Hydrophilic Matrices for Controlled Drug Delivery: An Improved Mathematical Model to Predict the Resulting Drug Release Kinetics (the "Sequential Layer" Model)

J. Siepmann[1,3] and N. A. Peppas[2]

Received March 17, 2000; accepted July 7, 2000

Purpose. The aims of this study were (i) to elucidate the transport mechanisms involved in drug release from hydrophilic matrices; and (ii) to develop an improved mathematical model allowing quantitative predictions of the resulting release kinetics.

Methods. Our previously presented model has been substantially modified, by adding: (i) inhomogeneous swelling; (ii) poorly water-soluble drugs; and (iii) high initial drug loadings. The validity of the improved model has been tested experimentally using hydroxypropyl methylcellulose (HPMC)-matrices, containing either a poorly or a freely water-soluble drug (theophylline or chlorpheniramine maleate) at various initial loadings in phosphate buffer pH 7.4 and 0.1 N HCl, respectively.

Results. By overcoming the assumption of homogeneous swelling we show that the agreement between theory and experiment could be significantly improved. Among others, the model could describe quantitatively even the very complex effect on the resulting relative release rates (first slowing down, then accelerating drug release) observed when increasing the initial loading of poorly water-soluble drugs.

Conclusions. The practical benefit of this work is an improved design model that can be used to predict accurately the required composition and dimensions of drug-loaded hydrophilic matrices in order to achieve desired release profiles, thus facilitating the development of new pharmaceutical products.

KEY WORDS: controlled release; diffusion; hydrophilic matrix; hydroxypropyl methylcellulose (HPMC); modeling; swelling.

[1] College of Pharmacy, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany.

[2] School of Chemical Engineering, Purdue University, West Lafayette, Indiana 47907.

[3] To whom correspondence should be addressed at Laboratoire de Pharmacie Galénique, Faculté de Pharmacie, Université d'Angers, 16, Boulevard Daviers, 49100 Angers, France. (e-mail: siepmann@med.univ-angers.fr)

ABBREVIATIONS: c, concentration; c_{1crit}, critical water concentration at the surface of the system; D, diffusion coefficient; D_{crit}, diffusion coefficient at c_{1crit}; half-height [n], half-height of layer [n] for numerical analysis; i, integer for numerical analysis; I + 1, number of space intervals along the radial axes for numerical analysis; j, integer for numerical analysis; J + 1, number of space intervals along the axial axes for numerical analysis; k, subscript, indicating the diffusing species: k = 1: water, k = 2: drug; layer [n], "sequential" layer for numerical analysis; n, integer for numerical analysis; r, radial coordinate; Δr [n], 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; radius [n], radius of layer [n] for numerical analysis; t, time; w_d, initial drug loading of the tablet (% w/w drug); z, axial coordinate; Δz [n], 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, angular coordinate.

INTRODUCTION

Hydrophilic polymers are the dominant vehicles used for the preparation of oral controlled drug delivery systems. From a commercial point of view, hydroxypropyl methylcellulose (HPMC) is the most prominent carrier material in pharmaceutical applications (1). The mechanisms of drug release from these systems is rather complex as a series of processes has to be taken into account.

Upon contact with biological fluids, water penetrates into the tablet and dissolves the drug, which then diffuses out of the tablet. In contrast to purely diffusion-controlled drug delivery systems, also swelling and polymer dissolution have to be taken into account. Above a certain, critical water concentration, the polymer undergoes the transition from the glassy to the rubbery state, leading to dramatic changes in volume, concentration and diffusion coefficients of the involved species. In the case of poorly water-soluble drugs, the drug dissolution process has to be taken into account as well. If high quantities of water-soluble additives are added, or in the case of high initial drug loadings, the resulting increasing porosity of the system during drug release also has to be considered.

Surprisingly, only a few studies investigating the exact mechanisms of drug release from hydrophilic polymer-matrices have been reported in the literature. In contrast to unswellable and water-insoluble carriers (e.g., ethylcellulose), there is a significant lack of exact mathematical models allowing quantitative predictions of the resulting drug release kinetics. Thus, the development of new pharmaceutical products based on hydrophilic polymers usually requires time-consuming series of experiments to optimize the formulation parameters.

To analyze in detail the occurring mass transfer processes during drug release, various techniques have been applied, mostly based on NMR measurements. For example, Gao et al. (2–3) determined the drug and water diffusion coefficients within HPMC-gels, and showed that they depend on the initial polymer content. Rajabi-Siahboomi et al. (4) showed that there was a diffusive gradient across the gel layer of hydrating HPMC-matrices, and that this gradient was affected by the degree of substitution of the polymer. The concentration profiles of the swelling polymer within cylindrical HPMC-matrices were determined experimentally by Fyfe and Blazek (5).

Major factors influencing the resulting drug release mechanisms from hydrophilic polymer matrices include the water-solubility of the incorporated drug, and the initial drug loading of the system. Various studies have investigated these aspects experimentally and theoretically. For example, Eyjolfsson (6) studied the release kinetics of a practically water-insoluble drug within two types of HPMC-matrices, and observed non-Fickian release behavior. Slightly water-soluble drugs were incorporated into HPMC-matrices by Maggi et al. (7) and the HPMC content and viscosity grade (molecular weight) were varied to produce a wide range of drug release rates. These matrices were further combined with a fast disintegrating, drug-containing layer to achieve biphasic release patterns. The effect of the initial content of melatonin on the release kinetics from HPMC-tablets was studied by Lee et al. (8). They found slightly decreasing release rates with increas-

0724-8741/00/1000-1290$18.00/0

ing drug loadings. In contrast, Pham and Lee (9) found increasing release rates of fluorescein from HPMC-matrices with increasing initial drug loadings, whereas Picker (10) reported first decreasing and then increasing relative release rates of theophylline from HPMC-tablets. The drug and polymer release profiles from HPMC-matrices, containing flurbiprofen, adinazolam mesylate or alprazolam (drugs that provide a wide range of drug solubilities) were measured by Skoug et al. (11). With increasing dose, erosion appeared to contribute more to the overall release mechanism.

