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Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles

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Abstract

The aim of this study was to develop methods for the design of hydroxypropyl methylcellulose (HPMC) tablets with specified drug profiles. This was achieved by the use of a mathematical model developed to predict the release kinetics of water-soluble drugs from HPMC matrices. The required model parameters were determined experimentally for propranolol HCl and chlorpheniramine maleate in 0.1 N HCl and phosphate buffer pH 7.4, respectively. Then, the effects of the dimensions and aspect ratio (radius/height) of the tablets on the drug release rate were evaluated. Independent experiments were conducted to verify the theoretical predictions. Acceptable agreement between theory and experiment was found, irrespective of the type of release medium and drug. However, statistical analysis revealed a structure in the resulting residuals. Drug release rates are overestimated at the beginning and underestimated at the end of the process. Possible explanations and modifications of the model are thoroughly discussed. Both, theoretical and experimental data showed that a broad spectrum of drug release patterns can be achieved by varying the size and shape of the tablet. The effect of the initial matrix radius on release was found to be more pronounced than the effect of the initial thickness. The practical benefit of the proposed method is to predict the required size and shape of new controlled drug delivery systems to achieve desired release profiles, thus significantly facilitating the development of new pharmaceutical products.

Keywords: Controlled release; Geometry; Hydrophilic matrix; Hydroxypropyl methylcellulose; Modeling

1. Introduction

Hydroxypropyl methylcellulose (HPMC) is the dominant hydrophilic polymer carrier used for the preparation of oral controlled drug delivery systems (Colombo, 1993). To improve its applications in the pharmaceutical field, various investigators have studied its swelling and drug

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release characteristics. Similarly, several mathematical models have been published, to elucidate the water and drug transport processes and to predict the resulting drug release kinetics (Korsmeyer et al., 1986a,b; Cohen and Erneux, 1988a,b; Gao et al., 1995; Ju et al., 1995; Siepmann et al., 1999a,b). The mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into consideration. These include the diffusion of water into the HPMC matrix, HPMC swelling, drug diffusion out of the device, polymer dissolution, axial and radial transport in a 3-dimensional system, concentration-dependent diffusivities of the species, moving boundaries, and changing matrix dimensions, porosity and composition. Each model makes certain assumptions, e.g. restriction of the transport phenomena to one dimension (Cohen and Erneux, 1988a,b), neglect of polymer swelling (Katzhendler et al., 1997), or neglect of polymer dissolution (Gao et al., 1995). Due to these assumptions, the applicability of the respective models is restricted to certain drug–polymer systems. For example, a model neglecting polymer dissolution can only be applied to systems with minor polymer dissolution during drug release, whereas a model assuming instantaneous drug dissolution cannot be used for poorly water-soluble drugs.

Ju et al. (1995) presented a model taking into account a concentration-dependent drug diffusion, polymer swelling and polymer dissolution. However, they restricted their analysis to radial diffusion. Recently, a novel mathematical model was proposed (Siepmann et al., 1999a), considering radial and axial drug and water diffusion in a 3-dimensional cylindrical system, concentration-dependent diffusivities, and changes in volume and composition of the matrix due to polymer swelling. The model assumes instantaneous drug dissolution and neglects polymer dissolution. Thus, it is only applicable to water-soluble drugs incorporated into hydrophilic polymers that do not dissolve to a significant extent during drug release. This model has already been revised (Siepmann et al., 1999b). However, with respect to its practical applicability, there are still two important limitations, (i) the model does not take into account the addition of inert fillers (e.g. lactose); and (ii) it is restricted to low drug loadings. Future studies will address these aspects. Gao et al. (1995) developed a model considering the effect of the addition of lactose on the drug release kinetics. An equation was derived, quantifying the dependence of the drug diffusivity on the lactose concentration. However, it was assumed that diffusion is the sole mechanism of drug release (e.g. ignoring swelling kinetics). Adinazolam mesylate and alprazolam were investigated in lactose–HPMC tablets. The predictive power of the model for low-dose alprazolam tablets was reasonable ($R^2 = 0.87$), whereas it was not as good ($R^2 = 0.52$) for high-dose alprazolam tablets.

The aim of this study was to use our previously revised model (Siepmann et al., 1999b) to simulate the effect of the aspect ratio and dimensions of drug-loaded HPMC tablets on the release rate. In addition, the validity of this model under various experimental conditions (e.g. different release media and different drugs) was investigated. The practical benefit is to provide a method that allows the calculation of the required shape and size of drug-containing HPMC matrices to achieve desired release profiles, thus significantly facilitating the development of new pharmaceutical products.

2. Experimental section

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received, chlorpheniramine maleate (Sigma Chemical Co., St. Louis, MO), propranolol HCl (Sigma Chemical Co.), HPMC (Methocel® K15M Premium Grade) (Colorcon, Nordmann Rassmann GmbH & Co., Hamburg, Germany).

2.2. Methods

Drug-containing HPMC-matrices (5% w/w chlorpheniramine maleate or propranolol HCl) were prepared by compressing a homogeneous mixture of the drug and polymer powders with a

tabletting machine (Korsch, EK 0, Berlin, Germany), equipped with punches of 2.0, 5.0, or 13.0 mm diameter (Ritter Pharma Technik GmbH, Hamburg, Germany).

Drug release was studied using the USP XXIII rotating paddle method [37°C, 100 rpm, 900 ml 0.1 M phosphate buffer (pH 7.4) USP XXIII, or 0.1 N HCl]. At predetermined time intervals, 2 ml samples (which were replaced with fresh medium) were withdrawn, filtered and assayed spectrophotometrically (chlorpheniramine maleate, $\lambda = 264$ nm; propranolol HCl, $\lambda = 290$ nm).

3. Mathematical analysis

A mathematical model (Siepmann et al., 1999b) quantifying the transport phenomena in cylindrical HPMC matrices, was used to predict the resulting drug release kinetics from various formulations. For a detailed description of this model the reader is referred to Siepmann et al. (1999b). Here, we present a brief summary of the major assumptions and the most important physical processes involved.

