

HPMC-Matrices for Controlled Drug Delivery: A New Model Combining Diffusion, Swelling, and Dissolution Mechanisms and Predicting the Release Kinetics

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Purpose. The purpose of this study was to investigate the drug release mechanisms from hydroxypropyl methylcellulose (HPMC)-matrices, and to develop a new model for quantitative predictions of controlled drug delivery.

Methods. The dissolved mass of pure HPMC-matrices and the drug release rate from propranolol HCl-loaded HPMC-matrices were determined experimentally. Based on Fick's second law of diffusion for cylinders, the transport of water and drug were modeled considering (i) both radial and axial diffusion, (ii) concentration-dependent drug diffusivities, (iii) matrix swelling and (iv) HPMC dissolution.

Results. Good agreement between theory and experiment (dissolved mass and drug release studies) was obtained, proving the validity of the presented model. The water and drug diffusivities are strongly dependent on the matrix swelling ratio. Diffusion, swelling and dissolution are the governing mechanisms involved in the overall drug release process.

Conclusions. The practical benefit of the presented model is to identify the required shape and dimensions of drug-loaded HPMC-matrices in order to achieve desired release profiles, thus facilitating the development of new controlled drug delivery products. This will be demonstrated in a future study.

KEY WORDS: controlled release; diffusion; hydroxypropyl methylcellulose (HPMC); modeling; polymer dissolution; swelling.

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ABBREVIATIONS: 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 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_{p0} , dry matrix mass at time $t = 0$; M_{pt} , dry matrix mass at time t ; r , radial coordinate; R^2 , correlation coefficient; R_0 , initial radius of the matrix; R_t , radius of the matrix at time t ; t , time; V_t , volume of the matrix at time t ; z , axial coordinate; 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.

INTRODUCTION

HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems (1). The transport phenomena involved in drug release from HPMC matrices are complex, because the micro- and macrostructure of HPMC exposed to water is strongly time-dependent. Upon contact with gastrointestinal fluid, HPMC swells significantly and finally dissolves. Numerous studies have been reported in the literature investigating the transport mechanisms and trying to predict the resulting drug release kinetics quantitatively.

Narasimhan and Peppas (2–4) developed mathematical models describing polymer dissolution quantitatively based on the theory of macromolecular disentanglement and chain reptation. They showed that the dissolution can be either disentanglement or diffusion controlled depending on the polymer molecular weight and the thickness of the diffusion boundary layer. Models for rubbery and glassy polymers were derived and the resulting dissolution kinetics and drug release rates were calculated.

Gao *et al.* (5–6) used a pulsed-field-gradient spin-echo NMR technique to determine the diffusivities in HPMC-gels. They found the drug and water diffusion coefficients to be exponentially dependent on the concentration of excipients, such as HPMC and lactose. These are excipients that are known as viscosity-inducing agents. In addition, they developed a novel optical imaging method to examine the dynamic swelling behavior of HPMC-based matrices *in situ*. The results show that the polymer concentration profiles and the gel layer thicknesses develop equally in both radial and axial directions, whereas the expansion of the matrix in the axial direction is more drastic than in the radial direction.

Pham and Lee (7) designed a new flow-through cell to provide well-defined hydrodynamic conditions during the experimental studies and to allow precise measurement of dissolution and swelling front positions versus time. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release were found to increase with either higher levels of drug loading or lower viscosity grades of HPMC. Rajabi-Siahboomi *et al.* (8) characterized the water mobility in the gel layer of hydrating HPMC matrices using NMR imaging. It has been shown that there is a diffusivity gradient across this layer and that it is affected by the degree of substitution of the polymer. Polymer concentration profiles within cylindrical HPMC matrices were also determined by Fyfe and Blazek (9) using NMR spectroscopy and NMR imaging techniques. Ju *et al.* (10–12) developed a comprehensive mathematical model distinguishing between the “macromolecular overlap concentration,” above which polymer chain entanglement starts, and the “polymer disentanglement concentration,” below which polymer chains detach from the matrix and diffuse through the diffusion layer into the bulk solution. It is expected that the “polymer disentanglement concentration” is greater than the “macromolecular overlap concentration” because the extent of chain entanglement at the “macromolecular overlap concentration” is almost zero since it is the on-set concentration for entanglement. The extent of chain entanglement at the “polymer disentanglement concentration” is much higher. In addition,

they proposed an equation to calculate the “polymer disentanglement concentration” for HPMC as a function of molecular weight.

However, most of the published models make important assumptions. For example, they neglect polymer swelling (13), neglect polymer dissolution (14), or they reduce the mathematical analysis to transport in only radial direction, ignoring axial transport (11). Yet, no model has been proposed that takes into account diffusion (concentration-dependent, in radial and axial directions, considering water and drug), swelling (three-dimensional, with subsequent volume, concentration, and matrix composition changes) and polymer dissolution simultaneously. It was the aim of this study to develop such a model to get further insight into the transport mechanisms and to accurately predict the resulting drug release kinetics from HPMC-matrices.