Colombo et al. (12) investigated the effect of both drug solubility and initial drug loading on the resulting mass transfer processes. Under certain conditions, three boundaries could be identified, corresponding to a swelling, diffusion and erosion front. The data obtained demonstrated that the distance between the diffusion and erosion front (dissolved drug gel layer thickness) is decisive for the release kinetics, and even more important than the distance between the swelling and erosion front (whole gel layer thickness).

Based on experimental findings, various mathematical models have been proposed to quantitatively describe the occurring mass transfer processes and to predict the resulting drug release kinetics (13–21). However, most of the reported models make certain assumptions that may not be satisfactory. For example, they neglect polymer swelling (18), neglect polymer dissolution (15), or present only one-dimensional transport (in the radial direction), ignoring the axial transport (14).

Recently, we proposed a new mathematical model that takes into account water and drug concentration-dependent diffusion, in the radial and axial direction, three-dimensional swelling, with subsequent volume, concentration, and matrix composition changes, and simultaneous polymer dissolution (20). Unfortunately, this model was only applied to freely water-soluble drugs at low initial drug loadings. In addition, upon water imbibition we assumed homogeneous swelling throughout the device (including dry tablet regions), leading to significant deviations between experimental and theoretical drug release data. The aim of the present study was to overcome these restrictions and to develop a more accurate and comprehensive mathematical model.

EXPERIMENTAL SECTION

Materials

The following chemicals were obtained from commercial suppliers and used as received: chlorpheniramine maleate (Sigma Chemical Co., St. Louis, MO), theophylline (Knoll Deutschland GmbH, Ludwigshafen, Germany), and hydroxypropyl methylcellulose (HPMC, Methocel® K15M Premium Grade, Colorcon, West Point, PA).

Methods

Drug-loaded HPMC-tablets (1–70% w/w initial drug content) were prepared by direct compression. The drug and polymer powders were blended thoroughly with a pestle and mortar. 500 mg were weighed and fed manually into the die of a single-punch tabletting machine (EK 0, Korsch, Berlin, Germany) to produce tablets using flat-faced punches (12 mm in diameter). The hardness of the tablets was kept constant (80 N, hardness tester - PTB 311, Pharma Test, Hainburg, Germany).

The USP XXIV rotating paddle method [37°C, 100 rpm, 900 mL 0.1 M phosphate buffer (pH 7.4) USP XXIV or 0.1 N HCl] was used to study the drug release kinetics. At predetermined time intervals, 2 mL samples (which were replaced with fresh medium) were withdrawn, filtered and assayed spectrophotometrically (Shimadzu UV-2101 PC UV-Vis scanning spectrophotometer, Columbia, SC) at the following wavelengths: chlorpheniramine maleate, $\lambda = 264$ nm; theophylline, $\lambda = 271$ nm.

MATHEMATICAL ANALYSIS

Model Development

The proposed improved 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 (i) the cylindrical geometry of the device; (ii) both, axial and radial direction of the mass transport; and (iii) the significant dependence of the water diffusion coefficient 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, increasing dimensions of the system, and increasing macromolecular mobilities.

(iii) Upon contact with water the drug dissolves and (due to concentration gradients) diffuses out of the device.

(iv) With increasing water content also the diffusion coefficient of the drug increases substantially.

(v) In the case of poor water-solubility, dissolved and non-dissolved drug coexist within the polymer-matrix.

(vi) In the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion.

(vii) The polymer itself dissolves.

Due to points (i), (ii), (iv), (vi), and (vii) the mathematical description of the diffusional processes requires strongly time-dependent terms.

Model Assumptions

The improved model is based on the following assumptions:

(i) There is no volume contraction upon mixing. The sum of the volumes of water, drug and polymer in the system are always equal to the total volume of the system.

(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) Drug dissolution within the matrix is fast compared to drug diffusion out of the matrix.

(v) The thermodynamic behavior of the system is ideal.

Water and Drug Diffusion

Water and drug diffusion is described by Fick's second law for cylindrical devices, taking into account axial and radial mass transfer with concentration-dependent diffusion coefficients (22):

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

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 is the axial coordinate, Θ is the angular coordinate, and t represents time [see also Figs. 1(a) and (b)].

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 (23) exponential dependence of the diffusion coefficients of water and drug, D_1 and D_2, is considered:

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

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

where β_1 and β_2 are dimensionless constants, characterizing this concentration-dependence (19). Also c_{1crit} denotes the water concentration, D_{1crit} and D_{2crit} the respective diffusion coefficients of water and drug at the interface matrix/release medium, where polymer disentanglement occurs (13,14,20,24–26).

Inhomogeneous Swelling

Upon water contact with the hydrophilic matrix, the polymer swells. Two major characteristics of this phenomenon are considered in the improved 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 diffusion coefficients of water and drug (as indicated by Eqs.3 and 4).

In contrast to our previously presented model (20), we no longer assume homogenous swelling throughout the system. Only the regions of the tablet, into which water imbibition really occurs, are considered to swell. For the mathematical implementation of this phenomenon, the tablet is considered to be structured by sequential layers (sections) as shown in Fig. 1(c). It consists of various single layers, that can be peeled off one after the other. First, water imbibes only into the outermost layer of the system. Thus, only this layer is considered to swell. Then, one after the other, the neighboring inner layers are also affected. Each layer of the system is considered to swell homogeneously. To minimize the resulting error (e.g., edges swell more rapidly than middle parts due to the higher relative surface area in contact with water or outer swollen layers), a certain minimum number of sequential layers has to be considered (for the presented calculations n = 50 has been chosen).

