A New Model Describing the Swelling and Drug Release Kinetics from Hydroxypropyl Methylcellulose Tablets

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Abstract □ A novel mathematical model for the water transport into and drug release from hydroxypropyl methylcellulose (HPMC) tablets is presented. Fick's second law of diffusion is used to describe the mass transfer processes in the three-component system drug/polymer/water. Numerical solutions of the respective set of partial differential equations are provided, considering axial and radial diffusion within cylindrical tablets. It is shown that the diffusion coefficients strongly depend on the water concentration (parameters quantifying this dependence have been determined). Swelling of the device is considered using moving boundary conditions, whereas dissolution processes are neglected. Experiments proved the applicability of the theory. The practical benefit of the new model is to calculate the required shape and dimensions of HPMC tablets to achieve a desired release profile.

Introduction

Hydroxypropyl methylcellulose (HPMC) is the dominant hydrophilic carrier material used for the preparation of oral controlled drug delivery systems.[1] One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of a drug. Upon contact with a dissolution medium, water or biological fluid diffuses into the tablet, resulting in polymer chain relaxation with volume expansion. Then, the drug diffuses out of the device.

Numerous studies have been reported in the literature to investigate the drug release kinetics from HPMC tablets.[2−4] The modification of the surface area of HPMC tablets in order to achieve a desirable release rate has been studied by Colombo et al.[5,6] Various techniques have been used to elucidate the physical processes involved in the release of drugs from HPMC tablets. For example, pulsed-field-gradient spin−echo NMR methods have been employed to measure the diffusivities of water and drugs in HPMC gels.[7] Recently, Fyfe and Blazek[8] investigated the hydrogel formation by NMR spectroscopy and NMR imaging techniques.

Yet, up to now there has not been any complete mathematical model that takes into account all the important phenomena occurring during drug release. Various simplifications have been made, e.g., neglect of the swelling process,[9] or assumption of constant diffusion coefficients.[11] Fu et al.[12] derived an analytical solution of Fick's second law, using cylindrical coordinates. The model is applicable to tablets that range from the shape of a flat disk (radius ≫ thickness) to that of a cylindrical rod (radius ≪ thickness), but they did not consider the volume expansion of the system and assumed constant diffusion coefficients.

A model for the prediction of the relative change in drug release rate as a function of formulation composition for HPMC tablets of adinazolam mesylate and alprazolam has been developed by Gao et al.[9] It is based on the equation derived by Higuchi[10] for the diffusional release of soluble drugs from polymeric matrixes, considering concentration dependent diffusivities. The swelling of the system is not taken into account, and the mathematical analysis reduced to one dimension. Cohen and Erneux[13,14] used free boundary problems to model swelling controlled release. Drug release is achieved by countercurrent diffusion through a penetrant solvent with the release rate being determined by the rate of diffusion of the solvent in the polymer.

Korsmeyer et al.[15] developed a model describing the diffusion of a penetrant and a solute in a swellable polymer slab and verified the model experimentally.[16] Concentration dependent diffusivities and dimensional changes in the system have been considered, but these theories[13−16] have been developed for thin films, not for cylindrical tablets.

The purpose of this study was to develop a new, physically realistic mathematical model, taking into account all the important processes including Fickian diffusion of water into and drug out of cylindrical tablets (in axial and radial direction, with concentration dependent diffusivities), as well as swelling. The model does not take into account dissolution processes. Thus, it is not valid for water-insoluble drugs whose release is governed by dissolution rather than by diffusion. To test the applicability of the new model, experiments were conducted with various drugs (chlorpheniramine maleate, diclofenac sodium, and propranolol hydrochloride) in different release media (0.1 M HCl, 0.1 M phosphate buffer (pH 7.4), and deionized water). The practical benefit of the new model is to optimize the shape and dimensions of HPMC tablets to achieve a desired release profile. For instance, the effect of the aspect ratio (radius/height) and size of the system on the release kinetics of a drug has been simulated.

Experimental Section

Materials—The following chemicals were obtained from commercial suppliers and used as received: chlorpheniramine maleate (Sigma Chemical Co., St. Louis, MO), diclofenac sodium (Lederle Arzneimittel GmbH, Wolfratshausen, Germany), propranolol hydrochloride (Sigma Chemical Co., St. Louis, MO), hydroxypropyl methylcellulose (Methocel K15M Premium Grade) (Colorcon, Nordmann Rassmann GmbH & Co., Hamburg, Germany).

Methods—The drug (20 mg) and HPMC were blended with a pestle in a porcelain mortar by geometric dilution. Tablets (200 mg, 13 mm diameter) were prepared by compressing the powder blend manually (Specac Hydraulic Press P/N 25.011, Specac Limited, Kent, UK; compaction force = 5 t, holding time = 15 s).

The USP XXIII rotating paddle method (37 °C, 50 rpm, 900 mL of deionized water, 0.1 M HCl or 0.1 M phosphate buffer (pH 7.4) USP XXIII) was used to study the drug release. The samples (2 mL, replaced with fresh medium) were withdrawn at predeter-

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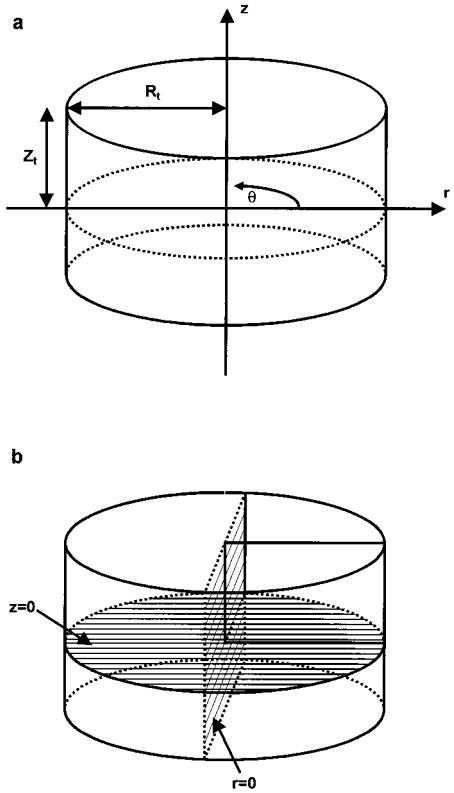

Figure 1—(a) Schematic of the tablet for mathematical analysis, with (b) symmetry planes in the axial and radial directions for the water and drug concentration profiles.

mined time intervals, filtered, and assayed spectrophotometrically (chlorpheniramine maleate, $\lambda = 264$ nm; diclofenac sodium, $\lambda = 276$ nm; propranolol hydrochloride, $\lambda = 290$ nm). All experiments have been conducted in triplicate.