Fick's second law in cylindrical co-ordinate systems, considering axial and radial mass transfer with concentration-dependent diffusivities (Crank, 1975), is used to describe water and drug transport:

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\} \quad (1)$$

Here, c_k and D_k are the concentration and diffusion coefficient of the diffusing species ($k = 1$, water; $k = 2$, drug), respectively; r denotes the radial coordinate; z the axial coordinate; θ the angle perpendicular to both axis; and t represents time. According to the free volume theory of diffusion, a Fujita-type (Fujita, 1961) exponential dependence of the diffusivities of water and drug, D_1 and D_2, is considered:

$$D_k = D_{k\mathrm{eq}}\exp\left(-\beta_k\left(1-\frac{c_1}{c_{1\mathrm{eq}}}\right)\right) \quad (2)$$

where β_1 and β_2 are dimensionless constants, characterizing this concentration-dependence, $c_{1\mathrm{eq}}$ denotes the water concentration, and $D_{1\mathrm{eq}}$ and $D_{2\mathrm{eq}}$ are the respective diffusion coefficients of water and drug in the equilibrium swollen state of the system (Siepmann et al., 1999a,b).

As HPMC is a hydrophilic polymer that swells to a significant extent upon contact with water, this phenomenon has to be taken into account. The model considers the two most important features of polymer swelling, (i) change in the volume of the system, resulting in a drastic change of the concentrations of all species; and (ii) increasing mobility of the macromolecules, leading to increasing diffusivities of water and drug (Eq. (2)).

HPMC is a water-soluble polymer. Depending on its degree of substitution and on its molecular weight, it dissolves more or less rapidly. This phenomenon was considered in our model according to the reptation theory (Narasimhan and Peppas, 1996a,b). Below a certain, critical polymer concentration, disentanglement of the HPMC macromolecular chains starts. The HPMC chains subsequently diffuse through the unstirred layer on the surface of the device into the bulk fluid. As discussed previously (Siepmann et al., 1999b), this process can be characterized using a single parameter, k_{diss}, based on the following equation:

$$M_{\mathrm{p}t} = M_{\mathrm{p}0} - k_{\mathrm{diss}}A_t t \quad (3)$$

Here, $M_{\mathrm{p}t}$ and A_t are the dry mass and the surface area of the matrix at time t, respectively.

At $t = 0$ the matrix is dry and the drug is uniformly distributed throughout the device. Thus, the water and drug concentrations at any position are equal to zero, and to the initial drug concentration, c_0, respectively:

$$t = 0 \quad c_1 = 0 \quad 0 \le r \le R_0 \quad 0 \le z \le Z_0 \quad (4)$$

$$t = 0 \quad c_2 = c_0 \quad 0 \le r \le R_0 \quad 0 \le z \le Z_0 \quad (5)$$

where R_0 is the initial radius of the matrix, and Z_0 denotes the initial half-height of the cylindrical matrix.

The boundary conditions used are as follows:

$$t > 0 \quad c_1 = c_{1\mathrm{sur}} \quad 0 \le r \le R_t \quad z = Z_t \quad (6)$$

$$t > 0 \quad c_1 = c_{1sur} \quad 0 \le z \le Z_t \quad r = R_t \tag{7}$$

$$t > 0 \quad c_2 = 0 \quad 0 \le r \le R_t \quad z = Z_t \tag{8}$$

$$t > 0 \quad c_2 = 0 \quad 0 \le z \le Z_t \quad r = R_t \tag{9}$$

$$t > 0 \quad \frac{\partial c_1}{\partial z} = 0 \quad 0 \le r \le R_t \quad z = 0 \tag{10}$$

$$t > 0 \quad \frac{\partial c_1}{\partial r} = 0 \quad 0 \le z \le Z_t \quad r = 0 \tag{11}$$

$$t > 0 \quad \frac{\partial c_2}{\partial z} = 0 \quad 0 \le r \le R_t \quad z = 0 \tag{12}$$

$$t > 0 \quad \frac{\partial c_2}{\partial r} = 0 \quad 0 \le z \le Z_t \quad r = 0 \tag{13}$$

Here, R_t and Z_t represent the time-dependent radius and half-height of the matrix; c_{1sur} denotes the water concentration at the surface of the system.

Owing to the concentration-dependence of the diffusion coefficients, the above set of partial differential equations was solved numerically, using finite-differences. In the following, only a brief description of this method is given. The time-dependent radius, R_t, and half-height, Z_t, of the cylindrical matrices are divided into I and J space intervals, Δr and Δz, respectively, generating a grid of $(I+1) \times (J+1)$ grid points. The time is divided into g time intervals Δt (for most of the simulations we have chosen, $I = J = 50$ and $g =$ 500 000). Using Eqs. (1), (2) and (6)–(13), the concentration profiles of water and drug for a new time-step ($t = t_0 + \Delta t$) can be calculated, when the concentration profile is known at the previous time-step ($t = t_0$). The concentration at a certain inner grid point ($i \times \Delta r$, $j \times \Delta z$) for the new time-step ($t = t_0 + \Delta t$) is calculated from the concentrations at the same grid point ($i \times \Delta r$, $j \times \Delta z$) and its four direct neighbors [$(i-1) \times \Delta r$, $j \times \Delta z$; $i \times \Delta r$, $(j-1) \times \Delta z$; $i \times \Delta r$, $(j+1) \times \Delta z$; $(i+1) \times \Delta r$, $j \times \Delta z$] at the previous time-step ($t = t_0$). The concentrations at the outer grid points ($i = 0$ v $i = I$ v $j = 0$ v $j = J$) for the new time-step ($t = t_0 + \Delta t$) are calculated using the boundary conditions (Eqs. (6)–(13)). At time $t = 0$ the concentration profile of the drug and water are given by the initial conditions (Eqs. (4) and (5)). Hence, the concentration profiles at $t = 0 + \Delta t$, $t = 0 + 2\Delta t$, $t = 0 + 3\Delta t$,..., $t = 0 + g\Delta t$ can be calculated sequentially.