As ideal mixing is assumed (no volume contraction upon

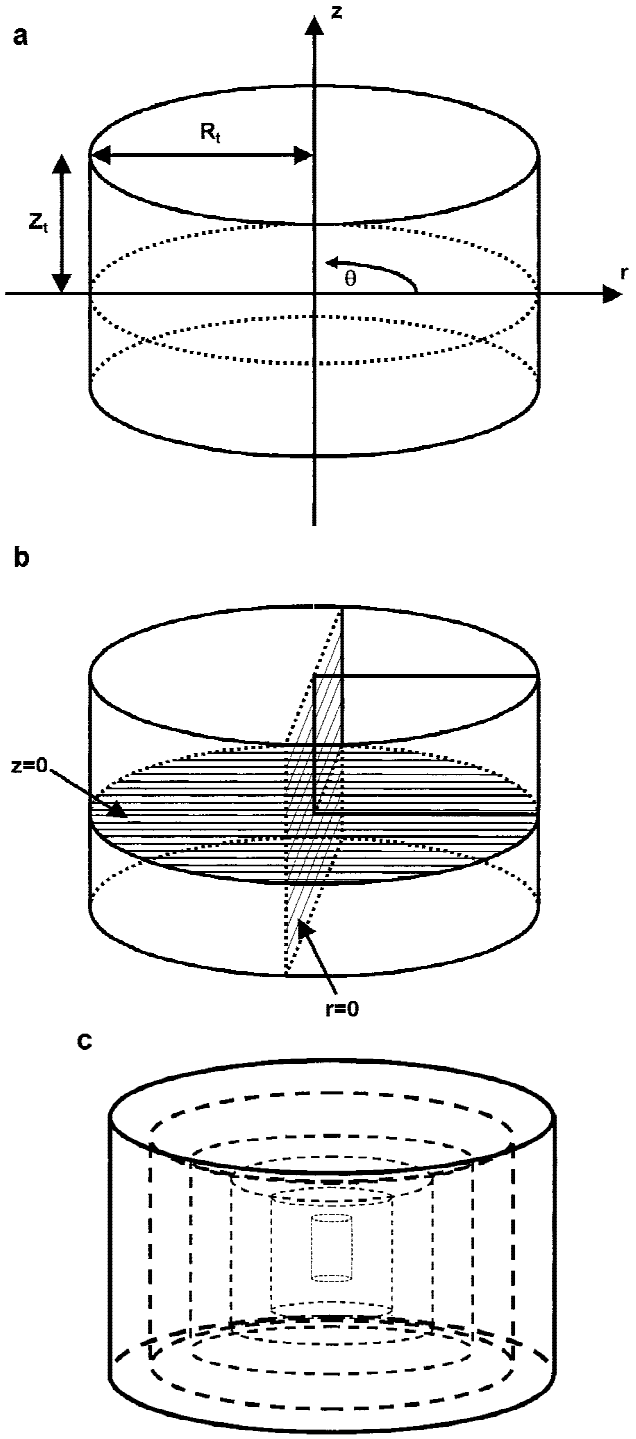

Fig. 1. (a) Schematic of the matrix for mathematical analysis, with (b) symmetry planes in axial and radial direction for the water and drug concentration profiles, (c) "sequential layer" structure for numerical analysis.

mixing drug, polymer and water), the total volume of the system at any instant is given by the sum of the volumes of the single components. The calculation of the new matrix dimensions is based on a mass balance considering drug, polymer and water. Furthermore, 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. In addition, the decrease in matrix volume (and thus decrease in radius and height) due to drug and polymer loss into the bulk fluid is considered.

Polymer Dissolution, Initial and Boundary Conditions, Numerical Solution of the Mathematical Equations

As the mathematical treatment of these aspects is analogous to our previous model, the reader is referred to the literature (19–21) for details. However, introducing the concept of "sequential layers" modified the structure of the grid needed for the numerical analysis. The time dependent radius, R_t, and half-height, Z_t, of the cylindrical matrices are divided into $(I + 1)$ and $(J + 1)$ space intervals, respectively, generating a grid of $(I + 1)x(J + 1)$ grid points (Fig. 2). "Sequential layers" are defined as follows. Layer [n] includes all grid points [i][j] with $i = (0 \text{ to } n) \wedge j = n$ and $i = n \wedge j = (0 \text{ to } n)$. The thickness of layer [n] is equal to $\Delta r[n]$ in radial and $\Delta z[n]$ in axial direction; radius [n] and half-height [n] denote the radius and half-height of layer [n], respectively.

Drug Dissolution

In the case of poorly water-soluble drugs (solubility <1 g drug/100 mL solution) or high initial loadings of moderately water-soluble drugs (1 g drug/10 mL solution > solubility > 1 g drug/100 mL solution), dissolved and non-dissolved drug coexist within the matrix. At each time step, the actual concentration of drug and water are calculated at each grid point within the tablet. If the total amount of drug exceeds the amount soluble under the actual conditions, the excess is considered to be non-dissolved and thus not available for diffusion.

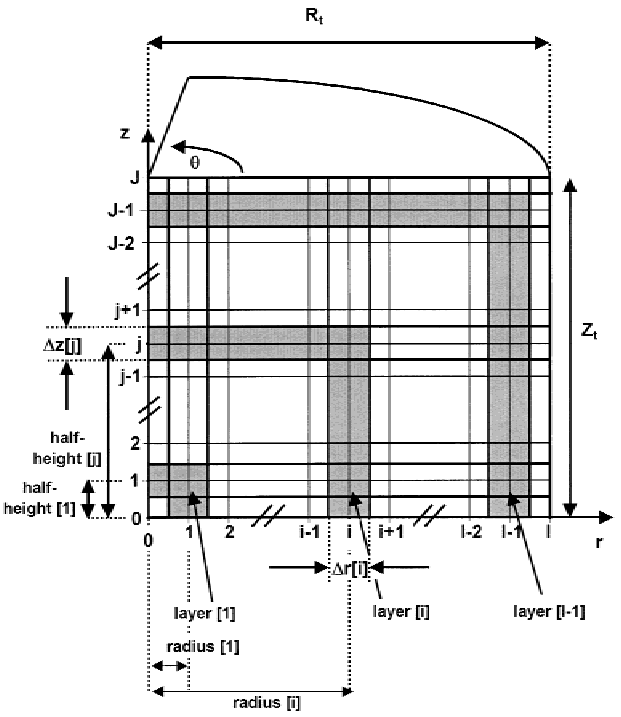

Fig. 2. Schematic of the matrix for numerical analysis.