Mathematical Modeling

A new model has been developed to describe water and drug transport in HPMC tablets. The following assumptions have been made: (i) Dissolution processes are neglected. (ii) Swelling is ideal, isotropic, and homogeneous throughout the device (including water-poor regions). The error resulting from this approximation only becomes significant in the case of extreme aspect ratios. The experimental results presented in this study and further results to be presented in a future paper prove the validity of this assumption for pharmaceutically common aspect ratios. (iii) The water concentration at the surface of the tablet is at its equilibrium value. (iv) Perfect sink conditions are maintained. (v) 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.

The mass transfer processes are based on Fick's second law of diffusion in cylindrical coordinates:[17]

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

Here, c_k and D_k are the concentration and diffusion coefficient of the diffusing species ($k = 1$: water; $k = 2$: drug), respectively, and r denotes the radial coordinate, z the axial coordinate, θ the angle perpendicular to both axis, and t represents time. As there is no concentration gradient of any component with respect to θ [Figure 1a], this equation can be transformed into:

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

Two important features of diffusion in swellable polymer systems are considered in this mathematical model: (i) strong concentration dependence of diffusivities and (ii) volume changes due to water imbibition and drug release.

According to the free volume theory, a Fujita-type[18] exponential dependence of the diffusion coefficients for water and drug, D_1 and D_2, can be written as:

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

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

where β_1 and β_2 are dimensionless constants, characterizing this concentration dependence. Also c_{1eq} (762 mg/mL[20]) denotes the water concentration and D_{1eq} and D_{2eq} the respective diffusion coefficients of water and drug in the equilibrium swollen state of the system.

A schematic of the tablet for mathematical analysis is given in Figure 1, parts a and b. The tablet is allowed to swell in both axial and radial direction. The swelling is assumed to be ideal. Hence, the total volume of the tablet at any instant is given by the sum of the volumes of polymer, water, and drug. At $t = 0$ the tablet is dry and thus the water concentration at any position is equal to zero. The drug concentration within the tablet is uniform and equal to its initial concentration, c_{in}. This can be written for water as:

$$t = 0 \qquad c_1 = 0 \qquad 0 \le r \le R_0 \qquad 0 \le z \le Z_0 \qquad (5)$$

and for drug as:

$$t = 0 \qquad c_2 = c_{in} \qquad 0 \le r \le R_0 \qquad 0 \le z \le Z_0 \qquad (6)$$

where R_0 is the initial radius of the tablet, and Z_0 denotes the initial half-thickness of the cylindrical tablet.

At the surface of the tablet, the concentration of water is assumed to be at its equilibrium value, c_{1eq}, for $t > 0$. The respective boundary conditions are written as follows:

$$t > 0 \qquad c_1 = c_{1eq} \qquad 0 \le r \le R_t \qquad z = Z_t \qquad (7)$$

and

$$t > 0 \qquad c_1 = c_{1eq} \qquad 0 \le z \le Z_t \qquad r = R_t \qquad (8)$$

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

$$t > 0 \qquad c_2 = 0 \qquad 0 \le r \le R_t \qquad z = Z_t \qquad (9)$$

$$t > 0 \qquad c_2 = 0 \qquad 0 \le z \le Z_t \qquad r = R_t \qquad (10)$$

To minimize computation time, the origin of the coordinate system is placed at the center of the tablet (Figure 1a). As can be seen in Figure 1b, there are two symmetry planes for the drug and water concentration profiles. Thus, only the concentration profiles within a quarter of the cylindrical tablet have to be calculated. The mathematical treatment of this phenomenon is given by the following

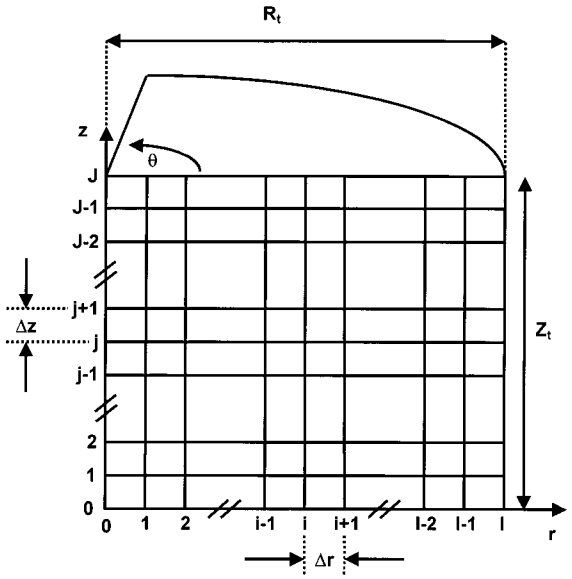

Figure 2—Schematic of the tablet for numerical analysis.

boundary conditions:

$$t > 0 \qquad \frac{\partial c_1}{\partial z} = 0 \qquad 0 \le r \le R_t \qquad z = 0 \qquad (11)$$

$$t > 0 \qquad \frac{\partial c_1}{\partial r} = 0 \qquad 0 \le z \le Z_t \qquad r = 0 \qquad (12)$$

for water, and

$$t > 0 \qquad \frac{\partial c_2}{\partial z} = 0 \qquad 0 \le r \le R_t \qquad z = 0 \qquad (13)$$

$$t > 0 \qquad \frac{\partial c_2}{\partial r} = 0 \qquad 0 \le z \le Z_t \qquad r = 0 \qquad (14)$$

for the drug.

Due to the concentration dependence of the diffusion coefficients, there is no analytical solution of this set of partial differential equations (eqs 2−14). Thus, they were solved numerically, using finite differences.

