Prediction of Drug Release from Hydroxypropyl Methylcellulose (HPMC) Matrices: Effect of Polymer Concentration

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INTRODUCTION

Hydrophilic polymer matrix systems have attracted considerable attention in the pharmaceutical area (1–3). Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer frequently used in hydrogel delivery systems. The adjustment of the polymer concentration and the viscosity grade and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rate (4,5). In general, these formulation and processing factors affect the drug release profiles both kinetically and mechanistically. The drug release mechanisms for hydrogel systems, which involve water penetration and polymer relaxation to form a viscous rubbery region (gel layer), have been thoroughly investigated. This rubbery region controls drug release by the viscous resistant force to drug diffusion or matrix erosion (5–7). The passage of a water-soluble drug, via diffusion, through this gel layer is approximately dependent on the square root of time and can be described in the following form (6–8):

$$Q = k'\sqrt{D_a t} = k\sqrt{t} \tag{1}$$

where Q is the amount of drug released in time, t; D_a is the apparent diffusion coefficient of drug through the rubbery region; and k' and k are kinetic constants.

To optimize the drug release profiles, selection of the HPMC concentration incorporated in the tablet matrix is one of the most common approaches. The purpose of this work is to predict the drug release profiles based on Eq. (1) if different polymer levels are used in the formulation.

MATERIALS AND METHODS

Materials. Chlorpheniramine maleate (CPM) USP and theophylline USP were used as the model actives in this study. Two grades of hydroxypropyl methylcellulose (HPMC), Methocel K100LV and K15M (Dow Chemicals), at various concentrations were incorporated in the tablet formulations. Povidone, dicalcium phosphate, lactose, and magnesium stearate were used as supplied.

Preparation of Tablets. Tablet formulations, shown in the respective plot and containing various concentrations of HPMC, were prepared by direct compression on a Carver Press. The target tablet weight was 400 mg. The compression force was fixed at 2000 lb with a punch of 7/16 in.

Dissolution Studies. Dissolution tests were performed in triplicate using a USP dissolution apparatus 1 (basket) at a rotation speed of 100 rpm in 900 mL of purified water. The drug released was determined by a UV spectrophotometer at 260 nm for cpm and 270 nm for theophylline.

RESULTS AND DISCUSSION

In many applications and, especially, for oral delivery, a hydrogel matrix consists of a drug entrapped in a hydrophilic polymer in a glass state. Drug release from such systems involves the simultaneous absorption of water and desorption of drug. It has been reported that the mechanisms occurring in drug release include drug diffusion through the swelling gel layer and device erosion of the swollen layer. To account for these dual release mechanisms, drug release can be simply expressed as the following one of many empirical equations:

$$Q = Kt^n \tag{2}$$

where n is the diffusional exponent for drug release, which gives an indication of the release mechanism.

For a water-soluble drug and relatively high-viscosity grade of HPMC, drug diffusion contributes predominantly to the overall dissolution. Drug release generally can be approximated using Eq. (1), which is square root of time dependent. To predict drug release from a matrix system with a different concentration of HPMC, several assumptions are made: (i) drug release can be approximately modeled using the square root of time relation [Eq. (1)]; (ii) the apparent diffusion coefficient of drug in the rubbery region is related to the tortuosity of the swelling layer [Eq. (3)]; (iii) the tortuosity of the swelling layer depends upon the degree of polymer hydration, which is directly proportional to the polymer concentration (C_p) in the matrix [Eq. (4)]; and (iv) the porosity of the swelling layer is constant.

$$D_a = \frac{\epsilon}{\tau} \tag{3}$$

$$\tau = \beta C_p \tag{4}$$

where ϵ and τ represent the porosity and tortuosity, respectively, of the swelling layer and β is the kinetic constant. Therefore, Eq. (1) can be modified to the following form:

$$Q = \alpha\sqrt{\frac{t}{C_p}} \tag{5}$$

where α is the kinetic constant. It is obvious that drug re-

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lease at a given time is directly related to the polymer concentration in the matrix.

Figure 1 shows the dissolution profiles from Formulation A containing various levels of Methocel K100LV. The results indicate that all of the experimental data can be fitted using Eq. (1), demonstrating that drug release kinetics approximately follows the square root of time relationship. The plot of the amount of drug released at different given times vs the reciprocal of the square root of polymer concentration in the matrix in Fig. 2 shows very good linearity, which indicates that all of the assumptions for Eq. (5) could be applicable. Therefore, it is possible to predict drug release from HPMC matrices at different polymer concentrations.