It is assumed that drug dissolution within the matrix is fast compared to drug diffusion out of the matrix. Under the given conditions, the water flow rate within the tablet is very low. Thus, drug diffusion through the unstirred layer directly surrounding the drug particles can be considered to be the rate limiting step of the drug dissolution process. According to the theory of Noyes and Whitney (27), the resulting dissolution velocity is determined by the (i) thickness of the unstirred layer; (ii) drug concentration difference (across this layer); (iii) surface area of the drug particles; and (iv) diffusion coefficient within the unstirred layer. On the other hand, the diffusion velocity of the drug out of the matrix depends on the (i) length of the diffusion pathway (dimensions of the matrix); (ii) concentration difference (matrix position vs. bulk fluid); and (iii) diffusion coefficient within the tablet. As an approximation the diffusion coefficients in both cases can be considered to be of the same order of magnitude. The diffusion pathways however differ significantly in length, the thickness of the unstirred layer directly surrounding the drug particles is much smaller than the diffusion pathway out of the device. The concentration differences strongly depend on time and position within the matrix. However, due to the fundamental difference in the length of the diffusion pathways, the driving force for drug dissolution can be considered to be higher than the driving force for drug diffusion out of the device. Thus, for most drugs and drug loadings it is reasonable to assume that the dissolution process is fast compared to the diffusion process out of the device. As both phenomena take place sequentially, the faster one can be neglected when calculating the overall mass transfer velocity.

Parameter Fitting

The required parameters (e.g., β_k- and D_{kcrit}-values) were either already known (19–21) 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 (21). Once knowing the required parameters characterizing a particular polymer-drug-release medium-combination, the proposed mathematical model is fully predictive.

RESULTS AND DISCUSSION

Parameter Fitting

Figure 3(a) shows the experimentally determined relative cumulative release of chlorpheniramine maleate from

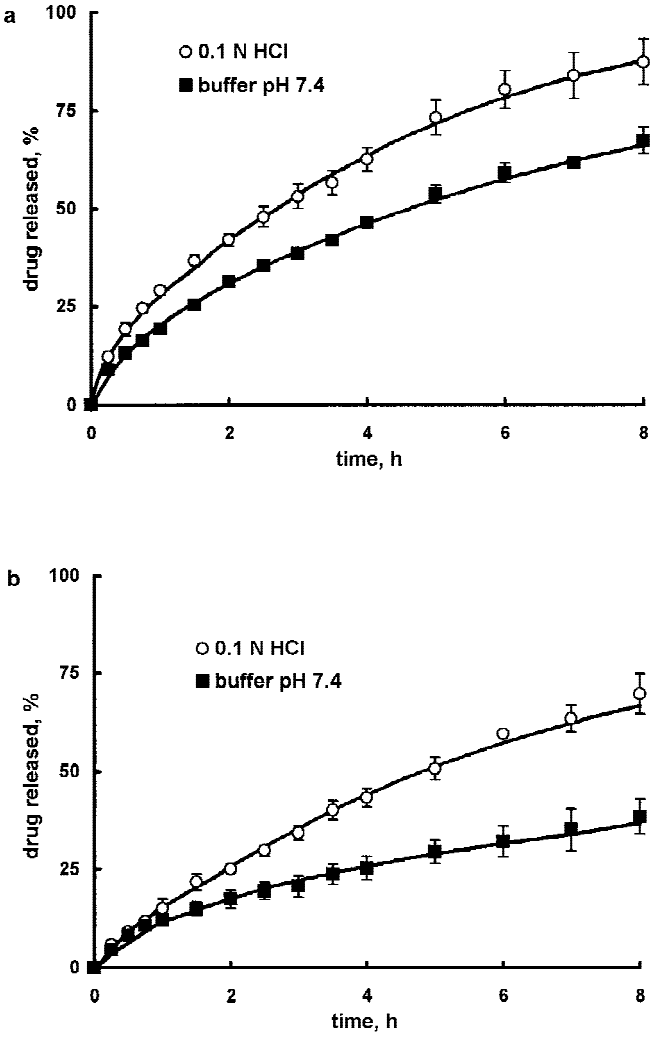

Fig. 3. Fit of the improved model to experimental drug release data: (a) chlorpheniramine maleate, (b) theophylline, in phosphate buffer (pH 7.4) and 0.1 N HCl, respectively (60% w/w initial drug loading, 500 mg tablets, R_0 = 0.6 cm, 37°C, curves: calculated values, symbols: experimental results, ○ 0.1 N HCl, ■ phosphate buffer pH 7.4).

HPMC-tablets (initial drug loading: 60% w/w) in phosphate buffer (pH 7.4) and 0.1 N HCl, respectively. Error bars indicate +/- 1 standard deviation, n = 3. As can be seen, drug release is faster in 0.1 N HCl than in phosphate buffer pH 7.4. This can probably be explained by the higher solubility of chlorpheniramine maleate in 0.1 N HCl (574 mg/mL), compared to phosphate buffer pH 7.4 (562 mg/mL) (28), and the faster dissolution of HPMC in this medium (20).

Figure 3(a) also shows the fit of the improved mathematical model to the experimental data. The following parameters were obtained: β_2(chlorpheniramine maleate, 0.1 N HCl) = 7.0, D_{2crit}(chlorpheniramine maleate, 0.1 N HCl) = 1.7×10^{-6} cm^2/s; β_2(chlorpheniramine maleate, phosphate buffer pH 7.4) = 20, D_{2crit}(chlorpheniramine maleate, phosphate buffer pH 7.4) = 1.6×10^{-6} cm^2/s. As can be seen, the agreement between theory and experiment is very good. In both cases, the coefficient of determination, R^2, is equal to 1.00. Compared to our previous models (19–21) this is a significant improvement, which can probably be attributed to the more realistic description of the swelling process. In addition, the resulting residuals are now randomly distributed, indicating the absence of systematic deviations between theory and experiment.

Figure 3(b) illustrates the release kinetics of theophylline (initial drug loading: 60% w/w) from HPMC-tablets in phosphate buffer (pH 7.4) and 0.1 N HCl, respectively. Again, drug release in 0.1 N HCl is faster than in phosphate buffer (pH 7.4). This agrees well with the solubility of theophylline in these media (15.4 mg/mL in 0.1 N HCl, 12.0 mg/mL in phosphate buffer pH 7.4) (29) and the faster dissolution of HPMC in 0.1 N HCl. Higher drug concentrations within the tablets lead to higher driving forces for diffusion, and thus to increased release rates. In addition, the fit of the "sequential layer" model to these experimental results is shown. The following parameters have been obtained: β_2(theophylline, 0.1 N HCl) = 17, D_{2crit}(theophylline, 0.1 N HCl) = 7.7×10^{-6} cm^2/s; β_2(theophylline, phosphate buffer pH 7.4) = 15, D_{2crit}(theophylline, phosphate buffer pH 7.4) = 12×10^{-6} cm^2/s. Again, very good agreement between theory and experiment was found (R^2 = 1.00). Thus, the improved model is not only applicable to freely water-soluble drugs such as chlorpheniramine maleate, but also to poorly water-soluble drugs such as theophylline. Furthermore, the model is not restricted to a certain type of release medium.