The principle of this method is illustrated in Figures 2 and 3. The time dependent radius, R_t, and half-height, Z_t, of the cylindrical tablets 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 $g = 500000$). Using eqs 2−4 and eqs 7−14, 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 7−14). At time $t = 0$ the concentration profile of the drug and water are given by the initial conditions (eqs 5 and 6). 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 and drug within the system is calculated at each time step (by integrating the respective concentrations with respect to r, z, and θ).

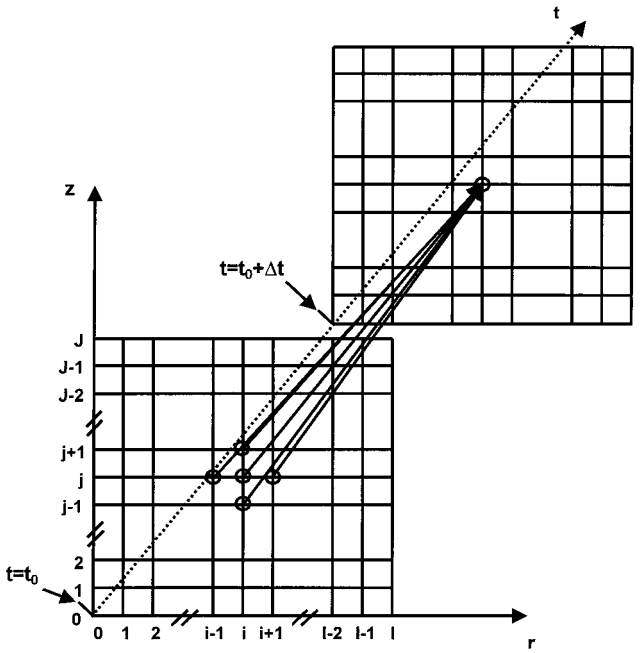

Figure 3—Principle of the numerical analysis: calculation of the concentration profile of a diffusing species at a new time step from the concentration profile at the previous time step.

Then, assuming ideal swelling, 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.

There are four unknown parameters in the presented model which have to be determined: β_1, β_2, D_{1eq}, and D_{2eq}. The constants β_1 and D_{1eq} are obtained by fitting eqs 2, 3, 5, 7, 8, 11, and 12 to experimental water uptake data of drug-free tablets ($c_{in} = 0$, thus, values for β_2 and D_{2eq} are not required) (least-squares method, combined with the Nelder−Mead method,[19] two-parameter fit), whereas the values for β_2 and D_{2eq} are subsequently determined by fitting the model (eqs 2−14) to experimental drug release data (two-parameter fit).

Results and Discussion

Water Uptake—Data for water uptake studies in HPMC were reported by Tahara.[20] Figure 4 shows the fit of the new model (to determine β_1 and D_{1eq}) to the experimentally determined relative amount of water taken up by HPMC tablets versus time. There is good agreement between theory and experiment (correlation coefficient = R^2 = 0.994). Thus, diffusion governs the water uptake into HPMC tablets. It was found that the diffusion coefficient of the diffusing species significantly depends on the water content of the system. The explanation for this phenomenon is based on the fact that the mobility of the polymer chains strongly depends on the water content of the tablet. Hence, the free volume available for diffusion is a function of the water concentration, resulting in concentration dependent diffusivities. The constant that characterizes this dependence, β_k, is specific for the diffusing molecules. For water, a value of $\beta_1 = 2.5$ was calculated. In addition, the diffusion coefficient of water within the fully swollen tablet was determined as $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s.

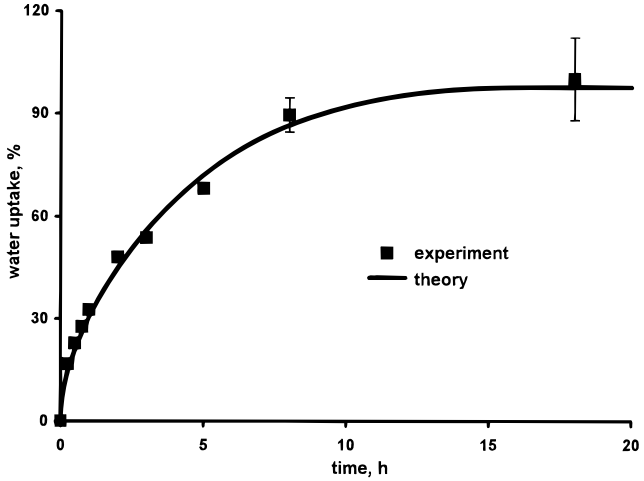

Figure 4—Fit of the model to the experimentally determined water uptake data.[20]

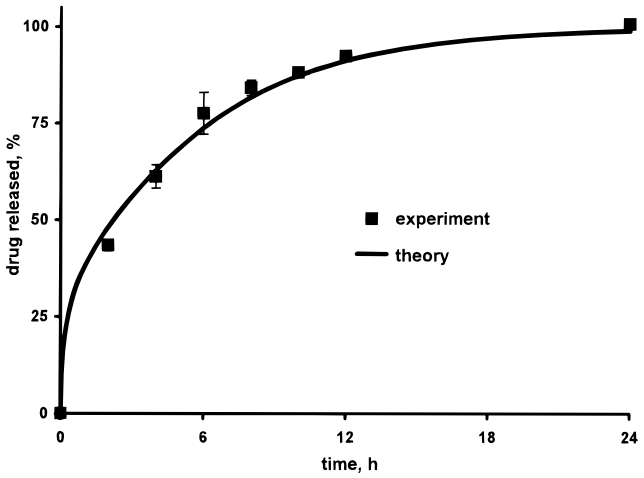

Figure 5—Fit of the model to the experimentally determined amount of propranolol hydrochloride released [release medium: phosphate buffer (pH 7.4)].

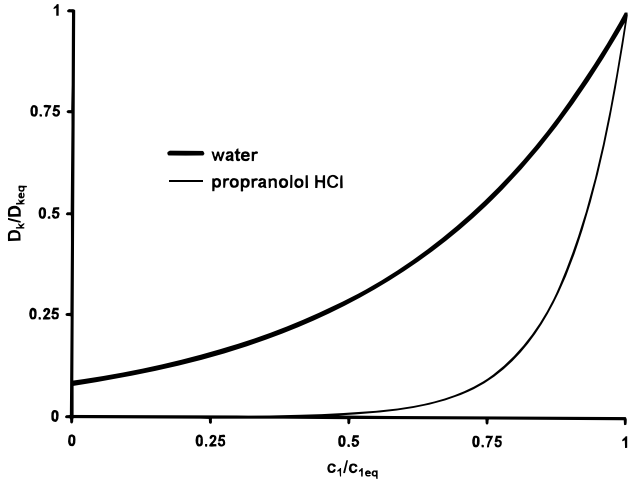

Figure 6—Normalized concentration dependencies (calculated) of the diffusion coefficients of water and propranolol hydrochloride on the water concentration in the system.