In addition, the total amount of water, polymer and drug within the system is calculated at each time-step (by integrating the respective concentrations with respect to r, z and θ). Then, assuming homogeneous swelling throughout the device and considering polymer dissolution, the new volume of the system is determined. With this knowledge, the new radius and height of the tablet are calculated. It is assumed that water imbibing in the axial direction leads to a volume increase in the axial direction, whereas water imbibing in the radial direction leads to a volume increase in the radial direction. The increase in volume in each direction is proportional to the surface area in this direction.

The required parameters (e.g. β_k and D_{keq} values) were either already known (Siepmann et al., 1999a,b) or had to be determined by fitting the model to experimental data. No more than two parameters were fitted simultaneously, and at least 12 experimental data points were used for each fit. The fitting procedure was based on the minimization of the resulting differences between experimental and theoretical values (least squares method). The optimization of the unknown parameters was based on a modified simplex method (Nelder–Mead method). To evaluate the goodness of fit, the coefficient of determination, R^2, was calculated as follows (Sachs, 1992):

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (y(x)_{i,exp} - y(x)_{i,theo})^2}{\sum_{i=1}^{n} (y(x)_{i,exp} - y(x)_{arithm})^2} \tag{14}$$

where $y(x)_{i,exp}$ and $y(x)_{i,theo}$ are the experimental and theoretical y co-ordinates of a series of n data points, and $y(x)_{arithm}$, i, and x are the arithmetic mean of the experimental y co-ordinates of the series, an integer, and the x co-ordinate, respectively. In addition, the distribution of the resulting residuals $[y(x)_{i,exp} - y(x)_{i,theo}]$ versus time was investigated.

Once knowing the required parameters characterizing a particular polymer-drug-release medium-combination, the proposed mathematical model is fully predictive.

4. Results and discussion

4.1. Determination of model parameters and validity of the method

Using the numerical analysis, the given system of partial differential equations was solved with the respective initial and boundary conditions.

Fig. 1 shows the determination of the β_2 and D_{2eq} values for chlorpheniramine maleate in 0.1 N HCl by fitting the theory to experimental data. The measured amount of drug released from HPMC matrices with an initial radius of $R_0 = 2.5$ mm and an initial half-height of $Z_0 = 2.3$ mm, is plotted versus time. Drug release is complete within 8 h. In addition, the fit of the model to the experimental data is presented. It can be seen that there is good agreement between theory and experiment. The following values were obtained, β_2 (chlorpheniramine maleate in 0.1 N HCl) = 8.6, and D_{2eq} (chlorpheniramine maleate in 0.1 N HCl) = 10.5×10^{-7} cm^2/s. These results are in good agreement with data reported in the literature (Siepmann et al., 1999a).

The coefficient of determination, R^2 (Eq. (14)), can serve as a measure of the goodness of a fit. In the present case, $R^2 = 0.99$ was found. This value confirms the good agreement between theory and experiment, already noticed by visual observation. However, it must be pointed out that the value of R^2 alone is not sufficient to fully evaluate the goodness of a fit. The distribution of the resulting residuals also has to be considered. A random distribution of the latter is ideal. Any significant structure in the residuals indicates the presence of a systematic deviation between theory and experiment. In Fig. 2a, the residuals corresponding to the fit in Fig. 1 are illustrated (chlorpheniramine maleate release in 0.1 N HCl from matrices with $R_0 = 2.5$ mm and $Z_0 = 2.3$ mm). There seems to be a kind of structure in the distribution: in the first half the residuals are negative, in the second half they are positive. This is a first hint for a small, but significant deviation between theory and experiment.

Fitting a model to experimental data and achieving good agreement between theory and experiment is not yet a real proof of the validity of a model, especially not if several parameters are fitted simultaneously. To evaluate the validity of a model accurately, its predictive power must be tested. Therefore, the release kinetics of chlor

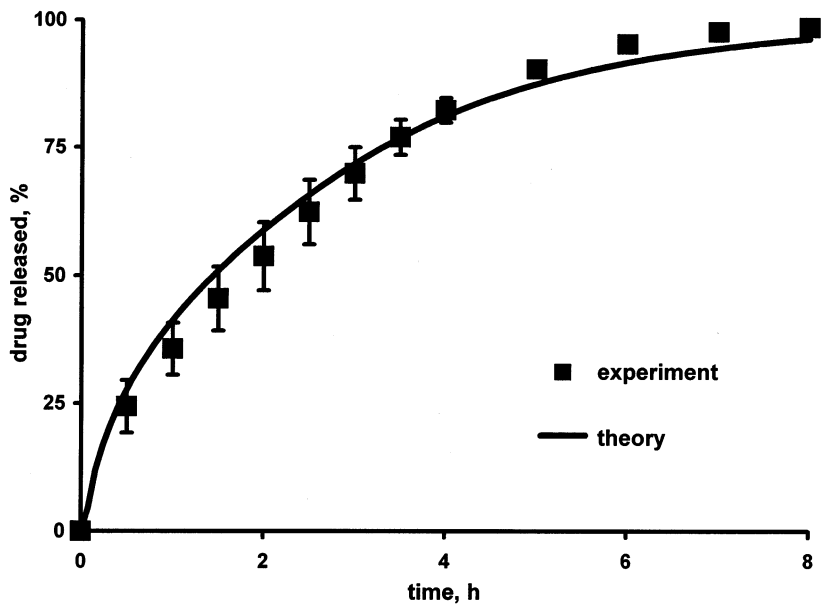

Fig. 1. Fit of the model to experimental data, chlorpheniramine maleate release in 0.1 N HCl from matrices with $R_0 = 2.5$ and $Z_0 = 2.3$ mm (error bars indicate $+/-1$ S.D., $n = 3$, $\beta_2 = 8.6$, $D_{2eq} = 10.5 \times 10^{-7}$ cm^2/s).