Effect of Drug Loading: Freely Water-Soluble Drugs

As can be seen in Figs. 4(a–d), the initial drug loading of the freely water-soluble drug chlorpheniramine maleate has a significant effect on the resulting drug release kinetics. With increasing drug content the release rate (relative and absolute values) increases in both media, 0.1 N HCl and phosphate buffer pH 7.4. This can be attributed to the different properties of the polymer networks, which result upon water imbibition and drug depletion. At 1% w/w initial drug loading the tablet-matrix consists mainly (99% w/w) of HPMC. Thus, upon swelling a tight network of polymer chains results, presenting a significant hindrance for drug diffusion. When increasing the initial loading of the drug, the network becomes more and more porous upon drug depletion. Thus, the probability for a drug molecule to jump from one cavity to another is highly increased compared to the tight polymer network resulting at low initial drug loadings. Consequently, the diffusion coefficient of the drug within the matrix increases with increasing initial drug content. These phenomena are taken into account by the improved model considering different β_2- and D_{2crit}-values for different initial drug loadings (Fig. 5 and Table 1). At each time step the composition of the system is calculated at each grid point. Thus, the physical conditions for drug and water diffusion and for polymer dissolution are known, in particular the degree of swelling of the polymer network. Knowing the actual water, polymer and drug concentrations within each microenvironment of the tablet, the resulting mass transfer rates can be calculated very accurately.

According to the presented theory, the diffusion coefficient at the interface matrix/release medium, D_{2crit}, is expected to increase with increasing matrix porosity upon drug depletion (and thus increasing initial drug loading). This tendency could be confirmed experimentally for both drugs and both release media (Fig. 5). The dependence of the β_2-values on the initial drug loading is more complex. At low initial drug contents a tighter polymer network results with smaller

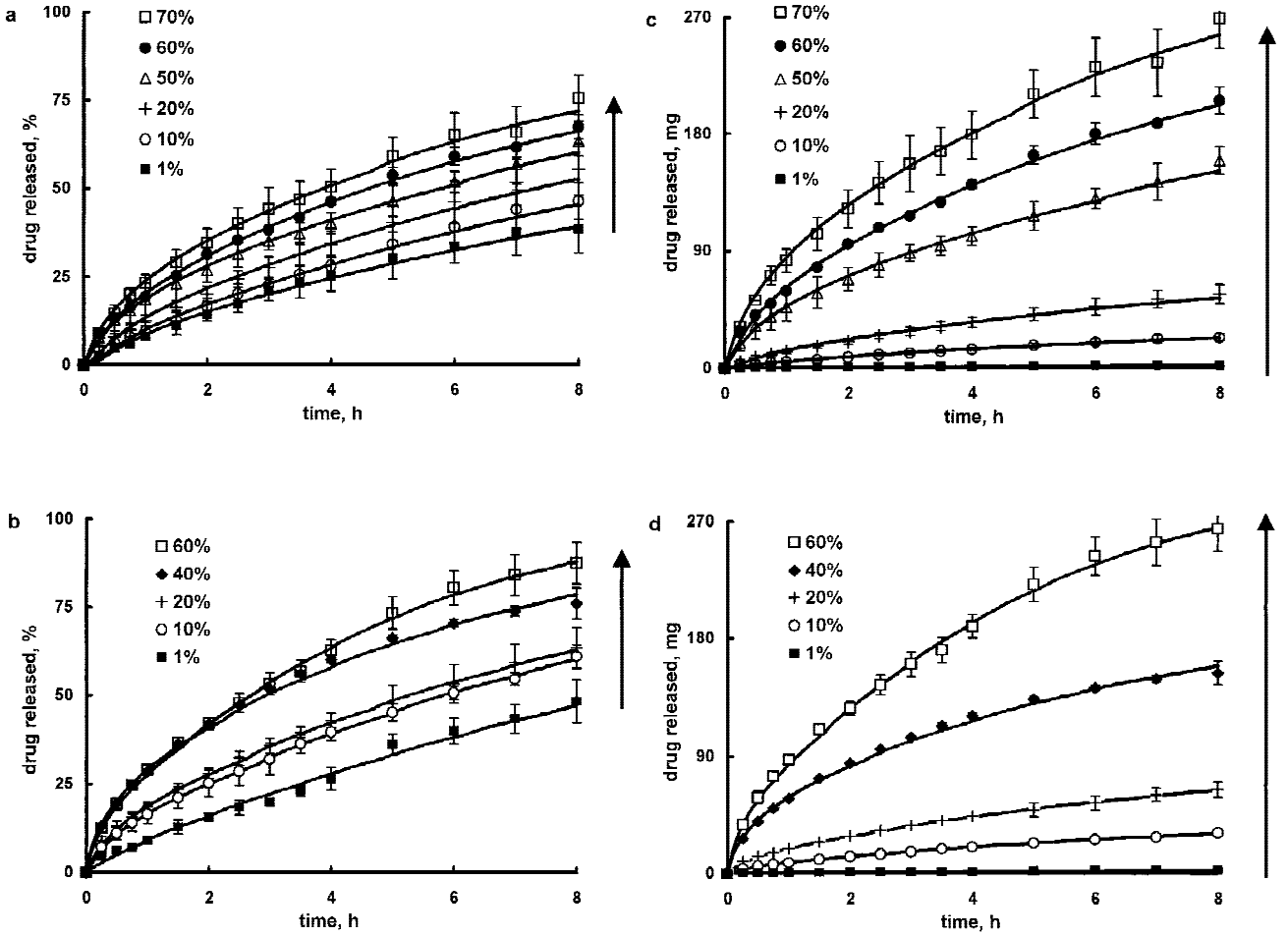

Fig. 4. Effect of the initial drug loading on the resulting release kinetics of chlorpheniramine maleate in (a) phosphate buffer (pH 7.4), relative values (□ 70%, ● 60%, △ 50%, + 20%, ○ 10%, ■ 1%), (b) 0.1 N HCl, relative values (□ 60%, ◆ 40%, + 20%, ○ 10%, ■ 1%), (c) phosphate buffer (pH 7.4), absolute values (□ 70%, ● 60%, △ 50%, + 20%, ○ 10%, ■ 1%), (d) 0.1 N HCl, absolute values (□ 60%, ◆ 40%, + 20%, ○ 10%, ■ 1%) (500 mg tablets, R_0 = 0.6 cm, 37°C, curves: calculated values, symbols: experimental results).

