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# A mathematical model to predict the release of water-soluble drugs from HPMC matrices

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A mathematical model to predict the fraction of water-soluble drug released as a function of release time (t, h), HPMC concentration ($C_H$, w/w), and volume of drug molecule (V, $nm^3$) was derived with ranitidine hydrochloride, diltiazem hydrochloride, and ribavirin as model drugs. The model is $\log (M_t/M_\infty) = 0.5 \log t - 0.3322 C_H - 0.2222 V - 0.2988$ ($n = 140$, $r = 0.9848$), where $M_t$ is the amount of drug released at time t, $M_\infty$ is the amount of drug released over a very long time, which corresponds in principle to the initial loading, n is the number of samples, and r is the correlation coefficient. The model was validated using isoniazid and satisfactory results were obtained. The model can be used to predict the release fraction of various soluble drugs from HPMC matrices having different polymer levels.

## 1. Introduction

Hydroxypropyl methylcellulose (HPMC) has been the dominant hydrophilic vehicle used in controlled release dosage forms because of its non-toxic nature, ease of compression, and accommodation to high levels of drug loading. It is desirable to accurately predict the drug release from HPMC matrices in the design of such dosage forms. Some attempts to quantitatively predict drug release from HPMC matrices have been reported in the literature.

Ford et al. proposed an empirical relationship between drug release rate and HPMC concentration (Ford et al. 1985). Drug release rate was correlated with the reciprocal HPMC concentration in their empirical model. Shah et al. reported a method for the prediction of the fraction of drug released as a function of HPMC concentration and release time (Shah et al. 1993). Gao et al. derived a mathematical model to predict the relative change in drug release rate as a function of formulation composition for HPMC-based extended-release tablets of adinazolam mesylate and alprazolam according to Higuchi theory (Gao et al. 1995). Siepmann et al. developed a mathematical model for the water transport into and drug release from HPMC tablets to calculate the required shape and size of HPMC tablets to achieve a desired drug release profiles (Siepmann et al. 1999, 2000). However, these prediction models must be established for each drug and are not available for other drugs.

In this study, a mathematical model to predict drug release from HPMC matrices was derived, which is applicable to various soluble drugs.

## 2. Investigations, results, and discussion

The fractions of ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin released from HPMC matrices are shown in Fig. 1.

Ritger and Peppas (1987) derived an equation for the Fickian release of soluble drugs from moderately swelling slabs, shown as eq. (1)

$$\frac{M_t}{M_\infty} = 4 \left(\frac{Dt}{\pi l^2}\right)^{1/2} \quad (1)$$

Here, $M_t$ is the amount of drug released at time t, $M_\infty$ is the amount of drug released over a very long time, which corresponds in principle to the initial loading. D is the drug diffusion coefficient, and l is the initial slab thickness.

Eq. (2) can be derived from eq. (1):

$$\log (M_t/M_\infty) = 0.5 \log t + 0.5 \log D + a_0 \quad (2)$$

Here, $a_0$ is a constant relevant to the initial slab thickness.

Gao and Fagerness (1995) used a pulsed-field-gradient spin-echo NMR technique to determine the diffusivities in HPMC-gels and found the drug diffusion coefficient to depend exponentially on HPMC concentration.

According to the free volume theory (Cohen and Turbull 1959), the size of the diffusing molecules affected their transfer rate. The jump from one cavity to another for a given cavity size distribution was easier for smaller molecules than for larger ones. Their diffusion coefficients were exponentially dependent on their molecular volumes. Therefore, D in eq. (2) can be expressed as eq. (3):