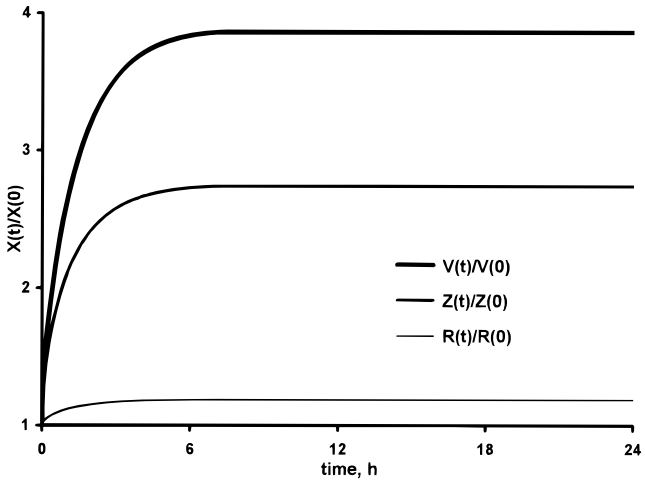

Figure 7—Swelling kinetics (calculated) of the HPMC tablets: increase in volume (*V*), half-height (*Z*), and radius (*R*).

Drug Release—The drug release kinetics of propranolol hydrochloride in 0.1 M phosphate buffer (pH 7.4) are shown in Figure 5 for tablet dimensions of $R_0 = 0.65$ cm, $Z_0 = 0.069$ cm. The new model was fitted to the experimentally determined relative amount of drug released versus time (correlation coefficient = $R^2 = 0.993$). Once more, diffusion governs the transfer kinetics, with concentration dependent diffusion coefficients. The two important parameters characterizing this process, the diffusion coefficient of the drug within the fully swollen tablet, D_{2eq}, and the constant β_2, characterizing the concentration dependence of D_2 on the water content, were determined as $D_{2eq} = 6.3 \times 10^{-7}$ cm^2/s, and $\beta_2 = 9.5$.

As expected from the free volume theory, D_{2eq} is less than D_{1eq}, and β_2 is greater than β_1. According to the theory, the size of the diffusing molecules significantly affects the transfer rate. The jump from one cavity to another for a given cavity size distribution is easier for smaller than for larger molecules. Hence, the diffusion coefficient of water in the fully swollen tablet is higher than the respective diffusion coefficient of propranolol hydrochloride.

Concerning the β-values, the relations are more complex. The dependence of the diffusivity on the water content of the system is a function of the molecular size of the diffusing species. The diffusion rate of small molecules within the polymer system is less affected by the mobility of polymer chains than is the diffusion rate of big molecules (above a certain minimum void size). For small diffusing molecules, much smaller than the average void size, diffusion occurs by localized activated jumps from one preexisting cavity to another; only a few monomer segments are involved. With larger diffusing species, preexisting cavities may be unable to accommodate the diffusing molecules. Therefore, larger numbers of monomer segments must be rearranged to allow the molecules to diffuse.[21] Thus, the relative increase of the diffusion coefficient of water with increasing water content is less steep than the respective increase of the diffusion coefficient of propranolol hydrochloride. These relations are illustrated for water and propranolol hydrochloride diffusivities in Figure 6, normalized to the equilibrium concentration of water and to the respective diffusion coefficients in the fully swollen tablet ($\beta_1 = 2.5$, $\beta_2 = 9.5$).

Swelling Kinetics—Swelling is associated with polymer chain relaxation with volume expansion. The increasing dimension of the system is considered in the new model by moving boundary conditions (eqs 7−14). It is assumed that the total volume of the system is equal to the sum of the volumes of the polymer, water, and drug. The increasing radius, R_t, half-height, Z_t, and volume, V_t, of the tablets can be calculated. Figure 7 shows the respective data of propranolol hydrochloride containing tablets ($R_0 = 0.65$ cm, $Z_0 = 0.069$ cm, release medium: phosphate buffer (pH 7.4), $\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s), normalized to the

respective initial values at $t = 0$. It is shown that the swelling of the tablet is much faster than the release of the drug (Figure 5 shows the release profile of the same tablets). The water uptake is complete after approximately 6 h, whereas the drug is released over a period of approximately 24 h. This is due to the higher mobility of the water molecules in the system, resulting in higher diffusion coefficients in the fully swollen tablet. In addition, the β-value of water is much smaller than the β-value of propranolol hydrochloride.

The increase in radius and height is very high at the beginning and then declines with time. Interestingly, the relative increase in height is approximately 9-fold of the relative increase in radius. The reason for this phenomenon is the difference in the surface area of the tablet in both directions. In the axial direction the surface area is much greater than in the radial direction (2.65 cm^2, instead of 0.56 cm^2). Hence, more water can imbibe in the axial direction and cause the tablet to swell in this direction. The increase in volume of the tablet (by a factor equal to 4) is very important for the additional imbibition of water and for the drug release kinetics. As shown above, both processes are governed by diffusion. Increasing dimensions of the tablets lead to increasing diffusion pathways and thus to decreasing diffusion rates. The effect of the increasing diffusion pathways competes with the effect of the increasing diffusivities of the diffusing species, due to the increasing polymer mobility.