EXPERIMENTAL SECTION

Materials

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

Methods

Pure HPMC-tablets (200 mg, 13 mm diameter) were prepared by compressing the polymer powder manually (Specac Hydraulic Press P/N 25.011, Specac Limited, Kent, UK; compaction force = 50 kN, holding time = 15 s). Propranolol HCl-containing HPMC-matrices (5% w/w drug loading, 5 mm diameter) were prepared by compressing a homogeneous mixture of the drug and polymer powders using a tableting machine (Korsch, EK 0, Berlin, Germany).

The USP XXIII rotating paddle method [37°C, 50 rpm, 900 mL 0.1 M phosphate buffer (pH 7.4) USP XXIII] was used to study the dissolution of pure HPMC-tablets and the drug release from propranolol HCl-containing HPMC-matrices. At predetermined time intervals, pure HPMC-tablets were withdrawn from the medium and oven-dried at 105°C to constant mass. For the drug release studies, 2 mL samples (which were replaced with fresh medium) were withdrawn at predetermined time intervals, filtered and assayed spectrophotometrically ($\lambda = 290$ nm).

MATHEMATICAL ANALYSIS

Release Mechanism

The proposed new model takes into account a series of transport phenomena occurring during drug release.

(i) At the beginning of the release process, there are steep water concentration gradients at the polymer/water interface, resulting in water imbibition into the matrix. To describe this process adequately, it is important to consider (a) the cylindrical geometry of the device, (b) both axial and radial directions of the mass transport, and (c) the significant dependence of the water diffusivity on the matrix swelling ratio. In dry systems the diffusion coefficient is very low, whereas in highly swollen

gels it is of the same order of magnitude as in pure water (self-diffusion coefficient).

(ii) Due to the imbibition of water the polymer swells, resulting in dramatic changes of polymer and drug concentrations, increased dimensions of the system, and increasing macromolecular mobilities.

(iii) With increasing water content the drug diffusivity increases and the drug diffuses out of the device.

(iv) The polymer itself dissolves, resulting in time-variant matrix composition, matrix dimensions and diffusion pathways.

All these processes have to be taken into account simultaneously.

Model Assumptions

The new model is based on a series of assumptions:

(i) Matrix swelling is ideal throughout the device: The sum of the volumes of water, drug and polymer in the system are always equal to the total volume of the system; there is no volume contraction upon mixing.

(ii) Perfect sink conditions are maintained.

(iii) Water imbibing in axial/radial direction leads to a volume increase in axial/radial direction that is proportional to the relative surface area in this direction.

(iv) The concentration-dependence of the diffusivities of water and drug is time-invariant.

(v) The drug is dissolved instantaneously in the release medium. However, the model can be modified (considering the presence of solid and dissolved drug within the system) to be applicable to poorly water-soluble drugs, too.

Diffusion

The mathematical description of water and drug diffusion is based on Fick's second law for cylindrical devices, taking into account axial and radial mass transfer with concentration-dependent diffusivities (15):

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

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 [Fig. 1(a)], and t represents time.

As there is no concentration gradient of any component with respect to θ , this equation can be transformed into:

$$\frac{\partial c_k}{\partial t} = \frac{\partial}{\partial r} \left(D_k \frac{\partial c_k}{\partial r} \right) + \frac{D_k}{r} \frac{\partial c_k}{\partial r} + \frac{\partial}{\partial z} \left(D_k \frac{\partial c_k}{\partial z} \right) \quad (2)$$

According to the free volume theory of diffusion, a Fujita-type (16) exponential dependence of the diffusivities of water and drug, D_1 and D_2 , is considered:

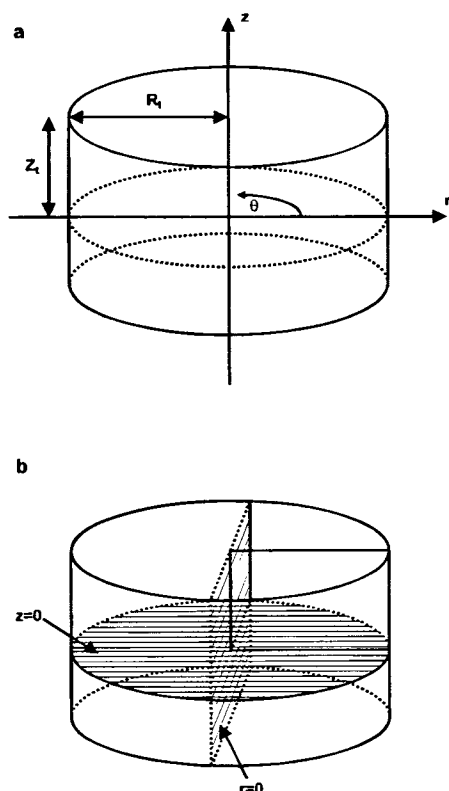


Fig. 1. (a) Schematic of the matrix for mathematical analysis, with (b) symmetry planes in axial and radial directions for the water and drug concentration profiles.

$$D_1 = D_{1cq} \exp\left(-\beta_1\left(1 - \frac{c_1}{c_{1cq}}\right)\right) \quad (3)$$

$$D_2 = D_{2cq} \exp\left(-\beta_2\left(1 - \frac{c_1}{c_{1cq}}\right)\right) \quad (4)$$

where β_1 and β_2 are dimensionless constants, characterizing this concentration-dependence. Also c_{1cq} denotes the water concentration, D_{1cq} and D_{2cq} the respective diffusion coefficients of water and drug in the equilibrium swollen state of the system (17). As previously described (17) the constants β_1 , β_2 , D_{1cq} and D_{2cq} have been determined by fitting a simplified theory (neglecting polymer dissolution) to adequate experimental data. It is reasonable to assume that the concentration-dependence of the diffusivities of the two species on the water content of the system is time-invariant.