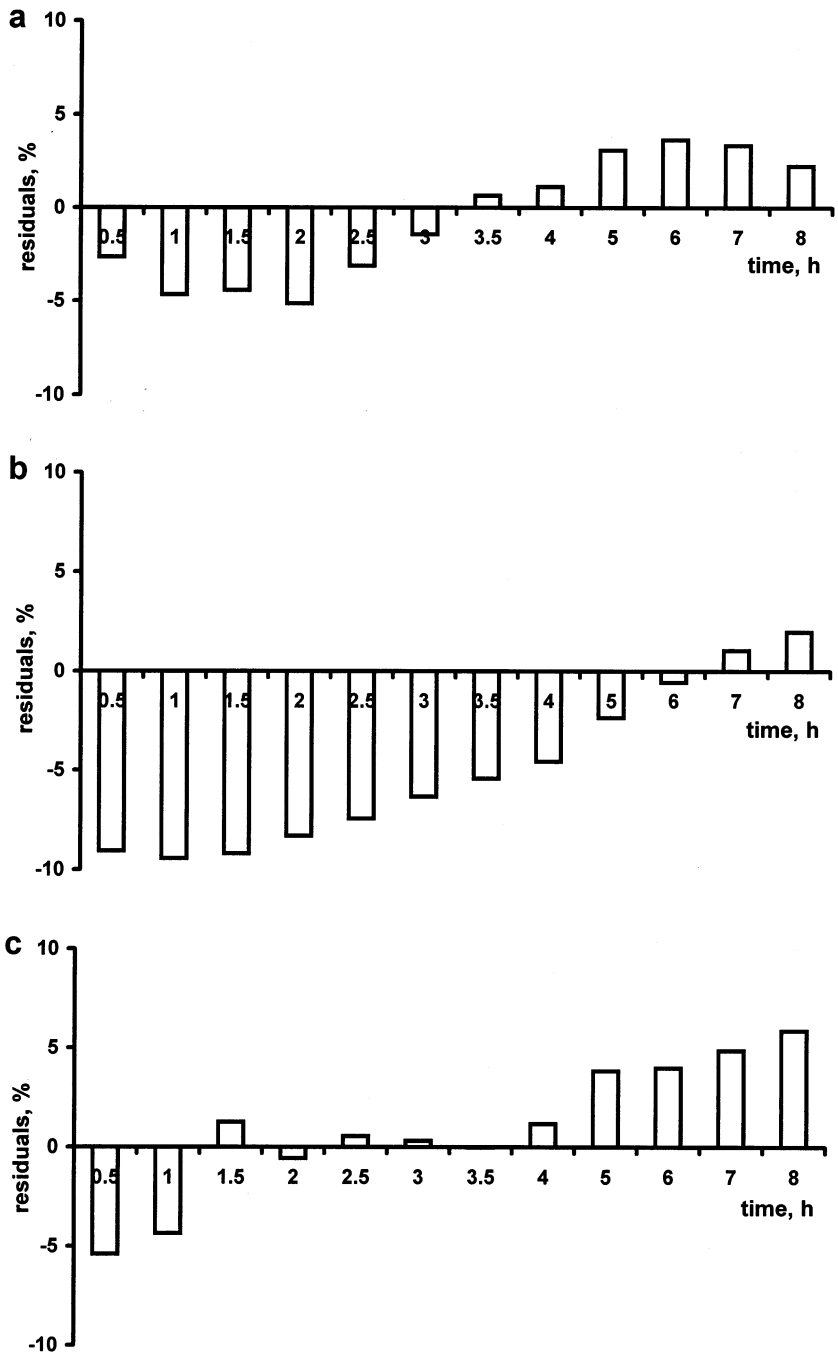

Fig. 2. Residual analysis, (a) chlorpheniramine maleate release in 0.1 N HCl from matrices with $R_0 = 2.5$ mm and $Z_0 = 2.3$ mm; (b) chlorpheniramine maleate in 0.1 N HCl from matrices with $R_0 = 6.5$ mm and $Z_0 = 1.3$ mm; and (c) propranolol HCl release in phosphate buffer pH 7.4 from matrices with $R_0 = 2.5$ mm and $Z_0 = 1.3$ mm.

pheniramine maleate in 0.1 N HCl from cylindrical matrices with an initial radius of $R_0 = 6.5$ mm, and an initial half-height of $Z_0 = 1.3$ mm were calculated using the mathematical model ($\beta_2 = 8.6$, and $D_{2eq} = 10.5 \times 10^{-7}$ cm^2/s). Then, independent release experiments were conducted and compared with the theoretical predictions (Fig. 3). Acceptable agreement between predicted and independently determined experimental data was obtained. Again, the coefficient of determination was calculated ($R^2 = 0.97$) and the resulting residuals plotted versus time (Fig. 2b). Negative deviations dominate at the beginning. Their absolute values decline with time. Finally, the deviations become positive. The analysis of further residual distributions (referring to different drugs, release media and tablet dimensions, data not shown) confirmed the hypothesis of a small, but significant systematic deviation between theory and experiment. A typical example is shown in Fig. 2c (propranolol HCl release in phosphate buffer pH 7.4 from matrices with $R_0 = 2.5$ mm and $Z_0 = 1.3$ mm). At the beginning of the process the drug release rate is overestimated, whereas at the end it is underestimated. The initial overestimation might be attributed either to the experimental conditions or to the model assumption of homogenous swelling:

- Due to entrapped air and the resulting low apparent density some of the investigated tablets floated during a certain time period in the glass vessel. Others were partially sticking to the vessel wall. In both cases the surface area of the matrix exposed to the bulk fluid was reduced, resulting in decreased release rates. These phenomena were only observed at the beginning of the experiment. A modification of the release apparatus could be used to overcome this problem. However, the experimental set-up would no longer match the USP XXIII specifications. Thus, the results would no longer be directly comparable to those of other research groups.
- Due to the assumption of homogenous matrix swelling the diffusion coefficients in dry tablet regions are overestimated. Thus, the resulting drug release rates are overestimated. This phenomenon only occurs when there is still a dry matrix core, hence only during the first few hours.