cavities available for diffusion. According to the free volume theory (30), the mobility of a diffusing molecule is a function of its own size and of the average void size. If preexisting cavities are too small to accommodate the diffusing species, larger numbers of monomer segments first have to rearranged to allow the molecule to diffuse. This situation occurs more frequently in tight polymer networks. Within porous systems the probability that the preexisting cavity size is sufficient to allow localized jumps is much higher, and thus no monomer segments have to be rearranged. Consequently, the mobility of the macromolecules in porous systems is not as important as in tight networks. Hence, the dependence of the drug diffusion coefficient on the water content of the system is more pronounced within tight polymer networks compared to porous polymer networks. Thus, the β_2-values are expected to decrease with increasing initial drug loading. Again, this tendency could be confirmed experimentally for both drugs and both release media (Fig. 5).

To minimize the number of required experiments, it was highly desired to establish functional relationships between the β_2- and D_{2crit}-values and the initial drug content. As can be seen in Fig. 5 and Table 1, exponential functions were found to best describe the observed dependencies, for both drugs and both release media. The practical benefit of these equations is to predict the parameters β_2 and D_{2crit} for new initial drug loadings. Knowing these values, the resulting drug release kinetics can be calculated and the effect of varying the initial radius and half-height of the tablet can be simulated (21).

It has to be pointed out that there is a distinct difference between the absolute and relative amount of drug released, in particular when varying the initial drug loading. Comparing Figs. 4(a) and (b) (relative values) to Figs. 4(c) and (d) (absolute values), it can be seen that the effect of the initial drug loading on the resulting drug release kinetics is equal in tendency, but different in extent. The impact on the absolute amount released vs. time is much more pronounced than on the relative amount vs. time. With respect to the resulting drug concentrations at the site of action and thus the therapeutic effect of the drug, the absolute amounts of drug released are more important than the relative ones. However, when adjusting the number of tablets administered, the absolute amounts of drug can easily be varied, but not the shape of the relative release profiles.

Effect of Drug Loading: Poorly Water-Soluble Drugs

The effect of the initial drug loading of the tablet on the resulting release kinetics is more complex in the case of