Based on Eq. (5), the relationship of the fraction of drug released, Q_i, with the polymer concentration at a given time may be obtained by linear regression from limited experiments. For example, at time $t_1, t_2, \ldots, t_i, \ldots, t_n$, the regression equations for the amount of drug released ($Q_1, Q_2, \ldots, Q_i, \ldots, Q_n$) in relation to the polymer concentration are as follows:

$$Q_i = a_i + b_i \frac{1}{\sqrt{C_p}} \quad \text{(at time } t_i,\ i = 1, 2, \ldots, i, \ldots, n) \tag{6}$$

From Eq. (5), the amount of drug released (Q_i) is a function of the square root of time (t_i) at a given polymer concentration (C_p). It is possible that both a_i and b_i are functions of the square root of time if C_p is a constant. Therefore, Eq. (6) could be further derived as expressed by Eq. (9).

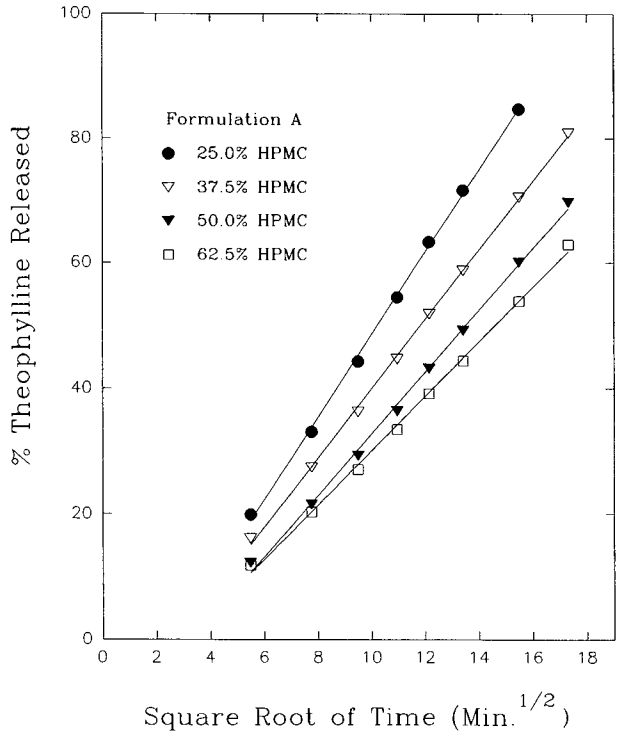

Fig. 1. Theophylline release profiles from formulation A consisting of 12.5% theophylline, 5.0% povidone, and 0.7% magnesium stearate with different HPMC (Methocel K100LV) levels and anhydrous lactose QS to 100% (SD within the symbols).

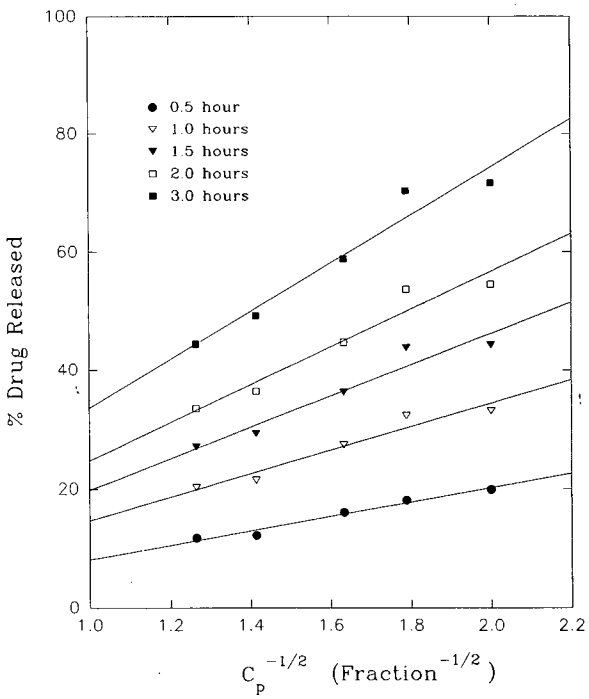

Fig. 2. Relationship of drug release and polymer concentration in Formulation A (SD within the symbols).

$$a_i = c + k_a\sqrt{t_i} \tag{7}$$

$$b_i = d + k_b\sqrt{t_i} \tag{8}$$

$$Q_i = \left(c + k_a\sqrt{t_i}\right) + \left(d + k_b\sqrt{t_i}\right)\frac{1}{\sqrt{C_p}} = \left(c + \frac{d}{\sqrt{C_p}}\right) + \left(k_a + k_b\frac{1}{\sqrt{C_p}}\right)\sqrt{t_i} \tag{9}$$

where c, d, k_a, and k_b are regressional constants. Therefore, Eqs. (5), (6), (8), and (9) can be used to establish a working equation to predict and optimize drug release from HPMC matrices having various polymer concentrations using only a limited number of experiments. In summary, the steps involved in establishing a working equation using a limited number of experiments include (i) dissolution testing for two or three formulations consisting of the different polymer concentrations; (ii) determining whether drug release follows the square root of time using Eq. (1); (iii) least curve fitting of the drug released versus the polymer concentration in the formulations at the different given times using Eq. (6) to obtain series of the a_i and b_i values; (iv) least curve fitting using Eqs. (7) and (8) to obtain c, d, k_a, and k_b values; and (v) substituting c, d, k_a, and k_b values into Eq. (9), which gives a working equation.

