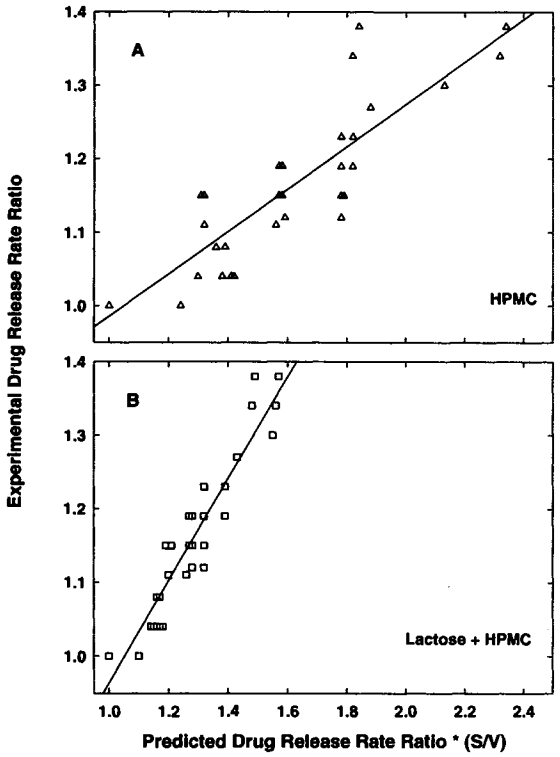

Figure 4. Correlation between the experimental and predicted drug release rate ratios for 35 formulations of ER alprazolam tablets 0.5 mg which vary in formulation composition. The predicted release rates were calculated using diffusion data for (A) HPMC and (B) lactose plus HPMC. The predicted drug release rates have been multiplied by the S/V ratio (see equation 6).

ER Alprazolam Tablets

We assumed that the diffusivity data obtained for adinazolam could be applied to alprazolam because of the similarity in chemical structure (see Figure 3). Thus, we investigated the use of equation 6 for predicting drug release from ER alprazolam tablets at two different doses (0.5 and 3 mg). In contrast to adinazolam, where drug load was allowed to vary, we evaluated the two doses of ER alprazolam tablets separately based on previous data which suggested a transition in release mechanism with dose (1). The correlation plots for ER alprazolam tablets 0.5 mg are presented in Figures 4 and 5. Figure 4 presents the correlation between the experimental and predicted drug release rate ratios, while Figure 5 presents the empirical relationship between experimental DRR ratio and inverse HPMC concentration ratio. Regression results for these plots, along with regressions comparing the effect of S/V ratio, are presented in Table 2. The analogous results for ER alprazolam tablets 3 mg are presented in Table 3. Note that the predicted release rates for ER alprazolam tablets are obtained by incorporating only lactose and HPMC (ignoring drug) into the model; the results obtained by including drug diffusivity into the model were identical. This is not unexpected, because the drug concentrations in the formulation studies were fixed at 0.5 and 3 mg and the percent composition of alprazolam is small (0.1 to 1%) relative to that of lactose and HPMC.

The conclusions stated above for ER adinazolam mesylate tablets are applicable to ER alprazolam tablets 0.5 mg. A significant improvement is obtained by accounting for the S/V ratio change among the various formulations. The best theoretical prediction is obtained by incorporating both HPMC and lactose terms into the model (slope = 0.70, R^2 = 0.88). The slope of 0.70 indicates that the predicted drug release rate overestimates the experimental release rate ratios. Again, this model is slightly better at explaining the

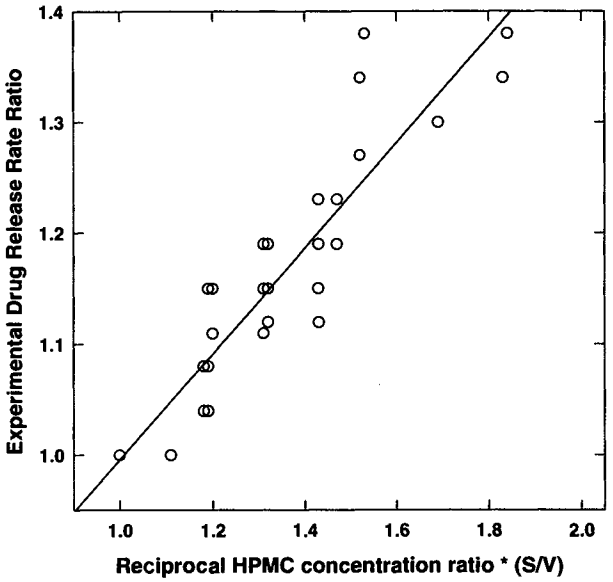

Figure 5. Empirical relationship between the experimental drug release rate and the reciprocal HPMC concentration of the dry tablet (corrected for S/V ratio) for the ER alprazolam 0.5 mg formulations shown in Figure 4.