Water and Drug Concentration Profiles—With the new model, further insight into the mass transfer mechanisms is achieved. The concentration profiles of both species, water and drug, can be calculated at any instant. Figure 8 shows the water profiles within the tablets ($R_0 =$ 0.65 cm, $Z_0 = 0.069$ cm, release medium: phosphate buffer (pH 7.4), $\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s) at 30 min (Figure 8a), and 3 h (Figure 8b). For reasons of clarity, the concentration profiles within only one-quarter of the tablet (as indicated in Figure 1b) are presented. Steep concentration gradients directed to the middle of the tablets are observed for small time periods. They are the driving force for additional water imbibition. The steepness of these curves declines with time; thus, the transfer rate declines with time. This effect overlaps with the two others, described above: the increasing diffusion pathways and the increasing diffusion coefficients. The respective concentration profiles of propranolol hydrochloride are presented in Figure 9 ($R_0 = 0.65$ cm, $Z_0 = 0.069$ cm, release medium: phosphate buffer (pH 7.4), $\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s, $\beta_2 = 9.5$, $D_{2eq} = 6.3 \times 10^{-7}$ cm^2/s), at 30 min (Figure 9a), and 3 h (Figure 9b). Again, at the beginning there are steep concentration gradients, which are declining with time. The high driving force at the beginning, in combination with short diffusion pathways, leads to high release rates, as can be shown theoretically as well as experimentally (Figure 5).

Concentration Dependent Diffusivities—As described above, the diffusion coefficients of water and drug strongly depend on the water content of the tablet. Thus, they are functions of both time (t) and position (r, z, θ) within the system. With the new model, the diffusivities can be calculated at any time and position.

Figure 10 shows the diffusion coefficient of propranolol hydrochloride at three different positions as a function of time: (i) at the surface of the tablet, (ii) within the tablet ($r = R_t/2$, $z = Z_t/2$, θ), and (iii) at the center of the tablet. The following parameters have been used: $R_0 = 0.65$ cm, $Z_0 = 0.069$ cm, $\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s, $\beta_2 = 9.5$, $D_{2eq} = 6.3 \times 10^{-7}$ cm^2/s (release medium: buffer pH 7.4). For reasons of clarity, the data are normalized to the respective diffusivities in the fully swollen system. The

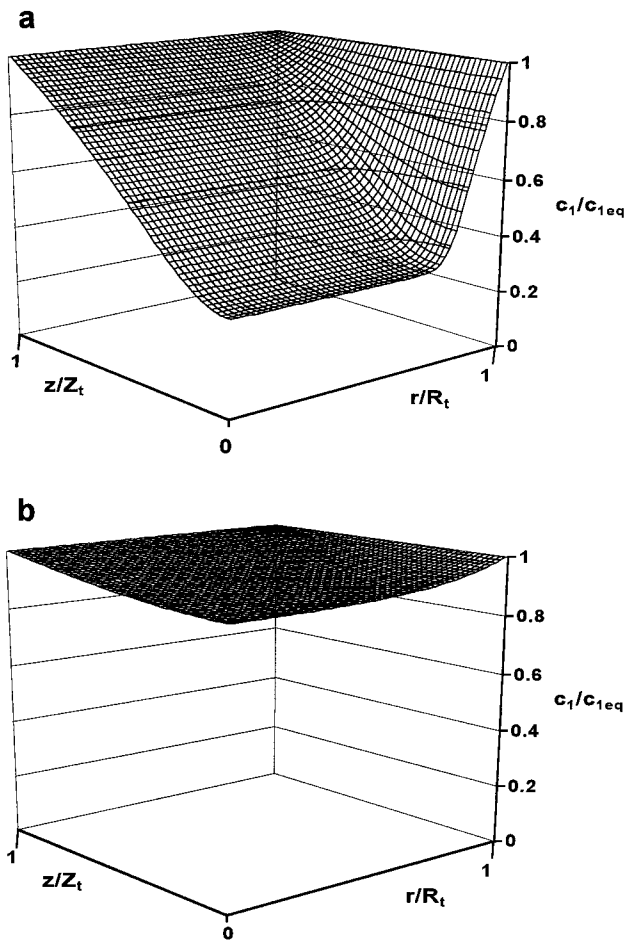

Figure 8—Concentration profile (calculated) of water within the tablets (containing propranolol hydrochloride): (a) $t = 30$ min, (b) $t = 3$ h [release medium: phosphate buffer (pH 7.4)].

diffusion coefficient levels off instantaneously to its equilibrium value at the surface of the tablet upon contact with the release medium. In contrast to this, the diffusivity within the tablet, as well as at the center, shows a sigmoidal behavior. First, it is very low and approximately constant. After a certain time period, it levels off and reaches its equilibrium value. The moment of leveling off is a function of the position (r, z, θ) within the tablet (Figure 10). The knowledge of these data is of great practical importance, when designing a new tablet with, e.g., nonuniform initial drug distribution, to achieve a desired release profile.

Influence of the Aspect Ratio of the Tablet on the Drug Release Kinetics—An easy tool to modify the release kinetics of a drug from a tablet is to vary its shape. The effect of the aspect ratio (radius/height) of the tablet on the drug release rate can be simulated with the new model. Figure 11 clearly shows the release kinetics of propranolol hydrochloride in phosphate buffer (pH 7.4) from three different types of tablet with the same volume (0.18 cm^3): (i) flat cylinders with $R_0/(2Z_0) = 20$, (ii) regular tablets with $R_0/(2Z_0) = 2$, and (iii) almost rod-shaped cylinders with $R_0/(2Z_0) = 0.2$ ($\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s, $\beta_2 = 9.5$, $D_{2eq} = 6.3 \times 10^{-7}$ cm^2/s). It is shown that the release rate from the flat tablets is significantly higher than from the other two types: 90% of the drug is released within only 4.5 h, instead of 18.9 and 21.6 h, respectively. The reason for this phenomenon is the difference in the surface area of the tablets: 7.3 cm^2 in the case of flat tablets, 2.3 cm^2 and 1.9 cm^2 for the regular and "rodlike" tablets, respectively. Within a certain range, determined