Two polymer concentrations (25 and 75% of Methocel K100LV) were incorporated in Formulation B and demonstrated a square root of time dependency. Based on these two experiments, series of the a_i and b_i values can be obtained by fitting the percentage of theophylline released at time t_i into Eq. (6). By fitting a_i and b_i values with the different given times, t_i, into Eqs. (7) and (8) to find c, d, k_a, and k_b values, the working equation to predict drug release from Formulation B can be obtained as follows:

$$Q = \left(\frac{1.034}{\sqrt{C_p}} - 14.603\right) + \left(2.355 + \frac{1.413}{\sqrt{C_p}}\right)\sqrt{t} \quad (10)$$

The same approach is used to introduce variables C_p and t into the working equation predicting drug release from Formulation C having 20 and 70% of Methocel K15M. Equation (11) is a working equation for Formulation C.

$$Q = \left(\frac{3.498}{\sqrt{C_p}} - 19.118\right) + \left(2.668 + \frac{1.128}{\sqrt{C_p}}\right)\sqrt{t} \quad (11)$$

Figures 3 and 4 present drug release data from dissolution experiments and theoretically calculated data using Eqs. (10) and (11) for Formulations B and C which have different concentrations of hydroxypropyl methylcellulose (Methocel K100LV or K15M) and different excipients (lactose or dicalcium phosphate). Interestingly, it was found that all of the experimental data from dissolution testing match the predicted data very well. This implies that the dissolution profiles can be predicted using the equations discussed above. Therefore, this approach could be successfully applied to optimize the hydrophilic polymer concentration in the formulation design of hydrogel delivery systems using only a minimum number of experiments.

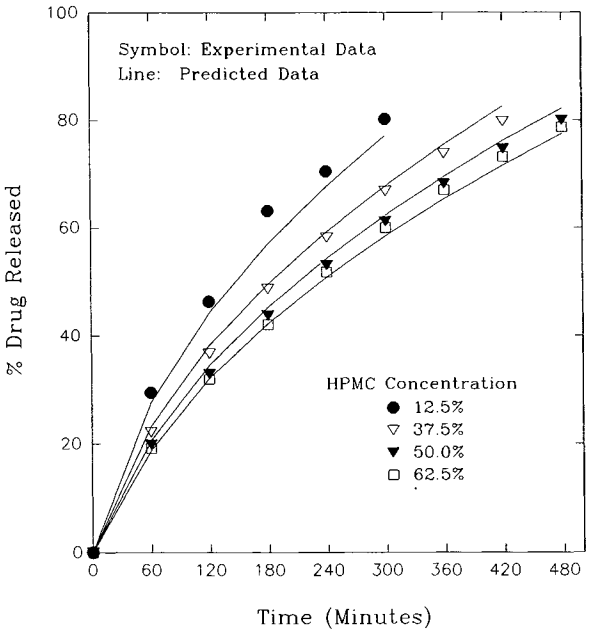

Fig. 3. Predicted vs experimental dissolution profiles of Formulation B consisting of 12.5% theophylline, 5.0% povidone, and 0.7% magnesium stearate with different HPMC (Methocel K100LV) levels and dicalcium phosphate QS to 100% (SD within the symbols).

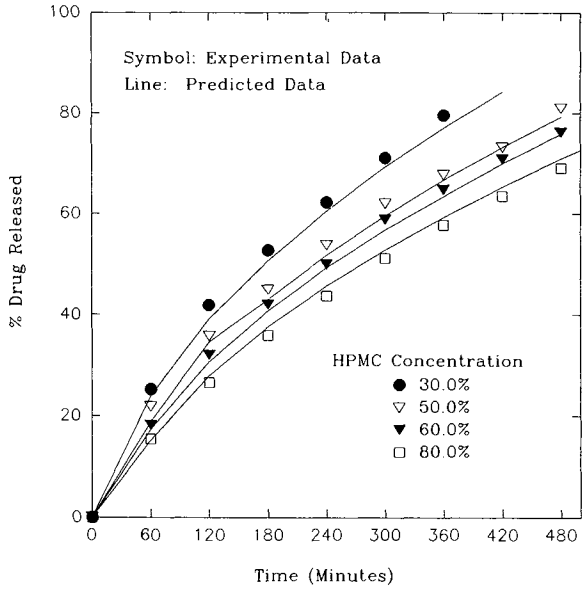

Fig. 4. Predicted vs experimental dissolution profiles of Formulation C consisting of 10% chlorpheniramine maleate and 1% magnesium stearate with different HPMC (Methocel K15M) levels and anhydrous lactose QS to 100% (SD within the symbols).

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