Table 2. Regression Statistics for Plots of Experimental Drug Release Rate Ratio (y) vs. Predicted Drug Release Rate Ratio or Reciprocal HPMC Concentration (x) for ER Alprazolam Tablets 0.5 mg (Abbreviations as in Table 1)

Independent variable	Slope (±s.d.)	Intercept (±s.d.)	R^2	sdres	Figure reference
	Predicted drug release rate ratio				
H	0.22 (0.04)	0.80 (0.06)	0.4868	0.076	—
L + H	0.49 (0.09)	0.52 (0.11)	0.4959	0.076	—
H*S/V	0.29 (0.03)	0.69 (0.05)	0.7373	0.055	4A
(L + H)*S/V	0.70 (0.05)	0.26 (0.06)	0.8779	0.037	4B
	Empirical relationships				
1/HPMC	0.34 (0.06)	0.69 (0.08)	0.4890	0.076	—
1/HPMC*S/V	0.48 (0.04)	0.51 (0.06)	0.8031	0.047	5
(Lactose/HPMC)*S/V	0.23 (0.03)	0.77 (0.05)	0.6993	0.058	—

experimental data than the empirical (1/HPMC) model (R^2 = 0.80). These data suggest that the assumption of similar diffusion coefficients between adinazolam and alprazolam is appropriate.

In contrast, the results obtained for ER alprazolam tablets 3 mg are quite different (cf. Tables 2 and 3). The data show the typical increase in the slope obtained by incorporating both HPMC and lactose into the theoretical model, however, there is not improvement in the fit (predictive power) by doing so. In addition, only a marginal increase in R^2, from about 0.47 to 0.54, is obtained on correcting for the S/V ratio. Thus, the predictive power of the model for the 3 mg strength appears to be less than that for the 0.5 mg strength. Similarly, the predictive power obtained for the empirical relationship (drug release rate vs. inverse HPMC concentration) is also poor.

The results obtained for ER alprazolam tablets are consistent with previous studies which have shown that there is a change in release mechanism with increase in dose for this formulation (1). Comparison of drug and polymer release data and mathematical modelling using the Higuchi equation indicated that the 0.5 mg tablet exhibited primarily a diffusion controlled release mechanism (like ER adinazolam mesylate tablets), while the 3 mg tablet exhibited measurable contribution from erosion of the tablet matrix.

Table 3. Regression Statistics for Plots of Experimental Drug Release Rate Ratio (y) vs. Predicted Drug Release Rate Ratio or Reciprocal HPMC Concentration (x) for ER Alprazolam Tablets 3 mg (Abbreviations as in Table 1)

Independent variable	Slope (±s.d.)	Intercept (±s.d.)	R^2	sdres
	Predicted drug release rate ratios			
H	0.30 (0.05)	0.80 (0.09)	0.4731	0.1095
L + H	0.67 (0.12)	0.41 (0.16)	0.4690	0.1099
H*(S/V)	0.35 (0.06)	0.73 (0.09)	0.5409	0.1022
(L + H)*(S/V)	0.76 (0.13)	0.33 (0.16)	0.5170	0.1049
	Empirical relationships			
1/HPMC	0.47 (0.08)	0.64 (0.12)	0.4856	0.1082
1/HPMC*S/V	0.56 (0.09)	0.54 (0.12)	0.5604	0.1000
(Lactose/HPMC)*S/V	0.29 (0.05)	0.81 (0.08)	0.5462	0.1016

