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# A predictive model for the release of slightly water-soluble drugs from HPMC matrices

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*Received October 16, 2003, accepted November 21, 2003*

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*Pharmazie 59: 624–626 (2004)*

A model to predict the fraction of slightly water-soluble drug released as a function of release time (t, h), HPMC concentration ($C_H$, w/w), drug solubility in distilled water at 37 °C ($C_s$, g/100 mL), and volume of drug molecule (V, $nm^3$) was derived when theophyline, tinidazole, and propylthiouracil were selected as model drugs. The model is $\log (M_t/M\infty) = 0.8683 \log t - 0.1930 C_s \log t + 0.5406 V \log t - 1.227 C_H + 0.1594 C_s + 0.4423 C_H C_s - 0.8655$ ($n = 130$, $r = 0.9969$), 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 sulfamethoxazole and satisfactory results were obtained. The model can be used to predict the release fraction of various slightly water-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 predict the drug release from HPMC matrices with enough accuracy in the design of drug-containing HPMC matrices.

Ford et al. (1985) proposed an empirical relationship between drug release rate and HPMC concentration. Drug release rate was correlated with the reciprocal HPMC concentration in their empirical model. Shah et al. (1993) reported a method for the prediction of the fraction of drug released as a function of HPMC concentration and release time. 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 based on the 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). Karasulu et al. developed mathematical equations for the calculation of theophylline release from different shaped matrix tablets (Karasulu et al. 2000; Karasulu and Ertan 2002). However, these prediction models and others must be established for each drug and are not available for other drugs (Velasco et al. 1999; Siepmann and Peppas 2001; Rinaki et al. 2003).

In this paper, a predictive model for the release of various slightly water-soluble drugs from HPMC matrices was derived.

## 2. Investigations, results, and discussion

The fractions of theophylline, tinidazole, propylthiouracil, and sulfamethoxazole released from HPMC matrices are shown in Fig. 1.

When the releases of theophylline, tinidazole, and propylthiouracil from tablets containing different HPMC levels were selected as a training set (shown in Fig. 1), the following regression equation was obtained using stepwise multiple regression analysis:

$$\log (M_t/M_\infty) = 0.8683 \log t - 0.1930\, C_S \log t + 0.5406\, V \log t - 1.227\, C_H + 0.1594\, C_s + 0.4423\, C_H C_s - 0.8655$$

$$n = 130\ r = 0.9969\ s = 0.02335\ F = 3249 \qquad (1)$$

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, t is the release time (h), $C_H$ is HPMC concentration (w/w), $C_s$ is the drug solubility in distilled water at 37 °C (g/100 mL), V is molecular volume of the drug ($nm^3$), n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic.

Fig. 2 presents the plots of the experimental $M_t/M_\infty$ values vs the calculated $M_t/M_\infty$ values from eq. (1).

Eq. (1) indicated good correlation between the fractional drug release and the release time, HPMC concentration, drug solubility and volume of drug molecule. Fig. 2 also showed that the calculated $M_t/M_\infty$ values of theophylline, tinidazole, and propylthiouracil released from HPMC matrices were in good agreement with corresponding experimental ones.