Swelling

The two major impacts of polymer swelling due to water imbibition are considered in the new model: (i) significant changes in the volume of the system, resulting in dramatic changes of the concentrations of all species, and (ii) increasing mobility of the macromolecules, leading to increasing diffusivities of water and drug [Eqs. (3) and (4)]. Swelling is considered in axial and radial directions and is assumed to be ideal.

The total volume of the matrix at any instant is given by the sum of the volumes of polymer, water and drug. The calculation of the new matrix dimensions is based on a mass

balance considering all system components: polymer, water and drug. It is assumed that water imbibing in axial direction leads to a volume increase in axial direction, whereas water imbibing in radial direction leads to a volume increase in radial direction, and that the resulting increase in volume in each direction is proportional to the surface area in this direction. Based on these assumptions, the time-dependent radius and height of the matrix are calculated. Furthermore, the decrease in matrix volume (and thus decrease in radius and height) due to drug loss into the bulk fluid is considered.

Polymer Dissolution

Polymer dissolution is considered based on the reptation theory (2–3) in the new model. The initially dry HPMC-matrix is a non-swollen system of entangled macromolecules (Fig. 2). Upon water imbibition the polymer swells, resulting in decreasing polymer concentrations and increasing macromolecule mobilities. On a molecular level, the snake-like motion of the polymer chains (reptation) permanently changes the structure of the network. Entangled chains can either disentangle or modify their entanglement configuration, and disentangled chains can entangle. At high and moderate polymer concentrations, the resulting macrostructure of the system is approximately time-invariant. However, below a certain polymer concentration, the number of disentangling polymer chains exceeds the number of newly entangled macromolecules, resulting in a destruction of the HPMC network. Figure 2 illustrates these processes. Once the macromolecules are disentangled, they diffuse through the unstirred layer surrounding the device, which is characterized by a distinct polymer concentration gradient. Then, convection leads to a homogeneous distribution of the polymer chains within the bulk fluid.

There are numerous mathematical models trying to quantify the process of polymer dissolution (2–3, 10–13). Even for the system water and HPMC there exists a number of proposed models (10–13). Most of them neglect the convective transport within the well stirred medium. As all the above described processes take place sequentially, the slowest ones determine the overall dissolution rate, and the fast ones are negligible. Usually, the velocities of convective mass transfer processes in well stirred media are much higher than the velocities of diffusional processes. Thus, it is reasonable to neglect the convective transfer to simplify the mathematical treatment.

The most controversially discussed question in the literature is whether the chain disentanglement or the diffusion of the disentangled macromolecules through the unstirred layer, or both processes determine the overall dissolution kinetics (2, 11–12). To prove one of these theories, accurate experimental data concerning the kinetics of chain reptation and macromolecule diffusion are required. These data are very difficult to obtain (12).

The presented new model does not require this type of knowledge. It is applicable in any case. If polymer chain disentanglement is the dominant process and if perfect sink conditions are maintained, the number of macromolecules leaving the network (normalized to the surface area) is constant. Thus, the dissolution kinetics are determined by a characteristic “disentanglement time,” which can reasonably be assumed to be time-invariant. If the diffusion of the macromolecules through the unstirred layer is the dominant step and if perfect sink

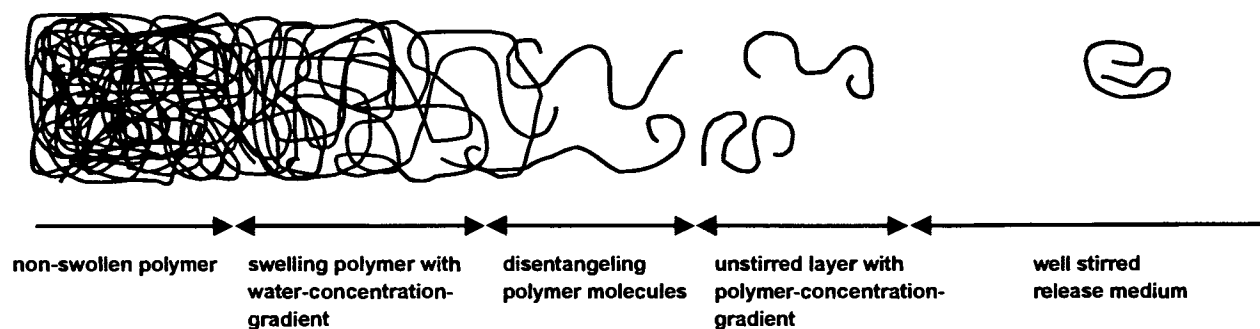


Fig. 2. Schematic of the processes involved during polymer dissolution.

conditions are maintained, the overall dissolution velocity is determined by the diffusivity of the macromolecules, the concentration gradient within the unstirred layer, the thickness and surface of the latter. The diffusivity of the macromolecules strongly depends on the polymer concentration, which is non-constant within the unstirred layer. However, upon exposure to the bulk fluid this concentration gradient will soon be linear (steady state), and the overall dissolution velocity per surface area can be characterized by a single constant. Even if the velocities of both processes are of the same order of magnitude, a constant dissolution velocity per surface area results.