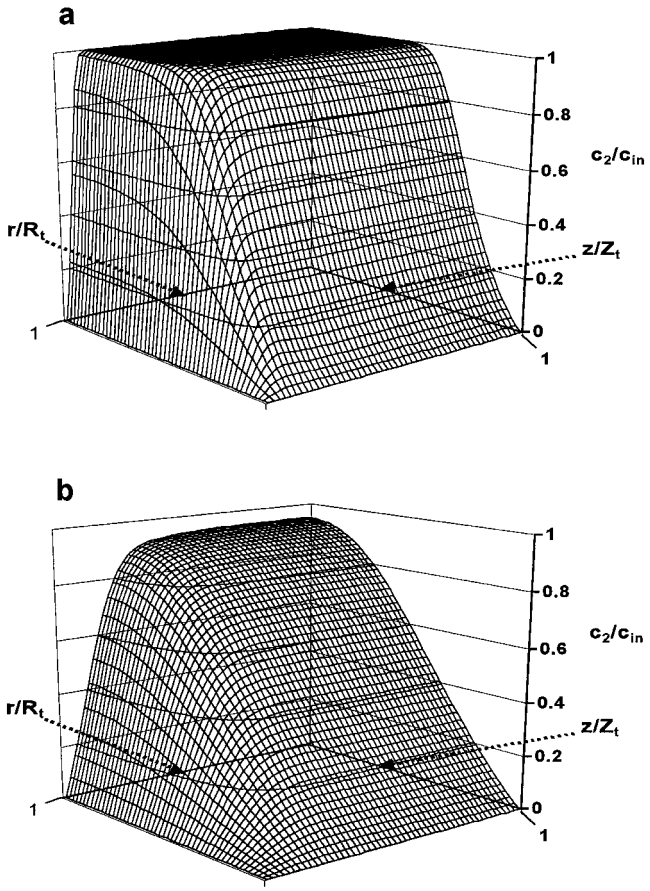

Figure 9—Concentration profile (calculated) of propranolol hydrochloride within the tablets: (a) $t = 30$ min, (b) $t = 3$ h [release medium: phosphate buffer (pH 7.4)].

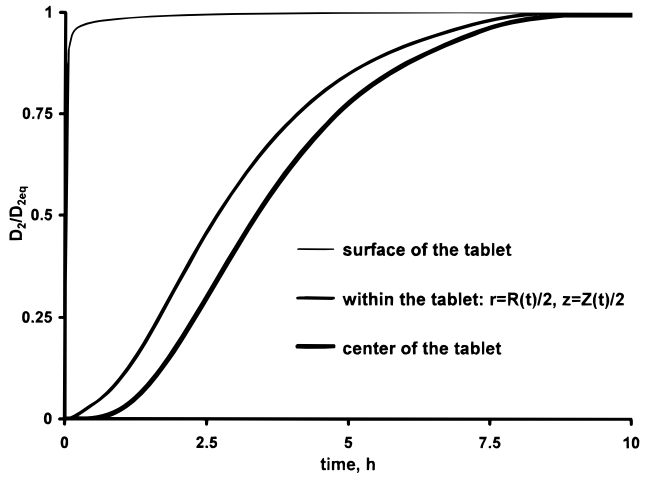

Figure 10—Diffusion coefficient (calculated) of propranolol hydrochloride at different positions within the tablet versus time [release medium: phosphate buffer (pH 7.4)].

by the applicability of the tablets, the variation of the aspect ratio (radius/height) is thus a very easy and effective tool to modify the release rate of the system. With the new model, the optimal shape can be calculated to achieve a desired release profile, without the need of experiments.

Influence of the Tablet Size on the Drug Release Kinetics—Another convenient method to achieve a desired release profile is to vary the size of the tablet. This effect is illustrated in Figure 12. Three types of propranolol hydrochloride tablets (with the same aspect ratio = radius/height = 1.25 and initial drug concentration $c_{in} = 109$ mg/

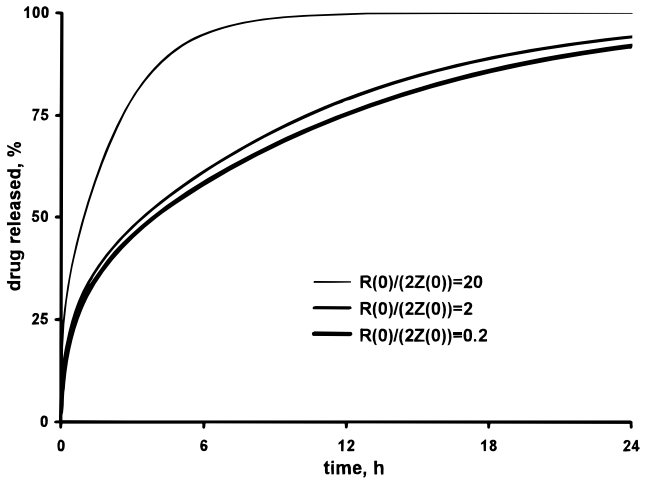

Figure 11—Influence of the aspect ratio (radius/height) of the tablet on the release kinetics (calculated) of propranolol hydrochloride [release medium: phosphate buffer (pH 7.4)].

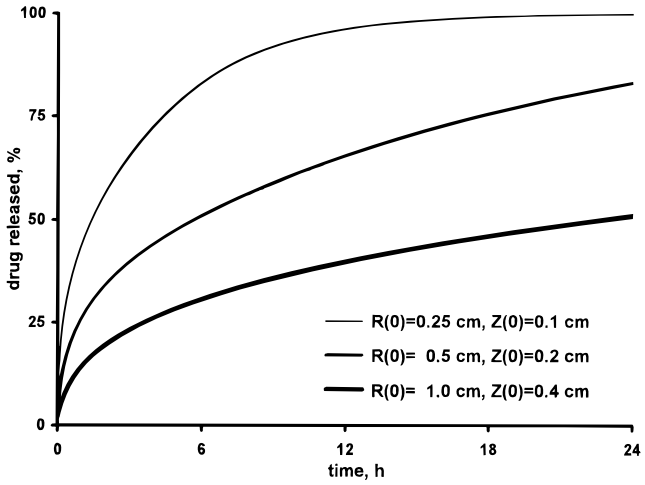

Figure 12—Effect of the size of the tablet on the release kinetics (calculated) of propranolol hydrochloride [release medium: phosphate buffer (pH 7.4)].

mL) have been investigated in phosphate buffer (pH 7.4): (i) small ones, with $R_0 = 0.25$ cm and $Z_0 = 0.1$ cm, (ii) medium-sized ones, with $R_0 = 0.5$ cm and $Z_0 = 0.2$ cm, and (iii) large ones, with $R_0 = 1.0$ cm and $Z_0 = 0.4$ cm ($\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s, $\beta_2 = 9.5$, $D_{2eq} = 6.3 \times 10^{-7}$ cm^2/s). As expected, a very strong influence of the size of the tablet on the release rate is observed: Within 24 h, 99.8% of the drug has been released from the small, 83.1% from the medium-sized, and only 50.9% from the large tablets. The explanation for this phenomenon is obvious. Small tablets have a higher relative surface area (referred to the volume) than large tablets. In addition, the diffusion pathways are much longer in large tablets than in small ones. Thus, the relative amount of drug released versus time is much higher for small tablets. To release the same absolute amount of drug, more small tablets have to be administered than large ones. The variation of the size of the tablets is a very effective and easy tool to achieve a desired release rate. The new model can be used to simulate the drug release kinetics for different tablet sizes. Thus, the required dimensions to obtain a certain release profile can be predicted, avoiding time-consuming experiments.