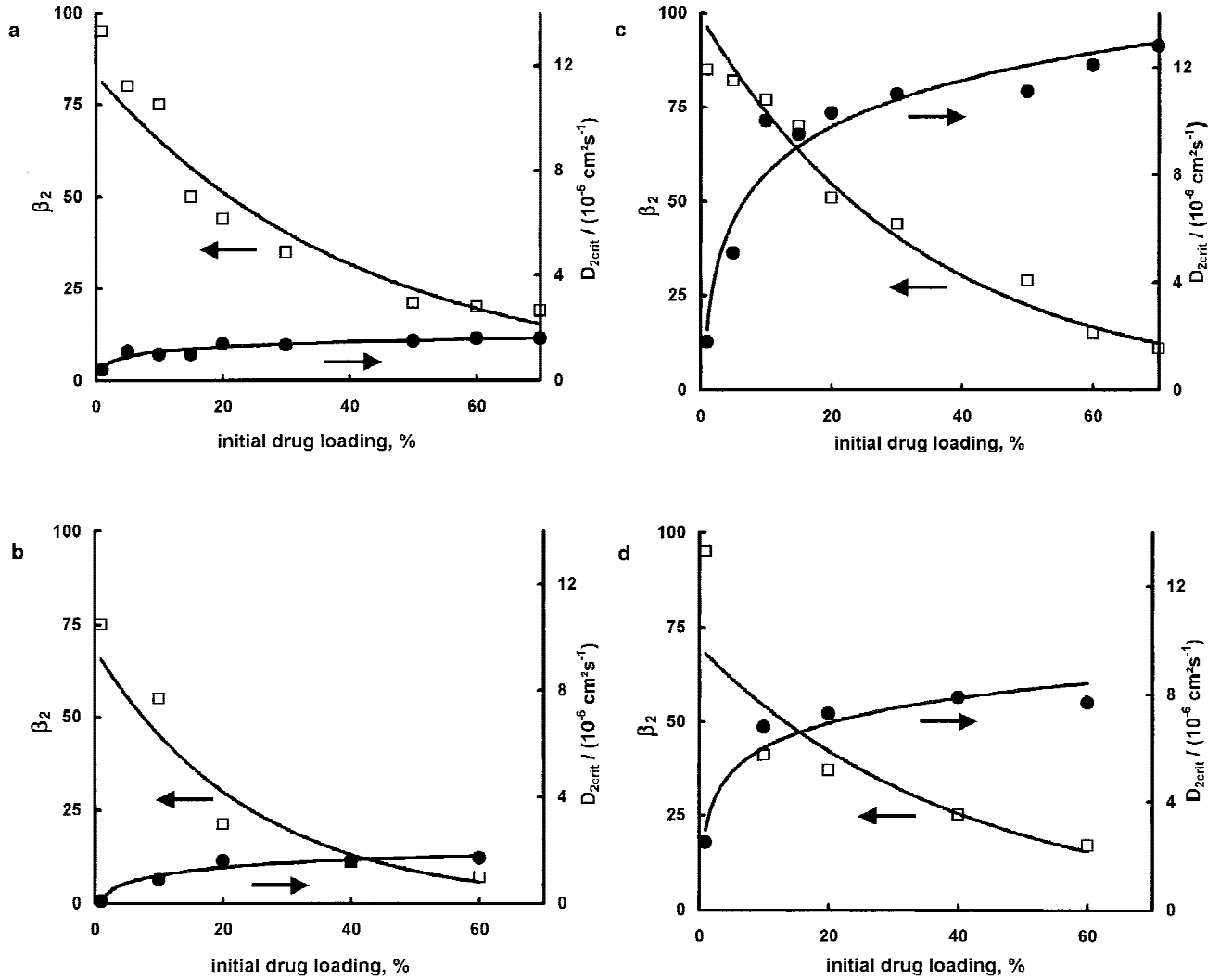

Fig. 5. Dependence of the β_2- and D_{2crit}-values on the initial drug loading in different release media: (a)chlorpheniramine maleate, phosphate buffer (pH 7.4), (b) chlorpheniramine maleate, 0.1 N HCl, (c) theophylline, phosphate buffer (pH 7.4), (d) theophylline, 0.1 N HCl (37°C, curves: calculated values, symbols: experimental results, □ β_2-values, ● D_{2crit}-values).

poorly water-soluble drugs compared to freely water-soluble drugs. This is illustrated in Figs. 6(a–d) for theophylline in 0.1 N HCl and phosphate buffer pH 7.4, respectively. With increasing initial drug loading the relative release rate first decreases and then increases, whereas the absolute release rate monotonically increases in both media.

These findings are in good agreement with data recently reported in the literature (10) and might be explained as follows. Analogous to freely water-soluble drugs, the porosity of the matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rates. But for poorly water-soluble drugs another phenomenon also has to be taken into account. When the amount of drug present at a certain position within the matrix exceeds the amount of drug soluble under the given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within the tablet. When increasing the initial drug loading of poorly water-soluble drugs this excess of drug remaining within the matrix increases. In the case of constant absolute amounts of drug released within a certain time period this leads to decreased relative release rates, simply due to the different 100%-reference-values. This effect might even overcompensate the effect of increasing absolute amounts of drug

Table 1. Quantitative Relationships Between the Initial Drug Loading of the Tablet (% w/w drug = w_d) and the Constants Characterizing the Dependence of the Drug Diffusion Coefficient on the Water-Concentration within the Matrix

Drug	Release medium	β_2	$D_{2crit}/(10^{-6}\ cm^2s^{-1})$
Chlorpheniramine maleate	Phosphate buffer pH 7.4	$83.1 \times \exp(-0.0241 \times w_d)$	$0.265 \times \ln w_d + 0.476$
	0.1 N HCl	$68.4 \times \exp(-0.0413 \times w_d)$	$0.412 \times \ln w_d + 0.103$
Theophylline	Phosphate buffer pH 7.4	$99.2 \times \exp(-0.0297 \times w_d)$	$2.52 \times \ln w_d + 2.23$
	0.1 N HCl	$69.8 \times \exp(-0.0252 \times w_d)$	$1.34 \times \ln w_d + 2.94$