The new model considers a dissolution rate constant, k_{diss} , that characterizes this velocity per surface area quantitatively:

$$M_{pt} = M_{p0} - k_{diss} \cdot A_t \cdot t \quad (5)$$

Here, M_{pt} and M_{p0} are the dry matrix mass at time t , and $t = 0$, respectively, A_t denotes the surface area of the system at time t . The dissolution rate constant, k_{diss} , is determined by fitting the new model to experimental data (dry matrix mass versus time, one-parameter-fit).

Initial and Boundary Conditions

A schematic of the matrix for mathematical analysis is given in Figs. 1(a) and (b). 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:

$$t = 0 \quad c_1 = 0 \quad 0 \leq r \leq R_0 \quad 0 \leq z \leq Z_0 \quad (6)$$

$$t = 0 \quad c_2 = c_0 \quad 0 \leq r \leq R_0 \quad 0 \leq z \leq Z_0 \quad (7)$$

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

According to the theory of polymer dissolution (2–4, 10–12), the water concentration at the surface of the matrix, c_{1sur} , can be calculated from the polymer disentanglement concentration. Thus, the corresponding boundary conditions can be written as follows:

$$t > 0 \quad c_1 = c_{1sur} \quad 0 \leq r \leq R_t \quad z = Z_t \quad (8)$$

$$t > 0 \quad c_1 = c_{1sur} \quad 0 \leq z \leq Z_t \quad r = R_t \quad (9)$$

Here, R_t and Z_t represent the time-dependent radius and half-height of the matrix. The drug concentration at the surface of the matrix is assumed to be equal to zero (perfect sink condition):

$$t > 0 \quad c_2 = 0 \quad 0 \leq r \leq R_t \quad z = Z_t \quad (10)$$

$$t > 0 \quad c_2 = 0 \quad 0 \leq z \leq Z_t \quad r = R_t \quad (11)$$

To minimize computation time, the origin of the coordinate system is placed at the center of the matrix [Fig. 1(a)]. As can be seen in Fig. 1(b), there are two symmetry planes for the drug and water concentration profiles. Thus, only the concentration profiles within a quarter of the cylindrical matrix have to be calculated. The equations describing this phenomenon are given by the following boundary conditions:

$$t > 0 \quad \frac{\partial c_1}{\partial z} = 0 \quad 0 \leq r \leq R_t \quad z = 0 \quad (12)$$

$$t > 0 \quad \frac{\partial c_1}{\partial r} = 0 \quad 0 \leq z \leq Z_t \quad r = 0 \quad (13)$$

$$t > 0 \quad \frac{\partial c_2}{\partial z} = 0 \quad 0 \leq r \leq R_t \quad z = 0 \quad (14)$$

$$t > 0 \quad \frac{\partial c_2}{\partial r} = 0 \quad 0 \leq z \leq Z_t \quad r = 0 \quad (15)$$

Owing to the concentration dependence of the diffusion coefficients, the described 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. 2 to 4 and Eqs. 8 to 15, 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 ($i = 0 \vee i = I \vee j = 0 \vee j = J$) for the new time step ($t = t_0 + \Delta t$) are calculated using the boundary conditions (Eqs. 8 to 15). At time $t = 0$ the concentration profile of the drug and water are given by the initial conditions (Eqs. 6 and 7). Hence, the concentration profiles at $t = 0 + \Delta t, t = 0 + 2 \Delta t, t = 0 + 3 \Delta t, \dots, t = 0 + g \Delta t$ 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 ideal swelling and considering polymer dissolution (Eq. 5), 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 axial direction leads to a volume increase in axial direction, whereas water imbibing in radial direction leads to a volume increase in radial direction. The increase in volume in each direction is proportional to the surface area in this direction.

For the implementation of the mathematical model the programming language C++ was used (Borland C++ V.5.0 Developer).

RESULTS AND DISCUSSION

Polymer Dissolution

The experimentally determined dry tablet mass of pure HPMC-cylinders ($R_0 = 0.65$ cm, $Z_0 = 0.07$ cm) exposed to phosphate buffer (pH 7.4), is shown in Fig. 3 (a) for early

times. Interestingly, the relative mass loss of the investigated system does not exceed 8% during the first 8 h.

Figure 3 (a) also shows the fit of the new model to these data. There is good agreement between theory and experiment (correlation coefficient = $R^2 = 0.98$). Thus, HPMC dissolution kinetics can be accurately characterized using a single rate constant [$k_{\text{diss}} = 5.5 \cdot 10^{-5}$ mg/(s·cm²)] was obtained for phosphate buffer (pH 7.4)] and taking into account the changing surface area of the device (which is calculated at each time step, based on the new radius and half-height of the tablet).