Effect of Lactose

The effect of lactose upon the drug release rate is an issue of interest. We demonstrated a significant decrease in adinazolam diffusion coefficient with increase in lactose concentration (6). Evidently, lactose presents a physical barrier or obstruction which affects both drug and water diffusivities (6,9) in aqueous solutions. Comparison of the K values for HPMC (7.85) and lactose (3.48) implies that lactose shows roughly half of the obstruction power of HPMC for the same weight concentrations of each component. The obstruction effect on drug diffusion due to lactose is therefore not negligible in comparison to HPMC, especially when one considers that it is often present in hydrophilic matrix ER formulations at a high concentration (20–80% w/w). For ER adinazolam mesylate tablets, our studies indicate that a ±25% variation in lactose concentration does not impact drug release, while for ER alprazolam tablets, an *increase* in lactose concentration causes an increase in drug release rate (data not shown). Because the lactose and HPMC concentrations in the tablet are interdependent, the interpretation of the microscopic diffusion kinetics from this work in terms of the macroscopic drug release kinetics must be done with caution. For example, an increase in lactose concentration in the tablet will lead to a decrease in the HPMC concentration, which is the key factor affecting drug diffusion kinetics. Therefore, it is expected that the decrease in obstruction power caused by the decrease in HPMC concentration will overpower any increase in obstruction power due to the increase in lactose concentration. Furthermore, lactose concentration in the gel layer is not constant throughout the release experiment and is presumably being released with a comparable or higher diffusion rate due to its smaller molecular size and much higher concentration gradient. We hypothesize that the effect of lactose on the release kinetics may be manifested not only by its affect on the drug diffusion coefficient in the matrix, but also on the matrix swelling kinetics. Our model improves the predictive power by incorporating lactose and drug terms. In contrast, the empirical model usually yields poorer results by incorporating additional terms (see Tables 1–3).

Model Limitations

The limitations of the model presented here are clearly

evident. First, we only account for diffusion kinetics of the drug. A comprehensive analysis of the mechanism of release from matrix systems requires knowledge of not only the diffusion kinetics of the drug through the hydrated matrix, but also the swelling kinetics of the matrix. The predominant mechanism of drug release will be determined by the relative ratio of these processes. Quantifying the role of swelling kinetics is beginning to receive more attention in the literature as new techniques are applied to study this process (10–13). Preliminary experiments in our laboratory using optical image analysis have shown great promise in monitoring the swelling kinetics of HPMC based ER dosage forms.

Second, the drug diffusivities in concentrated polymer gels have been reported to show dramatically different behavior compared to that in dilute gels (9). The K values obtained for HPMC, lactose and adinazolam were derived from measurements of drug diffusivity in dilute HPMC gels and lactose solutions. The concentrations of lactose and HPMC in the gel layer, especially at the swelling front (glassy core/gel interface) are much higher. The predicted drug release results are based on extrapolating the diffusivity behavior from dilute to concentrated solutions and use the weight concentrations of the dry tablet to approximate the concentrations in the gel. Therefore, we expect deviations between the model and the experimental data. For instance, the systematic overestimation of the drug release rates for the formulations investigated in this work presumably result from such extrapolation.

Third, the predicted release rates are based on the assumption that the initial formulation composition is representative of the gel composition and that the drug diffusion coefficient is constant. In fact, the true composition of the gel changes with time due to the release of drug, lactose and HPMC from the matrix. We expect that the matrix will become "enriched" with polymer over time (due to the faster diffusivity and release of lactose and drug) resulting in a time-dependent diffusion coefficient of drug.

To summarize, we anticipate that improved predictions of drug release rate will be possible by incorporating both swelling kinetics and diffusion kinetics into a generalized theoretical model for matrix ER systems.

CONCLUSIONS

A mathematical model has been described for the prediction of the relative change in drug release rate of extended release adinazolam mesylate and alprazolam tablets as a function of formulation composition. The model is based on the equation derived by Higuchi for the diffusional release of soluble drugs from matrices and on our recent measurements of the concentration dependency of adinazolam diffusivity in dilute gels/solutions. The predictions incorporate the S/V ratio and the formulation composition of the dry tablet. Reasonable correlations were obtained between the experimental drug release rate and the predicted drug release rate ratios for both ER adinazolam mesylate tablets and the lower strength of ER alprazolam tablets. The best model for predicting drug release rates is obtained by incorporating all three concentration terms (adinazolam, lactose and HPMC) and by correcting for the S/V ratio of the dry tablet. The predictive power for the higher dose of ER alprazolam tablets was not as good. These results are consistent with previous knowledge of the release mechanisms of these formulations. ER adinazolam mesylate and the lower dose of ER alprazolam tablets exhibit primarily a diffusion controlled release mechanism, while the higher dose of ER alprazolam deviates from pure diffusional release. The limitations of the model are discussed and point to the need for continued study of the swelling kinetics of matrix ER systems.

ACKNOWLEDGMENTS

We acknowledge Paul Fagerness and Nick Stemm for their technical assistance, Paul for NMR expertise and Nick for preparing drug/HPMC gels for NMR analysis. Brent White is acknowledged for his early recognition of the importance of the diffusion measurements and for his ideas and encouragement during the course of this project. We also thank Jim Freeman, Ken Manning, John Landis, and Roger Gordon for their vision in supporting this project.

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