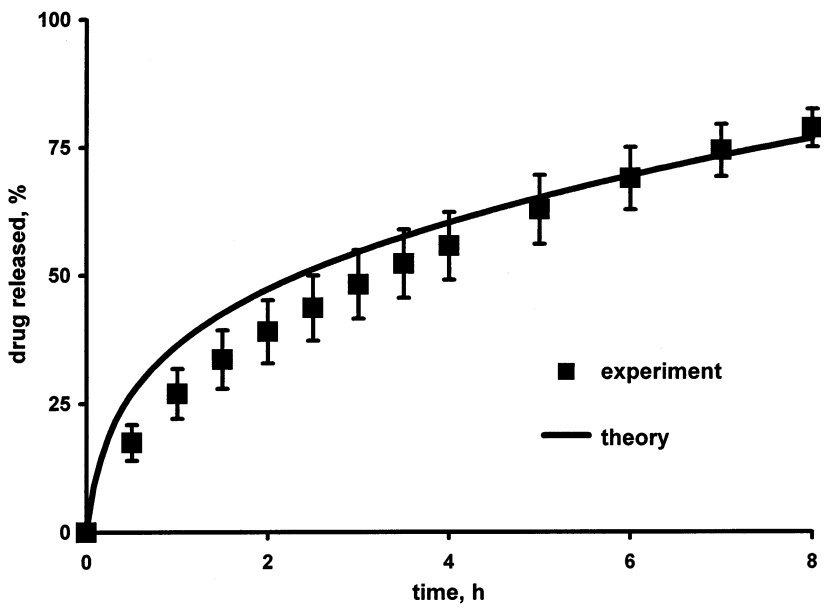

Fig. 3. Validity of the model, comparison between theoretical predictions and experiment for chlorpheniramine maleate in 0.1 N HCl from matrices with $R_0 = 6.5$ mm and $Z_0 = 1.3$ mm ($\beta_2 = 8.6$, $D_{2eq} = 10.5 \times 10^{-7}$ cm^2/s).

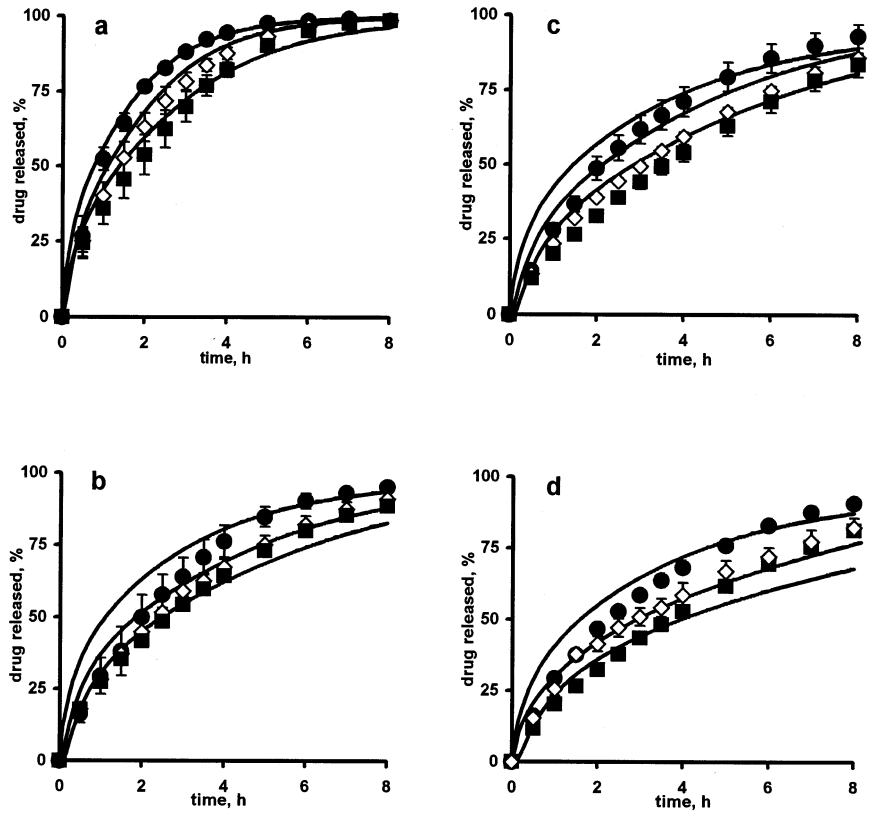

Fig. 4. Effect of the initial half-height of the matrix (with constant initial radius, $R_0 = 2.5$ mm) on the resulting relative amounts of drug released, (a) chlorpheniramine maleate in 0.1 N HCl; (b) chlorpheniramine maleate in phosphate buffer pH 7.4; (c) propranolol HCl in 0.1 N HCl; and (d) propranolol HCl in phosphate buffer pH 7.4 (experimental data, ● $Z_0 = 0.6$ mm; ◇ $Z_0 = 1.3$ mm; and ■ $Z_0 = 2.3$ mm; theoretical data, curves).

The tendency to underestimate drug release at the end of the process is most probably a direct consequence of the fitting procedure in combination with the initial overestimation.

4.2. Effect of the initial half-height of the matrix

There are two geometric parameters that can be changed for the design of cylindrical, drug-containing HPMC matrices, the initial radius, R_0, and the initial half-height, Z_0, of the device. First, we simulated the effect of the initial half-height of the matrix on the resulting drug release kinetics.

Fig. 4 shows the predicted release profiles of chlorpheniramine maleate and propranolol HCl in 0.1 N HCl and phosphate buffer pH 7.4, respectively. The following parameters have been used for the calculations, β_2(chlorpheniramine maleate in 0.1 N HCl) = 8.6, and D_{2eq}(chlorpheniramine maleate in 0.1 N HCl) = 10.5×10^{-7} cm^2/s; β_2(chlorpheniramine maleate in buffer pH 7.4) = 8.5, and D_{2eq}(chlorpheniramine maleate in buffer pH 7.4) = 8.7×10^{-7} cm^2/s; β_2(propranolol HCl in 0.1 N HCl) = 9.4, and D_{2eq}(propranolol HCl in 0.1 N HCl) = 6.9×10^{-7} cm^2/s; β_2(propranolol HCl in buffer pH 7.4) = 9.5, and D_{2eq}(propranolol HCl in buffer pH 7.4) = 6.3×10^{-7} cm^2/s. Here, the initial radius of the tablets was kept constant ($R_0 = 2.5$ mm), and the initial half-height was varied from $Z_0 = 0.6$ to $Z_0 = 2.3$ mm, representing the common matrix dimensions of pharmaceutical devices of this diameter. The initial drug loading was kept constant (5% w/w). As can be seen, there

is no drastic change in the release profile when varying the matrix height. Only a slight increase in the release rate with decreasing half-height is predicted. This is probably due to the increased relative surface area (absolute surface area/absolute volume) of the matrices.