The HPMC dissolution rate depends on the matrix shape and dimensions (determining the surface area of the device) and on the dissolution rate constant, k_{diss} . As indicated by Narasimhan and Peppas (2-4), the latter is a function of the type of dissolution medium and polymer. For example, for HPMC the most important features are the molecular weight and the type of substitution of the macromolecules.

Several different HPMC products are commercially available, differing in the degree of methyl-, and hydroxypropyl-methyl-substitution, and in the average chain length of the polymer. It is well known that the polymer dissolution velocity increases with decreasing chain length (18), probably due to

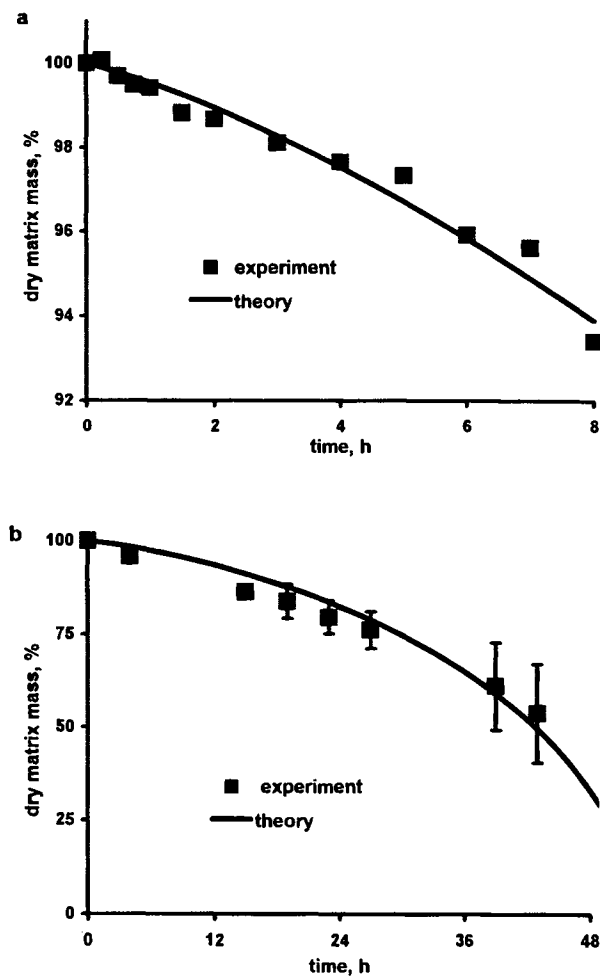


Fig. 3. Dry mass of pure HPMC-matrices [$R_0 = 0.65$ cm, $Z_0 = 0.07$ cm, $k_{\text{diss}} = 5.5 \cdot 10^{-5}$ mg/(s·cm²)] in phosphate buffer (pH 7.4) versus time: (a) fit of the new model to short-term experimental data, (b) prediction and experimental verification of long-term data.

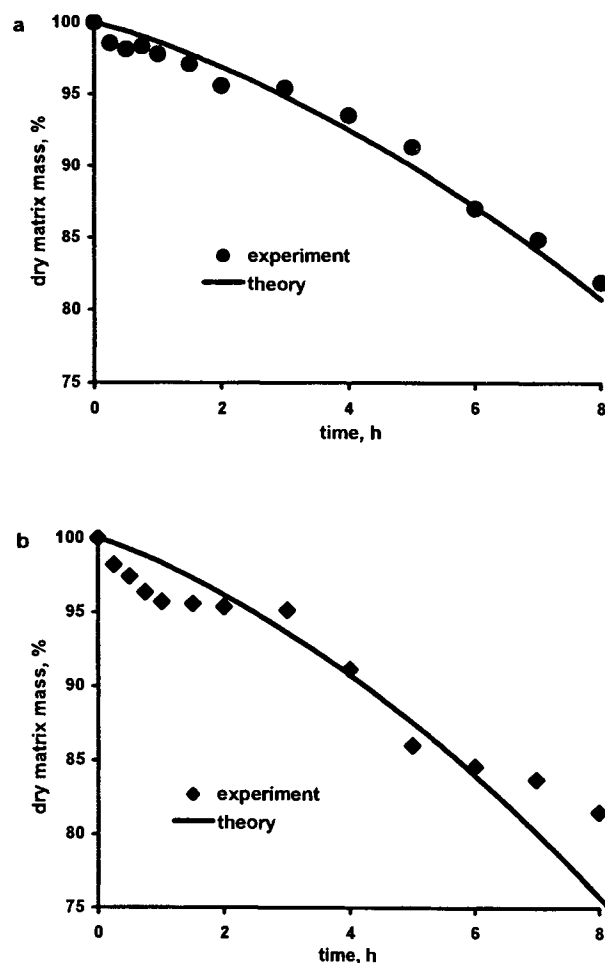


Fig. 4. Fit of the new model to the experimentally determined dry mass of pure HPMC-matrices ($R_0 = 0.65$ cm, $Z_0 = 0.07$ cm) in (a) deionized water [$k_{\text{diss}} = 1.6 \cdot 10^{-4}$ mg/(s·cm²)] and (b) 0.1 N HCl [$k_{\text{diss}} = 2.0 \cdot 10^{-4}$ mg/(s·cm²)].