$$D = D_0 \exp (-a_1 C_H - a_2 V) \quad (3)$$

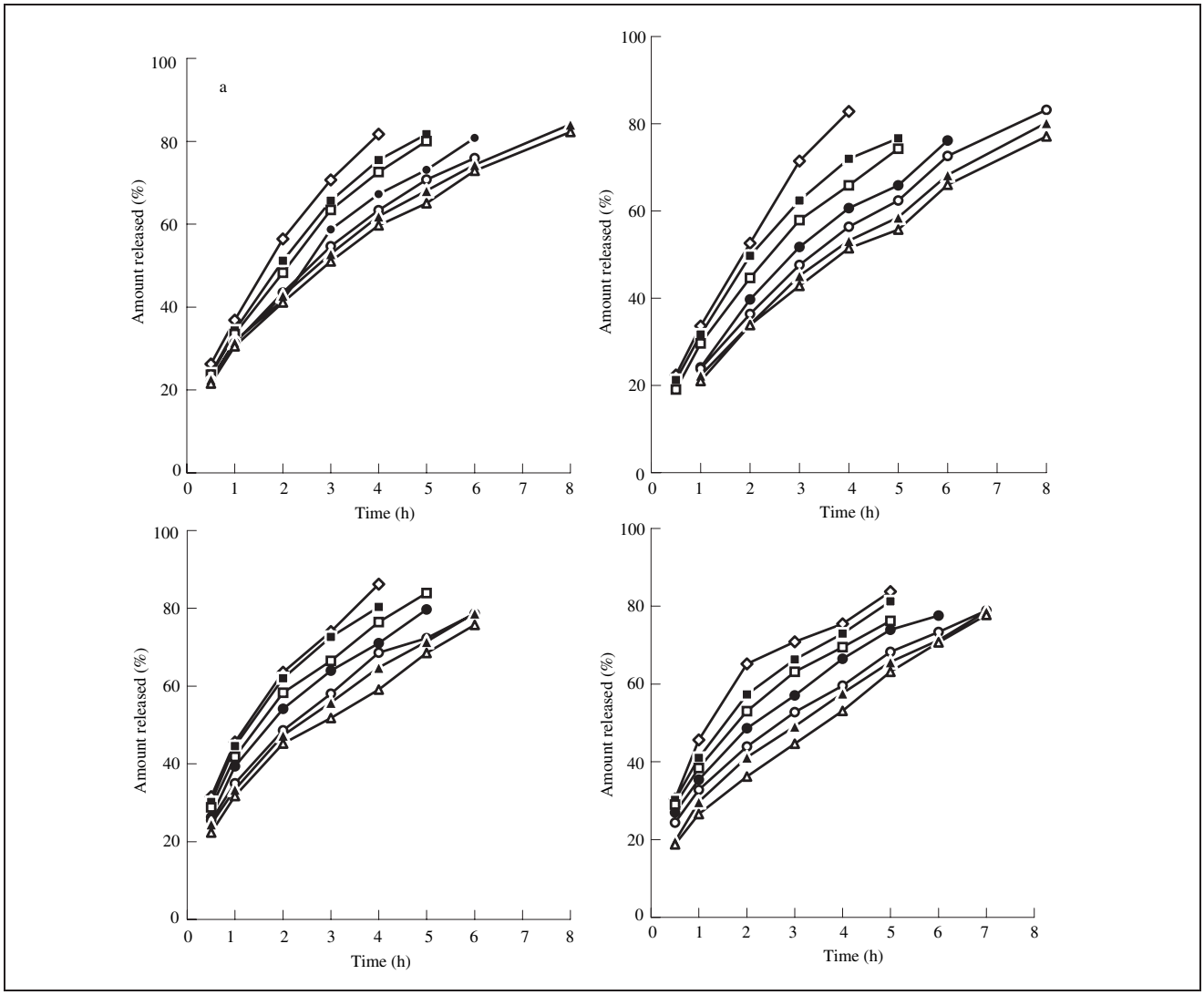


Fig. 1: Drug release (a, ranitidine hydrochloride; b, diltiazem hydrochloride; c, isoniazid; d, ribavirin) from tablets containing (w/w% HPMC K4M: ◇, 11; ■, 16.5; □, 22; ●, 33; ○, 44; ▲, 49.5; △, 55)

Here, $C_H$ is HPMC concentration (w/w), V is volume of drug molecule ($nm^3$), $D_0$, $a_1$, and $a_2$ are constants.
Substituting for D from eq. (3) into eq. (2) the following expression for log ($M_t/M_\infty$) is obtained.

$$\log (M_t/M_\infty) = 0.5 \log t - b_1 C_H - b_2 V + b_0 \qquad (4)$$

Here, $b_0$, $b_1$, and $b_2$ are constants. Eq. (4) can be used to establish a working equation to predict the release of various water-soluble drugs from HPMC matrices having various polymer concentrations. When the releases of ranitidine hydrochloride, diltiazem hydrochloride, and ribavirin from tablets containing different HPMC levels were selected as a training set (shown in Fig. 1), the following regression equation was obtained:

$$\log (M_t/M_\infty) = 0.5 \log t - 0.3322 C_H - 0.2222 V - 0.2988 \qquad (5)$$

$$n = 140 \qquad r = 0.9848 \qquad s = 0.03245 \qquad F = 1450$$

Here, n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic.
The calculated and experimental $M_t/M_\infty$ values were plotted in Fig. 2.
Eq. (5) shows good statistical significance and Fig. 2 indicates that the calculated $M_t/M_\infty$ values are in good agree-

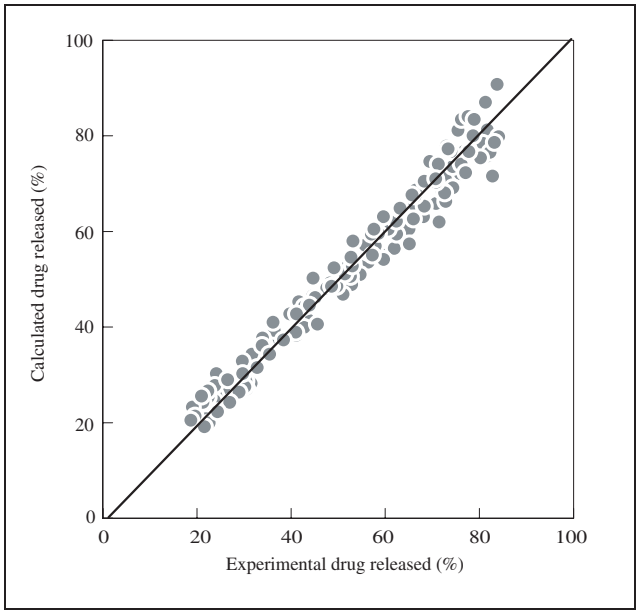


Fig. 2: Relationship between experimental and calculated $M_t/M_\infty$ values of ranitidine hydrochloride, diltiazem hydrochloride, and ribavirin released from HPMC matrices