However, it has to be pointed out, that only the percentages of drug released are illustrated in Fig. 4. The respective absolute amounts show different behavior (Fig. 5). With increasing half-height of the system, the initially incorporated absolute amounts of drug increase, leading to increase absolute amounts of drug released versus time. From a tablet designer's point of view, to achieve a certain shape of release profile, the relative amounts of drug released are more important. The respective absolute amounts of drug released, which determine the resulting drug concentrations at the site of action, can be adjusted by either varying the number of administered devices or by varying the drug loading of the system.

Figs. 4 and 5 clearly show that the effect of the initial half-height of the matrix on the resulting drug release kinetics is independent of the type of drug, and independent of the type of release medium. Thus, the variation of this parameter is a minor potent tool to modify the shape of the resulting drug release profile (relative values).

Then, independent release experiments were conducted to verify the theoretical predictions. Acceptable agreement ($R^2 > 0.87$) was obtained for all the investigated systems (Figs. 4 and 5), confirming again the predictive power of the mathematical model.

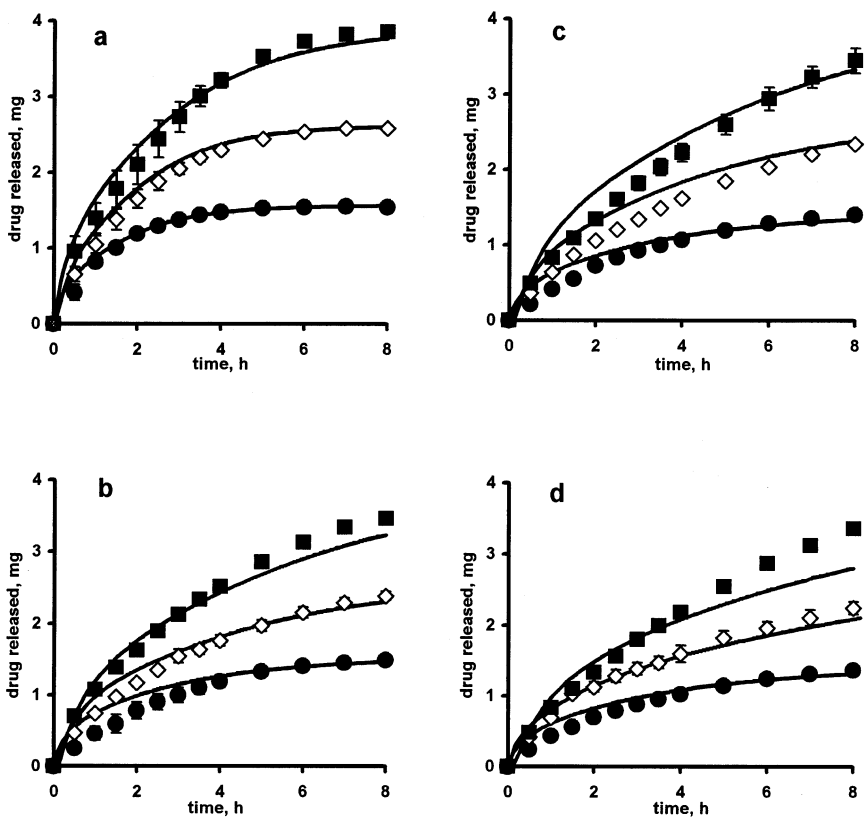

Fig. 5. Effect of the initial half-height of the matrix (with constant initial radius, $R_0 = 2.5$ mm) on the resulting absolute amounts of drug released, (a) chlorpheniramine maleate in 0.1 N HCl; (b) chlorpheniramine maleate in phosphate buffer pH 7.4; (c) propranolol HCl in 0.1 N HCl; and (d) propranolol HCl in phosphate buffer pH 7.4 (experimental data, ● $Z_0 = 0.6$ mm; ◇ $Z_0 = 1.3$ mm; and ■ $Z_0 = 2.3$ mm; theoretical data, curves).

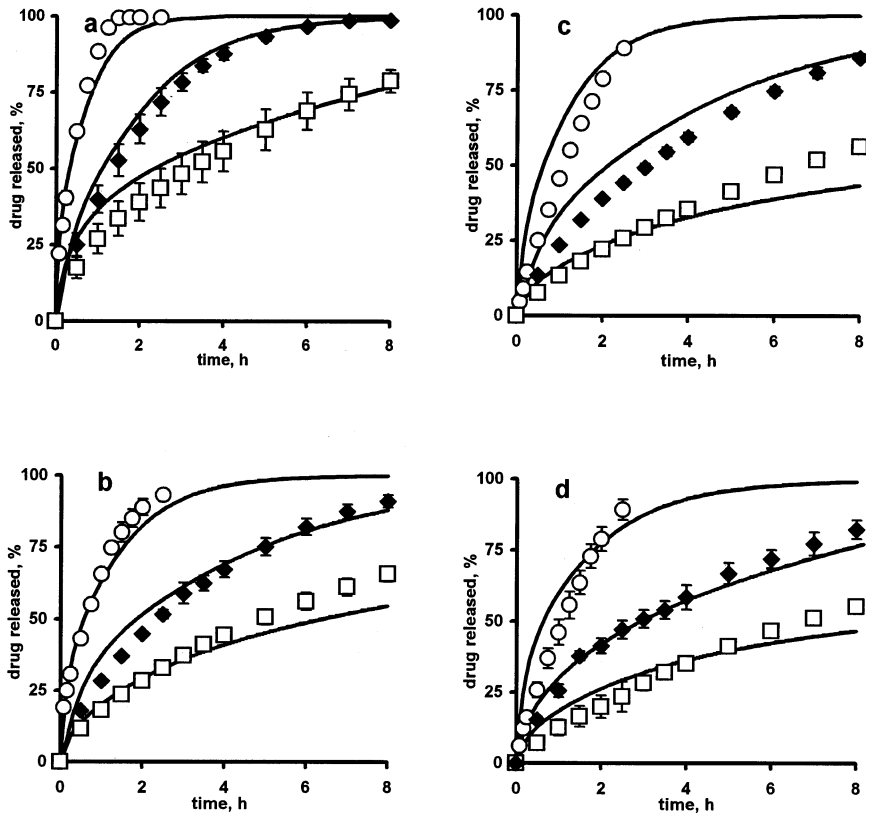

Fig. 6. Effect of the initial radius of the matrix (with constant initial half-height, $Z_0 = 1.3$ mm) on the resulting relative amounts of drug released, (a) chlorpheniramine maleate in 0.1 N HCl; (b) chlorpheniramine maleate in phosphate buffer pH 7.4; (c) propranolol HCl in 0.1 N HCl; and (d) propranolol HCl in phosphate buffer pH 7.4 (experimental data, **O** $R_0 = 1.0$ mm; ◆ $R_0 = 2.5$ mm; and □ $R_0 = 6.5$ mm; theoretical data, curves).