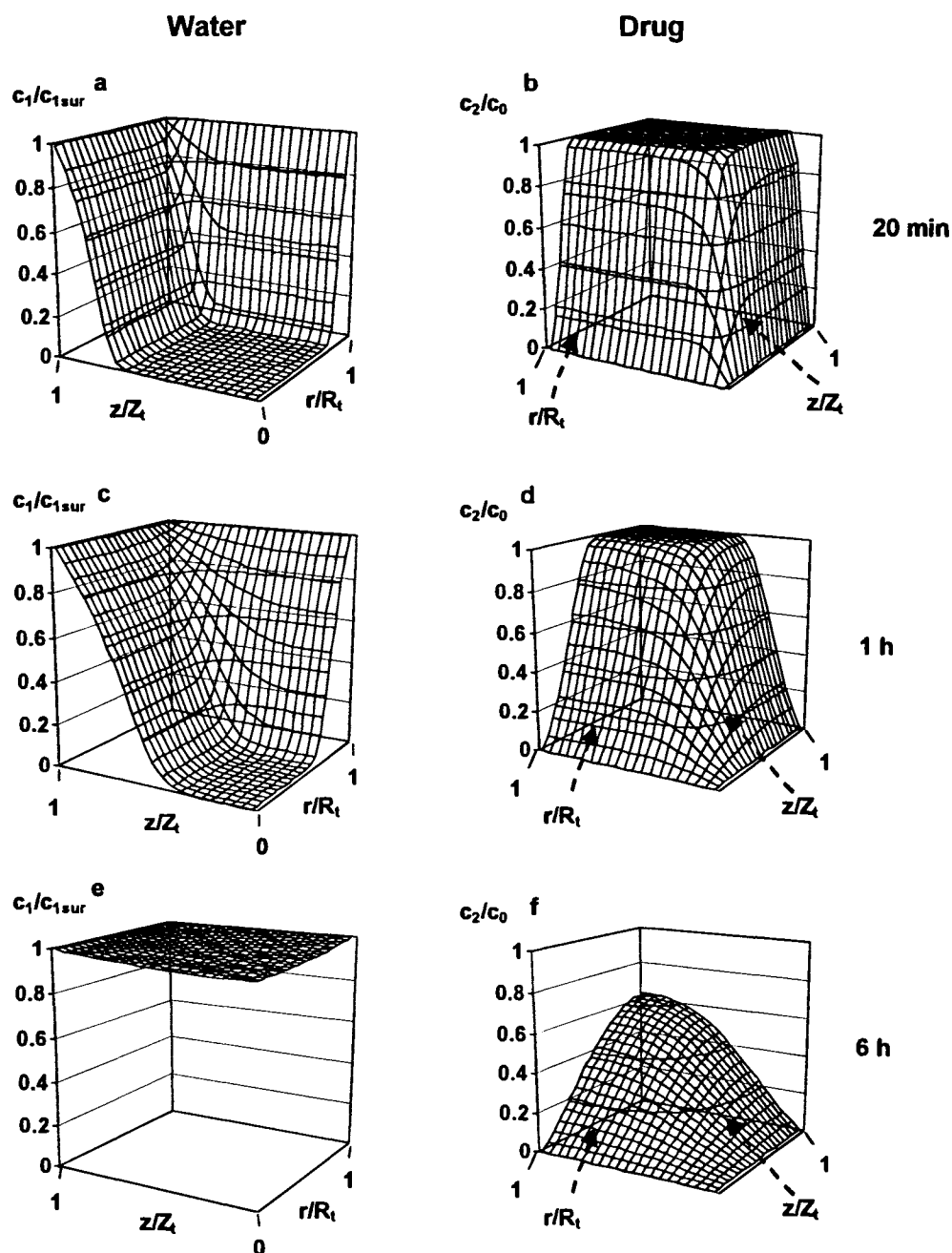


Fig. 5. Concentration profiles (calculated) of water (a, c, and e) and propranolol HCl (b, d, and f) within the HPMC-matrices at different times [$R_0 = 0.25$ cm, $Z_0 = 0.07$ cm, release medium: phosphate buffer (pH 7.4)].

shorter disentanglement times and/or higher diffusion coefficients within the unstirred layer. This is of great practical importance because for these systems the polymer dissolution must be considered in the mathematical model predicting the drug release kinetics. The presented model is valid for all (fast and slowly dissolving) types of HPMC.

Figure 3 (b) demonstrates its predictive power concerning the dissolved polymer mass versus time. The dissolution rate constant, k_{diss} , determined from the fit to early time points [Fig. 3 (a), $k_{\text{diss}} = 5.5 \cdot 10^{-5}$ mg/(s \cdot cm 2)], was used to calculate

the dry mass of pure HPMC-cylinders ($R_0 = 0.65$ cm, $Z_0 = 0.07$ cm), exposed to phosphate buffer (pH 7.4) for a prolonged period of time. Then, the dry tablet mass was also determined experimentally and the results were compared to the theoretical predictions [Fig. 3 (b), error bars indicate ± 1 standard deviation, $n = 3$]. Rather good agreement was obtained ($R^2 = 0.96$), proving the validity of the presented model.