Applicability of the Model—The release mechanism of a controlled drug delivery system can be affected by various parameters, e.g., type of drug and release medium. To prove the applicability of the presented model for

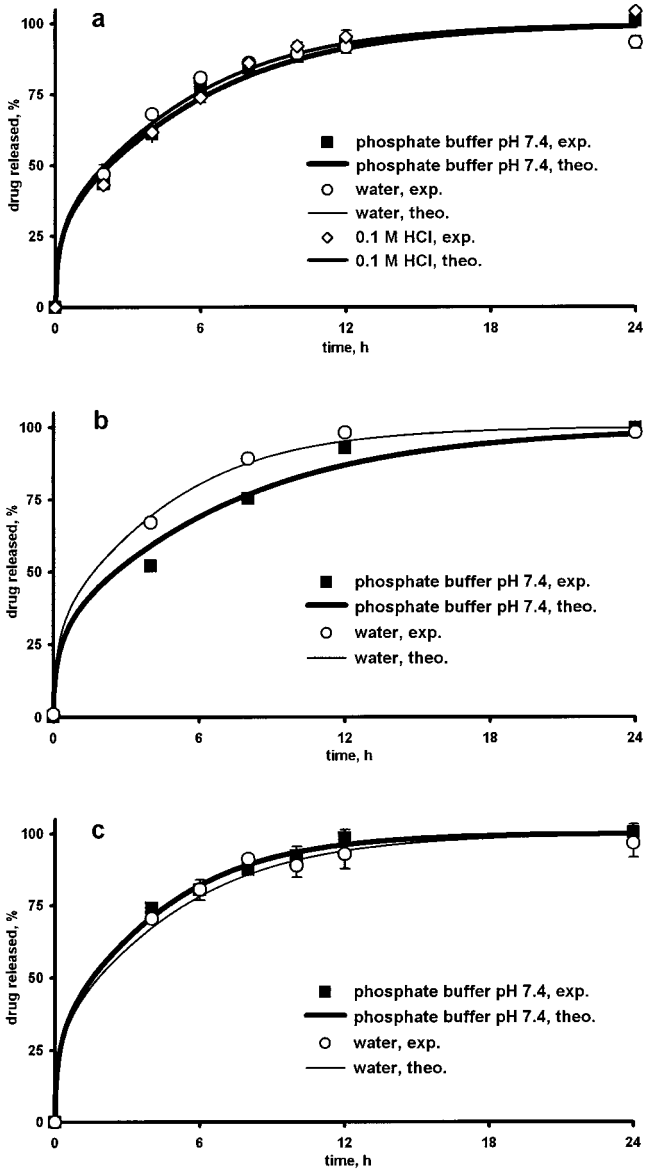

Figure 13—Applicability of the model for different drugs and release media: (a) propranolol hydrochloride, (b) diclofenac sodium, (c) chlorpheniramine maleate.

different drug-release media combinations, experiments have also been conducted with propranolol hydrochloride in 0.1 M HCl and deionized water, diclofenac sodium and chlorpheniramine maleate in deionized water and phosphate buffer (pH 7.4), respectively. Figure 13, parts a–c, show the theoretically ($\beta_1 = 2.5$, $D_{1eq} = 5.6 \times 10^{-6}$ cm^2/s, $R_0 = 0.65$ cm, $Z_0 = 0.069$ cm) and experimentally determined release kinetics. In each case, the experimentally determined data can be explained by the presented Fickian analysis considering concentration dependent diffusivities (correlation coefficient: $R^2 > 0.985$, Table 1). This is of great practical importance for the new model. It is not restricted to a certain drug-release medium combination. In addition, the respective diffusion coefficients in the fully swollen tablets, D_{2eq}, and the constants, characterizing the concentration dependence of the drug diffusivities on the water content of the tablet, β_2, have been determined (Table 1).

Influence of the Type of Release Medium on the Drug Release Kinetics—For propranolol hydrochloride, the calculated β_2-values in different release media (phosphate buffer (pH 7.4), deionized water, and 0.1 M HCl) are very similar: $\beta_2 = 9.5$, 9.4, and 9.4, respectively. This indicates the negligible effect of the type of release medium on the concentration dependence of the diffusivity. In addition, the diffusion coefficient of the drug within the fully swollen tablet varies only between 6.3×10^{-7} cm^2/s and 7.0×10^{-7} cm^2/s. Thus, the resulting release curves (Figure 13a) are very similar. For diclofenac sodium in phosphate buffer (pH 7.4) and deionized water, D_{2eq} was determined as 4.9×10^{-7} cm^2/s and 8.0×10^{-7} cm^2/s, respectively. The calculated β_2-values however, are approximately equal: $\beta_2 = 8.1$ and 8.3. As can be seen in Figure 13b, this results in a slightly different release rate of diclofenac sodium in phosphate buffer (pH 7.4) and deionized water. The explanation for this phenomenon is probably based on the different interactions of the phosphate buffer ions (K^+, Na^+, HPO_4^{2-}, $H_2PO_4^-$) with diclofenac sodium, HPMC, and water. The exact analysis of these interactions is beyond the scope of this study. For chlorpheniramine maleate, the following values have been calculated: D_{2eq}(buffer pH 7.4) $= 8.7 \times 10^{-7}$ cm^2/s, D_{2eq}(water) $= 7.3 \times 10^{-7}$ cm^2/s, β_2(buffer pH 7.4) $= 8.5$, and β_2(water) $= 8.4$. As in the case of propranolol hydrochloride, these values are approximately equal. The resulting release profiles are shown in Figure 13c, illustrating the negligible effect of the type of release medium on the liberation of chlorpheniramine maleate.