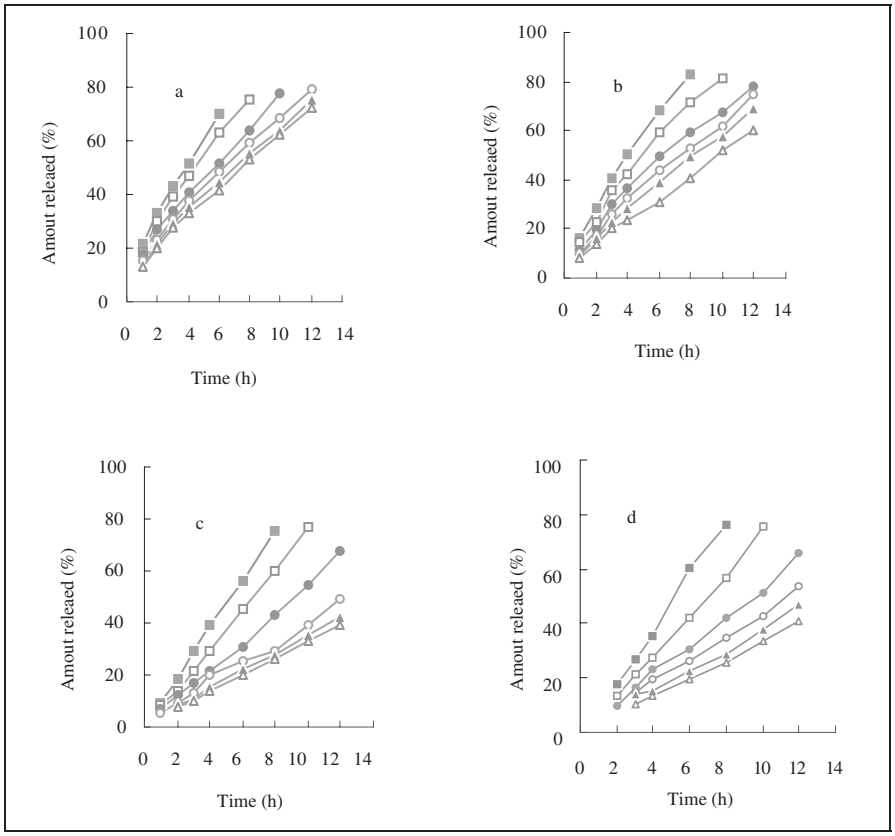


Fig. 1: Drug release (a, theophylline; b, tinidazole; c, propylthiouracil; d, sulfamethoxazole) from tablets containing (w/w% HPMC K4M: ■, 16.5; □, 22; ●, 33; ○, 44; ▲, 49.5; △, 55

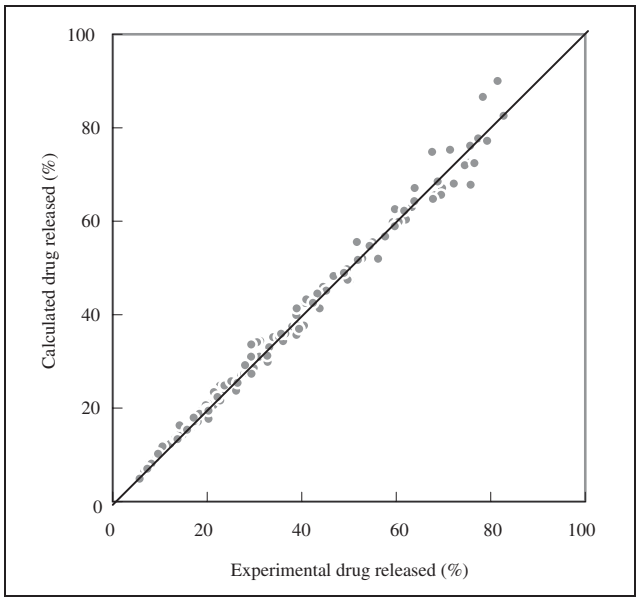


Fig. 2: Relationship between experimental and calculated $M_t/M_\infty$ values of theophylline, tinidazole, and propylthiouracil released from HPMC matrices

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

$$M_t/M_\infty = \exp(-1.993 - 2.825\,C_H + 0.3670\,C_S + 1.018\,C_H C_S)\,t^{0.8683 - 0.1930\,C_S + 0.5406\,V} \quad (2)$$

Compared with the power equation (Ritger and Peppas 1987):

$$M_t/M_\infty = kt^n \quad (3)$$

where k is a kinetic constant, and n is the diffusional exponent whose values for thin slab range between 0.5 and 1 depending on Fickian or anomalous release kinetics, the diffusional exponent and the kinetic constant in eq. (2) can be expressed as eq. (4) and eq. (5), respectively:

$$n = 0.8683 - 0.1930C_s + 0.5406\,V \quad (4)$$

$$k = \exp(-1.993 - 2.825\,C_H + 0.3670\,C_s + 1.018\,C_H C_s) \quad (5)$$

Slightly water-soluble drugs are released from HPMC matrices by both diffusion mechanism and erosion mechanism. As shown in eq. (4), the diffusional exponent values are greater and erosion mechanism becomes more important when compounds have less solubility and greater molecular size.