In addition, the influence of the type of release medium on the HPMC dissolution rate constant was investigated. Figures 4 (a) and (b) show the experimentally determined and calculated

dry mass of pure HPMC-tablets ($R_0 = 0.65$ cm, $Z_0 = 0.07$ cm) exposed to deionized water and 0.1 N HCl, respectively. The agreement between theory and experiment is good ($R^2 = 0.97$ for water) and acceptable ($R^2 = 0.87$ for 0.1 N HCl), respectively. The following polymer dissolution rate constants were obtained: k_{diss} (water) = $1.6 \cdot 10^{-4}$ mg/(s · cm²), and k_{diss} (0.1 N HCl) = $2.0 \cdot 10^{-4}$ mg/(s · cm²). Thus, HPMC dissolution is significantly faster in these two media compared to phosphate buffer (pH 7.4), and needs to be taken into account in a predictive model even for these tablet dimensions. The reason for this phenomenon is probably based on osmotic, solubility and/or charge effects. A detailed analysis of this behavior will be presented in the future. However, the new model considers the influence of all these aspects by using the experimentally determined polymer dissolution rate constant, k_{diss} .

Water and Drug Diffusion

When analyzing drug delivery from HPMC tablets, the water, HPMC and drug transport kinetics can be predicted for any matrix of any dimension, once the required parameters are independently available. Figures 5 (a) to (f) show the calculated water and drug concentration profiles within propranolol HCl-containing HPMC-matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) exposed to phosphate buffer (pH 7.4), at 20 min, 1 h, and 6 h, respectively. For reasons of simplicity, the water and drug concentrations are normalized to the water concentration at the surface of the system, $c_{1,\text{surf}}$, and to the initial drug concentration within the matrix, c_0 , respectively.

Rather steep water and drug concentration gradients are calculated at the beginning of the process. These high driving forces for diffusion lead to a fast water uptake and drug release, which is in good agreement with the calculated transport kinetics, illustrated in Figures 7 and 8. Snaar *et al.* (19) used NMR microscopy to determine the water concentration profiles in poly(vinyl alcohol) tablets experimentally. They also found significant water concentration gradients within the systems at early times. Interestingly, even after 1 h the model predicts the center of the matrix to be still dry, which is in good agreement with visual observations. After 6 h the calculated water concentration gradients become less steep. This leads to a decrease in the water uptake rate and volume expansion of the system, which is also in good agreement with the calculated swelling kinetics and system composition, illustrated in Figures 6 and 7. Although the predicted water uptake is almost complete at this time, there is still a significant amount of drug located within the system. This prediction was confirmed by independent experiments (Fig. 8). The drug release rate is much lower than at the beginning of the process, due to the decreased concentration gradients, although the diffusivity of the drug is much higher, due to the higher water content of the system. In conclusion, the decrease in driving force overcompensates the increase in mobility.

Swelling

The relative increase in volume, half-height and radius of cylindrical, propranolol HCl-containing HPMC-matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) exposed to phosphate buffer (pH 7.4) are shown in Figure 6, normalized to their initial values. Significant changes of the matrix dimensions are predicted.

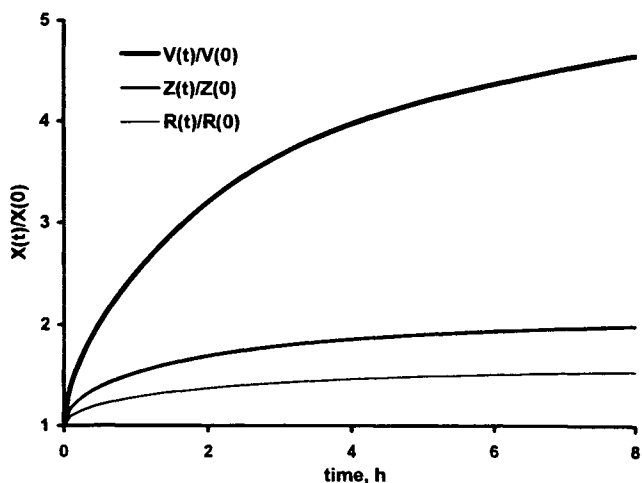


Fig. 6. Swelling kinetics (calculated) of propranolol HCl-containing HPMC-matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) exposed to phosphate buffer (pH 7.4): increase in volume (V), half-height (Z) and radius (R).