4.3. Effect of the initial radius of the matrix

The effect of the initial radius of the system on the resulting drug release kinetics was also simulated (Fig. 6). The initial half-height of the devices was kept at $Z_0 = 1.3$ mm, whereas the initial radius was varied from $R_0 = 1.0$ to $R_0 = 6.5$ mm. Again, the initial drug loading was kept constant (5% w/w). Chlorpheniramine maleate and propranolol HCl were investigated in 0.1 N HCl and phosphate buffer pH 7.4, respectively. Drastic changes of the drug release patterns were observed. With increasing initial radius the release rate is significantly decreased, probably due to the decreased relative surface areas of the systems. This phenomenon is independent of the type of drug and independent of the type of release medium (Fig. 6). Thus, the variation of the initial radius of the matrix is a more potent tool to affect the resulting drug release patterns than the variation of the initial half-height of the system within the investigated ranges. This might be attributed to the fact that the surface area of a cylinder is a function of the initial radius to the power of two and of the initial half-height to the power of one, respectively.

Again, independent release experiments were conducted and acceptable agreement between theory and experiment was found ($R^2 > 0.90$), indicating the predictive power of the model (Fig. 6).

4.4. Effect of the type of release medium

Fig. 7 shows the predicted and experimentally verified drug release profiles for propranolol HCl and chlorpheniramine maleate in 0.1 N HCl and phosphate buffer pH 7.4, from small ($R_0 = 1.0$ and $Z_0 = 1.3$ mm) and large matrices ($R_0 = 6.5$ mm and $Z_0 = 1.3$ mm), respectively. There is no effect of the type of release medium for propranolol HCl, whereas there is a certain, but small effect for chlorpheniramine maleate, irrespective of the size of the system. The explanation for this phenomenon is not straight forward, because both drugs show similar solubilities in 0.1 N HCl and phosphate buffer pH 7.4, respectively: chlorpheniramine maleate in 0.1 N HCl: 574 mg/ml; chlorpheniramine maleate in phosphate buffer pH 7.4: 562 mg/ml (Bodmeier and Paeratakul, 1991); propranolol HCl in 0.1 N HCl: 220 mg/ml; and propranolol HCl in phosphate buffer pH 7.4: 254 mg/ml (Bodmeier and Chen, 1989) at 37°C. Probably, different interactions between the involved components (drug, water, HPMC, phosphate buffer ions, protons and/or chloride ions) are responsible for this effect. The exact analysis of this phenomenon is beyond the scope of this paper.

4.5. Effect of the chemical structure of the drug

The resulting drug release kinetics of propranolol HCl and chlorpheniramine maleate in 0.1 N HCl and phosphate buffer pH 7.4 were predicted and experimentally verified from small ($R_0 = 1.0$ mm and $Z_0 = 1.3$ mm), and large matrices ($R_0 =$

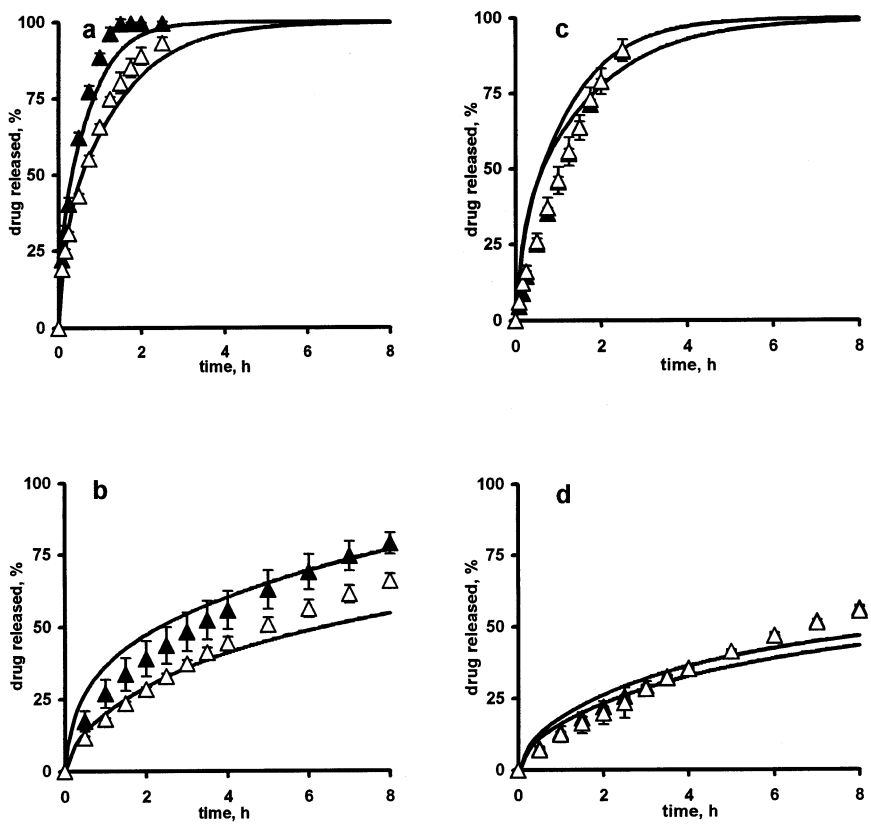

Fig. 7. Effect of the type of release medium on the resulting relative amounts of drug released, (a) chlorpheniramine maleate from matrices with $R_0 = 1.0$ mm and $Z_0 = 1.3$ mm; (b) chlorpheniramine maleate from matrices with $R_0 = 6.5$ mm and $Z_0 = 1.3$ mm; (c) propranolol HCl from matrices with $R_0 = 1.0$ mm and $Z_0 = 1.3$ mm; and (d) propranolol HCl from matrices with $R_0 = 6.5$ mm and $Z_0 = 1.3$ mm (experimental data, ▲ 0.1 N HCl, Δ phosphate buffer pH 7.4; theoretical data, curves).

