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. Skoug¹,³

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 ($D_\lambda$) 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 $D_\lambda$ 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-
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,

$$M_t = M_o \cdot S/V \cdot \left(\frac{D'}{\pi}\right)^{\frac{1}{2}}$$

(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,

$$D' = D/\tau$$

(2)

in which $D$ is the true self-diffusion coefficient of the drug in the release medium alone and $\tau$ 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. The slope of a plot of percent dissolved vs. the square-root of time (Equation 3) has units of $t^{-\frac{1}{2}}$; this quantity is hereafter referred to as the drug release rate (DRR),

$$DRR = \frac{M_t}{M_o} t^{-\frac{1}{2}} = S/V D'^{\frac{1}{2}}$$

(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:

$$D_A = D_A^\infty \exp(-K_C C_i)$$

(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; $D^\infty_A$ 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,

$$D_A = D_A^\infty \exp\left(-\sum_i K_i C_i\right)$$

(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,

$$\frac{DRR_1}{DRR_2} = \frac{\left(\frac{M_t}{M_o}\right)}{\left(\frac{M_t}{M_o}\right)} \left(\frac{\exp\left(\sum_i - K_i C_i\right)}{\sqrt{\frac{S}{V}}}ight) \sqrt{\frac{S}{V}}$$

(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-