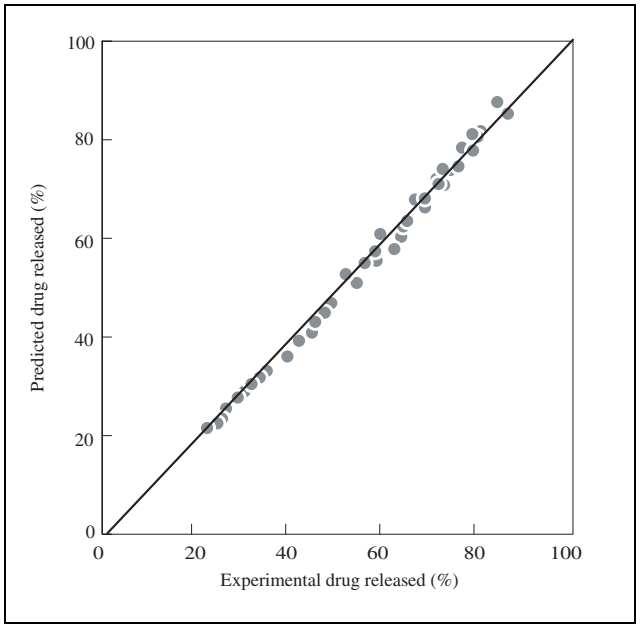


Fig. 3: Relationship between experimental and predicted $M_t/M_\infty$ values of isoniazid released from HPMC matrices

ment with the respective experimental ones. To further assess the predictive ability of eq. (5), the fractions of isoniazid released from HPMC matrices were selected as a test set (shown in Fig. 1c) and their plots of the experimental $M_t/M_\infty$ values vs the predicted $M_t/M_\infty$ values from eq. (5) were shown in Fig. 3.

Fig. 3 shows that the predicted fractions of isoniazid released from HPMC matrices are in good accordance with the respective experimental ones. The root mean square error of log ($M_t/M_\infty$) is only 0.0383 log unit for the test set.

Although eq. (5) neglects a possible erosion mechanism in addition to diffusion, both the calculated log ($M_t/M_\infty$) values for the training set and the predicted log ($M_t/M_\infty$) values for the test set agree well with the respective experimental results. The release of soluble drugs from HPMC by erosion is negligible. Eq. (5) can be used to predict the release fraction of various soluble drugs from HPMC matrices having different polymer levels.

## 3. Experimental

### *3.1. Materials*

Ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin were selected as model drugs, due to their range of desirable solubilities in water. Ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin have the solubilities of 125.5 g/100 mL, 59.25 g/100 mL, 21.67 g/100 mL, and 18.62 g/100 mL in distilled water at 37 °C, respectively. The polymer carrier used was HPMC (Methocel K4M). Dextrin was used as a filler. Magnesium stearate was used as a lubricant.

### *3.2. Tablet preparation*

Drug, HPMC (Methocel K4M), and dextrin were mixed and moistened with a 75% alcohol. The wet mass was forced through a 16 mesh sieve. The granules were dried two hours at 60 °C, and then calibrated through the same sieve. Magnesium stearate was added to the dry granules. The final mixture was compressed by a single punch press. The obtained tablet was 11 mm in diameter and 2.7 mm in thickness. Tablet hardness was $4 \pm 0.5$ kg. Total tablet mass was 300 mg containing 33% of drug, 1% of magnesium stearate, 66% of HPMC and dextrin. HPMC concentration was varied by changing the relative amount of HPMC and dextrin in order to keep the matrix weight and surface area constant.

### *3.3. Drug release*

All drug release experiments were carried out using a dissolution apparatus (rotating basket), rotating at 100 rpm in 1000 mL distilled water maintained at 37 °C. At predetermined time intervals, 5 mL samples (which were replaced with fresh medium) were withdrawn and the amount of drug released was determined spectrophotometrically at 314 nm for ranitidine hydrochloride, 235 nm for diltiazem hydrochloride, 263 nm for isoniazid, and 206 nm for ribavirin, respectively. Experiments were performed for six tablets in each formulation and mean values were obtained.

### *3.4. Calculation of molecular volumes*

The molecular volumes were calculated from the molecular geometries optimized using the semiempirical self-consistent field molecular orbital calculation AM1 method (Dewar et al. 1985) and the atomic radii used by Clark (Clark 1999). Ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin have the molecular volumes of 0.3876 $nm^3$, 0.4996 $nm^3$, 0.1569 $nm^3$, and 0.2529 $nm^3$, respectively.

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