Table 1—Parameters Characterizing the Diffusion of Drugs within HPMC Tablets

drug	release medium	$D_{2eq}, \times 10^7$ (cm^2/s)	β_2	R^2
propranolol hydrochloride	buffer pH 7.4	6.3	9.5	0.993
	deionized water	7.0	9.4	0.988
	0.1 M HCl	6.9	9.4	0.988
diclofenac	buffer pH 7.4	4.9	8.1	0.986
sodium	deionized water	8.0	8.3	0.997
chlorpheniramine	buffer pH 7.4	8.7	8.5	0.997
maleate	deionized water	7.3	8.4	0.991

Conclusions

The two major benefits of the presented model are: (i) the gain of further insight into the release mechanism of drugs from HPMC tablets and (ii) the ability to calculate the required shape and dimensions of HPMC tablets to achieve desired drug release profiles.

Notation

c	concentration within the tablet
c_{eq}	concentration in the equilibrium swollen state
c_{in}	initial concentration of the drug within the tablet
D	diffusion coefficient
D_{eq}	diffusion coefficient in the fully swollen tablet
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
k	subscript, indicating the diffusing species: $k =$ 1: water, $k = 2$: drug
j	integer for numerical analysis
J	number of space intervals along the axial axes for numerical analysis
r	radial coordinate
Δr	space interval along the radial axes for numerical analysis

R^2	correlation coefficient
R_0	initial radius of the tablet
R_t	radius of the tablet at time t
t	time
Δt	time interval for numerical analysis
V_t	volume of the tablet at time t
z	axial coordinate
Δz	space interval along the axial axes for numerical analysis
Z_0	initial half-height of the tablet
Z_t	half-height of the tablet at time t
β	constant, characterizing the dependence of the diffusion coefficient on the water concentration
θ	angle

References and Notes

1. Colombo, P. Swelling-controlled release in hydrogel matrixes for oral route. *Adv. Drug Del. Rev.* **1993**, *11*, 37−57.
2. Pham, A. T.; Lee, P. I. Probing the mechanisms of drug release from hydroxypropylmethyl cellulose matrixes. *Pharm. Res.* **1994**, *11*, 1379−84.
3. Colombo, P.; Bettini, R.; Massimo, G.; Catellani, P. L.; Santi, P.; Peppas, N. A. Drug diffusion front movement is important in drug release control from swellable matrix tablets. *J. Pharm. Sci.* **1995**, *84*, 991−7.
4. Liu, C.-H.; Kao, Y.-H.; Chen, S.-C.; Sokoloski, T. D.; Sheu, M.-T. In-vitro and in-vivo studies of the diclofenac sodium controlled-release matrix tablets. *J. Pharm. Pharmacol.* **1995**, *47*, 360−4.
5. Colombo, P.; La Manna, A.; Conte, U. System for the controlled release of active substances. U.S. Patent No. 4,-839,177, 1989.
6. Colombo, P.; Conte, U.; Gazzaniga, A.; Maggi, L.; Sangalli, M. E.; Peppas, N. A.; La Manna, A. Drug release modulation by physical restrictions of matrix swelling. *Int. J. Pharm.* **1990**, *63*, 43−8.
7. Gao, P.; Fagerness, P. E. Diffusion in HPMC gels. I. Determination of drug and water diffusivity by pulsed-field-gradient spin−echo NMR. *Pharm. Res.* **1995**, *12*, 955−64.
8. Fyfe, C. A.; Blazek, A. I. Investigation of hydrogel formation from hydroxypropylmethylcellulose (HPMC) by NMR spectroscopy and NMR imaging techniques. *Macromolecules* **1997**, *30*, 6230−7.
9. Gao, P.; Nixon, P. R.; Skoug, J. W. Diffusion in HPMC gels. II. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. *Pharm. Res.* **1995**, *12*, 965−71.
10. Higuchi, T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* **1963**, *52*, 1145−9.
11. Hariharan, D.; Peppas, N. A.; Bettini, R.; Colombo, P. Mathematical analysis of drug delivery from swellable systems with partial physical restrictions or impermeable coatings. *Int. J. Pharm.* **1994**, *112*, 47−54.
12. Fu, J. C.; Hagemeir, C.; Moyer, D. L.; NG, E. W. A unified mathematical model for diffusion from drug-polymer composite tablets. *J. Biomed. Mater. Res.* **1976**, *10*, 743−58.
13. Cohen, D. S.; Erneux, T. Free boundary problems in controlled release pharmaceuticals. I: Diffusion in glassy polymers. *SIAM J. Appl. Math.* **1988**, *48*, 1451−65.
14. Cohen, D. S.; Erneux, T. Free boundary problems in controlled release pharmaceuticals. II: Swelling-controlled release. *SIAM J. Appl. Math.* **1988**, *48*, 1466−74.
15. Korsmeyer, R. W.; Lustig, S. R.; Peppas, N. A. Solute and penetrant diffusion in swellable polymers. I. Mathematical modeling. *J. Polym. Sci. Polym. Phys. Ed.* **1986**, *24*, 395−408.
16. Korsmeyer, R. W.; von Meerwall, E.; Peppas, N. A. Solute and penetrant diffusion in swellable polymers. II. Verification of theoretical models. *J. Polym. Sci. Polym. Phys. Ed.* **1986**, *24*, 409−34.
17. Crank, J. *The Mathematics of Diffusion*, 2nd ed.; Clarendon Press: Oxford, 1975; pp 4−5.
18. Fujita, H. Diffusion in polymer-diluent systems. *Fortschr. Hochpolym.-Forsch.* **1961**, *3*, 1−47.
19. Hoffmann, U.; Hofmann, H. *Einfuehrung in die Optimierung*, Verlag Chemie GmbH: Weinheim, Germany, 1971; pp 127−31.
20. Tahara, K.; Yamamoto, K.; Nishihata, T. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. *J. Controlled Release* **1995**, *35*, 59−66.
21. Fan, L. T.; Singh, S. K. *Controlled release*: *a quantitative treatment*; Springer-Verlag: Berlin, 1989; pp 20−28.

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