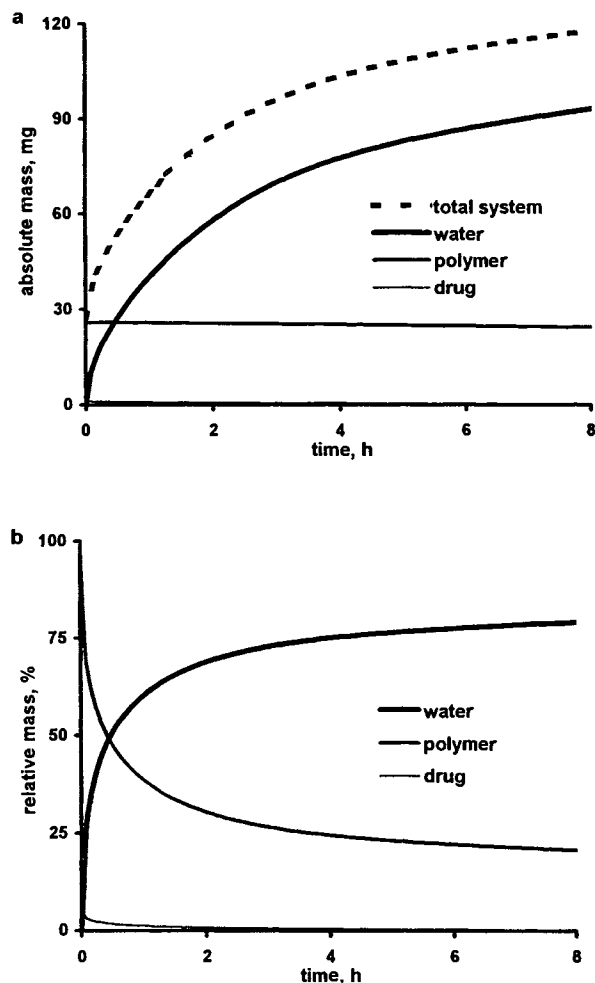


Fig. 7. Composition of propranolol HCl-containing HPMC matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) versus time (calculated): (a) absolute mass of the total system, water, polymer and drug, and (b) relative mass of water, polymer and drug [release medium: phosphate buffer (pH 7.4)].

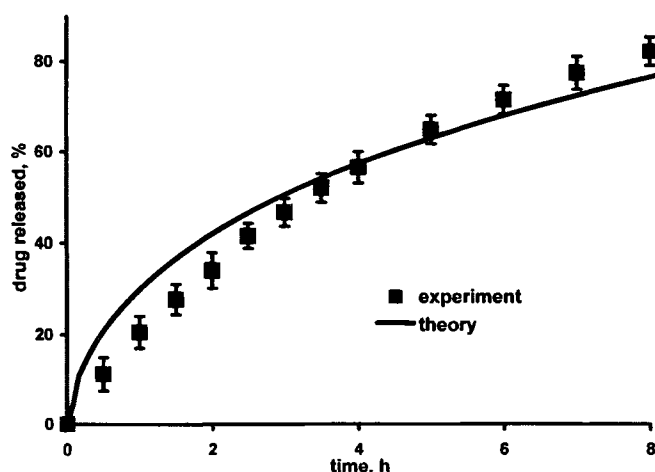


Fig. 8. Validity of the model: predicted and experimentally determined relative amount of propranolol HCl released from HPMC-matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) versus time [release medium: phosphate buffer (pH 7.4)].

Due to imbibing water, the radius and half-height of the system monotonically increase, resulting in a dramatic volume expansion of the system. As reported in the literature (6), the swelling of cylindrical HPMC-matrices in axial direction is much higher than in radial direction. This is in good agreement with the calculated swelling kinetics using the new model. In addition, the predicted 4-fold increase in volume within the first 8 h is in good agreement with data reported in the literature (6).

Matrix Composition

Due to the significant swelling of the system, the composition of the matrix changes dramatically with time [Figs. 7 (a) and (b)]. The absolute and relative mass of the system components have been calculated using the new model for propranolol HCl-containing matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) in phosphate buffer (pH 7.4). Within the first 8 h the absolute amount of polymer is about constant, but the relative amount significantly decreases, simply due to the high amount of imbibing water. The absolute amount of water taken up in this time period exceeds the 3-fold of the absolute initial mass of the total system.

It is obvious that the matrix composition dramatically changes with time, resulting in strongly time-dependent conditions for the occurring mass transport processes. Thus, it is very important to consider this feature in the mathematical model.

Practical Importance

The practical benefit of the presented model is to simulate the effect of the matrix design (initial radius and height) on the resulting drug release kinetics with a computer. Thus, it can be used to identify the required shape and dimensions of new controlled drug delivery systems to achieve desired release profiles.

To prove the predictive power of the presented model, it was used to calculate the resulting propranolol HCl release rate from cylindrical HPMC-matrices ($R_0 = 0.25$ cm, $Z_0 = 0.07$ cm) in phosphate buffer (pH 7.4) (Fig. 8). According to these predictions, almost 80% of the drug is to be released within

the first 8 h. Then, independent experiments were conducted and the results were compared to the theory (Fig. 8, error bars indicate ± 1 standard deviation, $n = 3$). The agreement between prediction and experiment is rather good ($R^2 = 0.93$). The deviation at the beginning of the process might be attributed to partial matrix sticking to the glass-vessel or floating of the systems, resulting in a decreased surface area exposed to the bulk fluid and thus decreased release rates. Theoretically, 99% of the drug is released within the first 18.5 h. Experimentally, a 24 h-value was determined, which confirmed complete drug release.

These simulations and the identification of the required shape and dimensions of drug-containing HPMC-matrices to achieve desired release profiles will be investigated in more detail in a future study.

CONCLUSIONS

The presented model gives further insight into the release mechanisms of drug-loaded HPMC-matrices and can be used to predict the required shape and dimensions of controlled drug delivery systems to achieve desired release profiles. Thus, the development of new products can be significantly facilitated.

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