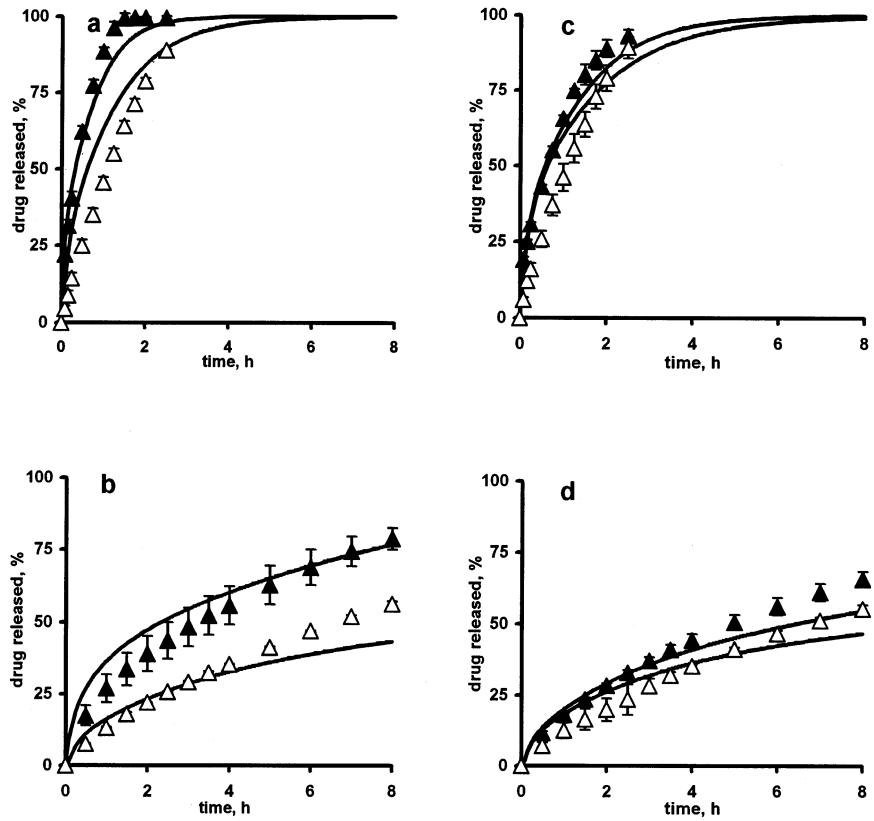

Fig. 8. Effect of the type of drug on the resulting release kinetics in, (a) 0.1 N HCl from matrices with $R_0 = 1.0$ mm and $Z_0 = 1.3$ mm; (b) 0.1 N HCl from matrices with $R_0 = 6.5$ mm and $Z_0 = 1.3$ mm; and (c) phosphate buffer pH 7.4 from matrices with $R_0 = 1.0$ mm and $Z_0 = 1.3$ mm; and (d) phosphate buffer pH 7.4 from matrices with $R_0 = 6.5$ mm and $Z_0 = 1.3$ mm (experimental data, ▲ chlorpheniramine maleate; Δ propranolol HCl; theoretical data, curves).

6.5 mm and $Z_0 = 1.3$ mm), respectively (Fig. 8). Chlorpheniramine maleate release is faster than propranolol HCl release, irrespective of the geometry of the system and of the type of release medium. This is probably due to the higher mobility and/or solubility of the chlorpheniramine maleate molecules within the swollen HPMC network, compared with propranolol HCl. The model takes this phenomenon adequately into account, using different β_2 and D_{2eq} values for chlorpheniramine maleate and propranolol HCl, respectively.

5. Conclusions

It has been shown that the previously presented mathematical model is capable of predicting the drug release kinetics from hydrophilic polymer matrices of various shapes and sizes, in different release media, and for different drugs. It can thus be used to calculate the required aspect ratio and dimensions of new controlled drug delivery systems to achieve desired release profiles, hence facilitating the development of new products.

6. Notation

A_t	surface area of the system at time t
C	concentration within the matrix
c_{eq}	concentration in the equilibrium swollen state
c_0	initial concentration of the drug within the matrix
c_{1sur}	water concentration at the surface of the system
D	diffusion coefficient
D_{eq}	diffusion coefficient in the fully swollen matrix
G	number of time intervals for numerical analysis
I	integer for numerical and residual analysis
I	number of space intervals along the radial axes for numerical analysis
J	integer for numerical analysis
J	number of space intervals along the axial axes for numerical analysis
K	subscript, indicating the diffusing species, $k=1$: water; $k=2$: drug
k_{diss}	polymer dissolution rate constant
M_{pt}	dry matrix mass at time t
N	integer
R	radial co-ordinate
Δr	space interval along the radial axes for numerical analysis
R^2	coefficient of determination
R_0	initial radius of the matrix
R_t	radius of the matrix at time t
t	time
Δt	time interval for numerical analysis
x	x co-ordinate of a series of n data points, for residual analysis
$y(x)_{arithm}$	arithmetic mean of the experimental y co-ordinates of a series of n data points, for residual analysis
$y(x)_{i,exp}$	ith experimental y co-ordinate of a series of n data points, for residual analysis
$y(x)_{i,theo}$	ith theoretical y co-ordinate of a series of n data points, for residual analysis
z	axial co-ordinate
Δz	space interval along the axial axes for numerical analysis
Z_0	initial half-height of the matrix
Z_t	half-height of the matrix at time t
β	constant, characterizing the dependence of the diffusion coefficient on the water concentration
θ	angle

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