HPMC concentration has little effect on the diffusional exponent but decreases the kinetic constant in the power equation, so decreases the release rate. Although it can be obtained from eq. (5) that HPMC concentration might increase the kinetic constant if $C_s$ is greater than 2.774 g/100 mL, eq. (1) was derived for the slightly water-soluble drugs (the $C_s$ values of all the model drugs are less than 1.65 g/100 mL) and cannot be extrapolated to drugs with greater solubility. Eq. (5) also indicates that drug solubility can increase the kinetic constant.

To futher assess the predictive ability of eq. (1), the fractions of sulfamethoxazole released from HPMC matrices were selected as a test set (shown in Fig. 1d) and their plots of the experimental $M_t/M_\infty$ values vs the predicted $M_t/M_\infty$ values from eq. (1) were shown in Fig. 3.

Fig. 3 shows that the predicted fractions of sulfamethoxazole released from HPMC matrices are in good accordance with experimental ones. The root mean square error of log ($M_t/M_\infty$) is only 0.0383 log unit for the test set. Eq. (1) can be used to predict the release fraction of slightly soluble drugs from HPMC matrices having different polymer levels.

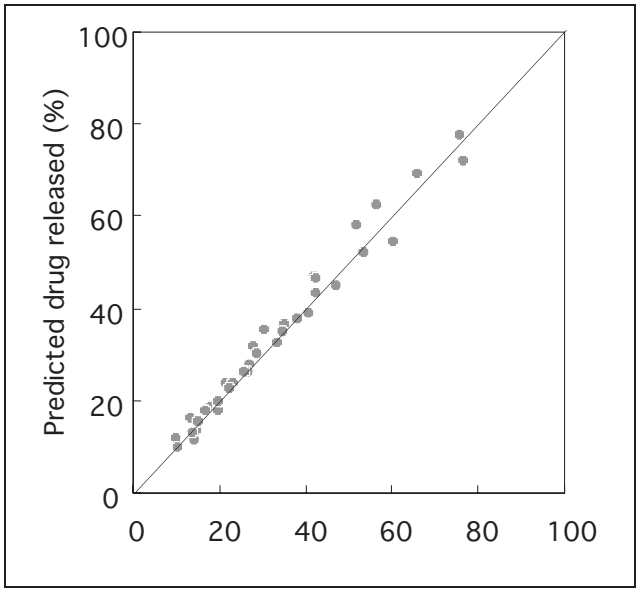


Fig. 3: Relationship between experimental and predicted $M_t/ M_\infty$ values of sulfamethoxazole released from HPMC matrices

## 3. Experimental

### *3.1. Materials*

Theophylline, tinidazole, propylthiouracil, and sulfamethoxazole were selected as model drugs, due to their range of desirable solubilities in water. Theophylline, tinidazole, propylthiouracil, and sulfamethoxazole have the solubilities of 1.646 g/100 mL, 1.126 g/100 mL, 0.2699 g/100 mL, and 0.1938 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 272 nm for theophylline, 317 nm for tinidazole, 274 nm for propylthiouracil, and 266 nm for sulfamethoxazole, 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). Theophylline, tinidazole, propylthiouracil, and sulfamethoxazole have the molecular volumes of 0.1981 $nm^3$, 0.2759 $nm^3$, 0.2023 $nm^3$, and 0.2668 $nm^3$, respectively.

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