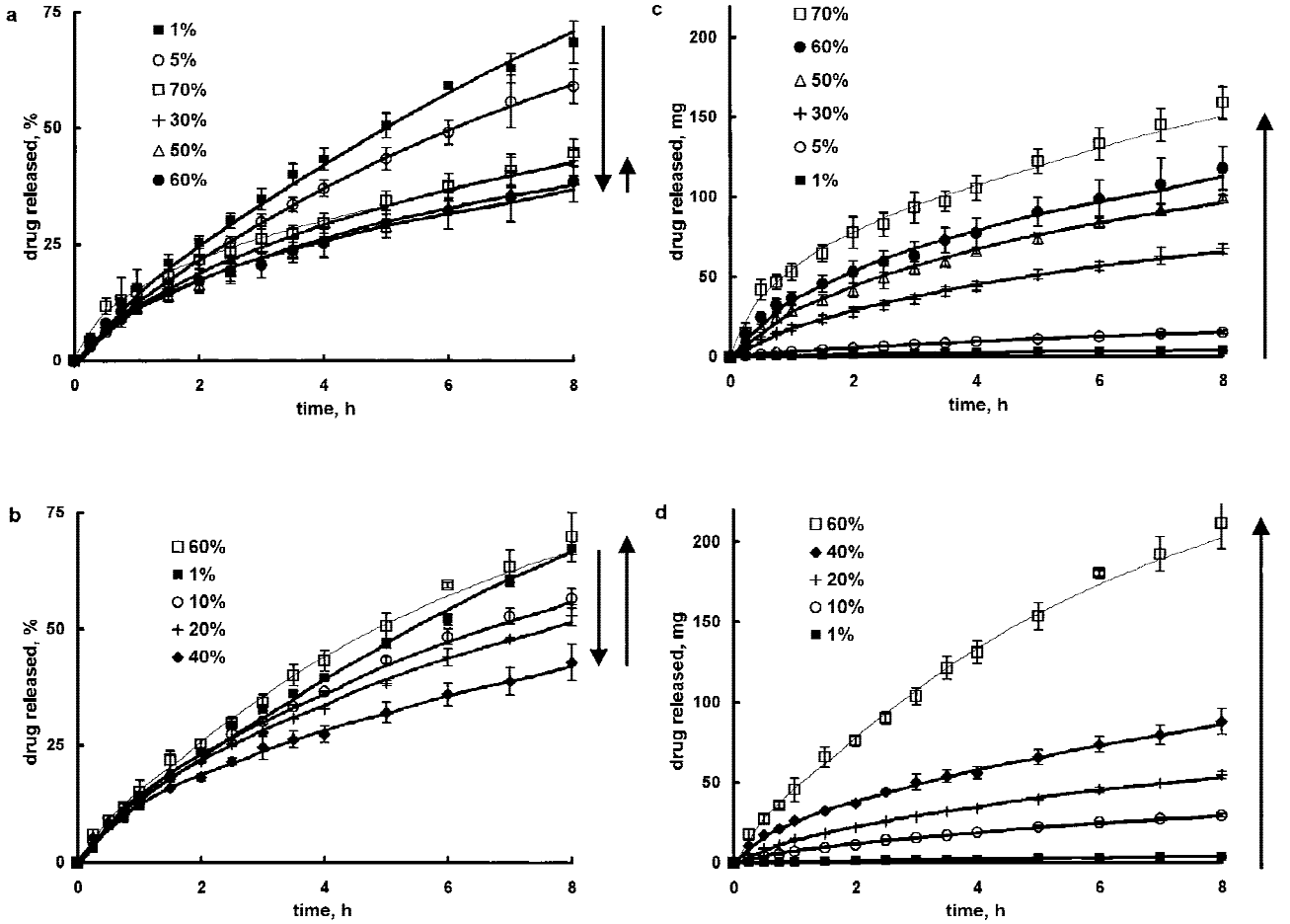

Fig. 6. Effect of the initial drug loading on the resulting release kinetics of theophylline in (a) phosphate buffer (pH 7.4), relative values (■ 1%, ○ 5%, □ 70%, + 30%, △ 50%, ● 60%), (b) 0.1 N HCl, relative values (□ 60%, ■ 1%, ○ 10%, + 20%, ◆ 40%), (c) phosphate buffer (pH 7.4), absolute values (□ 70%, ● 60%, △ 50%, + 30%, ○ 5%, ■ 1%), (d) 0.1 N HCl, absolute values (□ 60%, ◆ 40%, + 20%, ○ 10%, ■ 1%) (500 mg tablets, R_0 = 0.6 cm, 37°C, curves: calculated values, symbols: experimental results).

released, as it is probably the case in the presented drug release studies.

Increasing the initial theophylline loading from 1% to 60% w/w (phosphate buffer pH 7.4) or 1% to 40% w/w (0.1 N HCl), respectively, leads to a decrease of the relative cumulative release [Figs. 6(a) and (b)], whereas the absolute cumulative release increases [Figs. 6(c) and (d)]. A further increase of the initial drug loading (>60% in phosphate buffer pH 7.4, >40% w/w in 0.1 N HCl, respectively) inverses the resulting effect on the relative cumulative drug release. The increasing porosity of the system probably becomes more important than the solubility- and 100% reference-value-effect. The relative and absolute release rates increase. At low initial drug loadings the "porosity effect" is probably not as pronounced as at high initial drug loadings because HPMC is a highly swellable polymer. Thus, small pores are rapidly closed due to polymer swelling.

As can be seen in Figs. 6(a) vs. (b), the critical initial drug loading (above which the relative cumulative drug release increases) is higher in phosphate buffer pH 7.4 (approximately 60% w/w) than in 0.1 N HCl (approximately 40% w/w). This observation is in good agreement with the difference in solubility of theophylline in these release media: 12.0 mg/mL in phosphate buffer pH 7.4 compared to 15.4 mg/mL in 0.1 N HCl (29). With increasing drug solubility the concentration difference during drug release (matrix position vs. bulk fluid) increases, and thus the driving force for drug diffusion out of the device increases. Under theses conditions an increase of the porosity of the matrix upon drug depletion (due to an increased initial drug loading) has probably a more pronounced effect on the resulting absolute drug release rate than in the case of lower drug solubility and thus lower diffusion driving forces. Consequently, the critical initial drug loading (above which the relative release rate increases) decreases with increasing drug solubility.

These phenomena are not straightforward and have to be accurately taken into account when designing new controlled drug delivery systems. It is a crucial point for the practical importance of a mathematical model to consider these aspects and to predict precisely the resulting drug release rates. Again, adjusting the number of administered tablets, the absolute release profiles can easily be modified, but not the relative ones.

Model Validation

To prove the validity of a new mathematical model, it is not sufficient to show good agreement between theory and

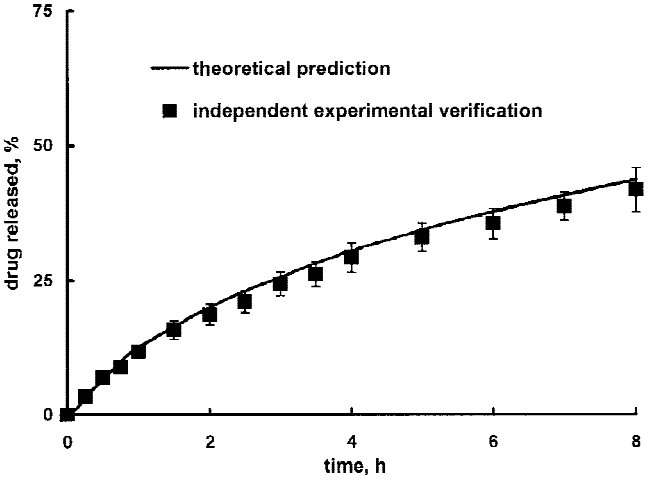

Fig. 7. Validity of the model: predicted and experimentally determined relative amount of theophylline released from HPMC-tablets with R_0 = 0.6 cm, Z_0 = 0.23 cm, and 40% w/w initial drug loading, release medium: phosphate buffer pH 7.4 (500 mg tablets, 37°C).

experiment when fitting the model to experimental data. It has to be demonstrated that the model is able to predict the resulting drug release kinetics for a new, unknown system. Then, independent experiments have to be conducted and the theoretical predictions have to be compared to the independent experimental data.

Using the presented mathematical model the release patterns of theophylline from HPMC-tablets with an initial radius R_0 = 0.6 mm, and an initial half-height Z_0 = 0.23 cm, and 40% w/w initial drug loading in phosphate buffer pH 7.4 were calculated. As can be seen in Fig. 7 these theoretical predictions could be verified by independent release experiments (R^2 = 0.99), proving the validity of the improved model. Further experimental and theoretical investigations, including different drugs, polymers, release media, initial drug loadings and the simulation of the effect of the initial radius and half-height of the device on the resulting drug release kinetics will be presented in a future publication.

REFERENCES

1. P. Colombo. Swelling-controlled release in hydrogel matrices for oral route. *Adv. Drug Del. Rev.* **11**:37–57 (1993).
2. P. Gao and P. E. Fagerness. Diffusion in HPMC gels. I. Determination of drug and water diffusivity by pulsed-field-gradient spin-echo NMR. *Pharm. Res.* **12**:955–964 (1995).
3. P. Gao and R. H. Meury. Swelling of hydroxypropyl methylcellulose matrix tablets. 1. Characterization of swelling using a novel optical imaging method. *J. Pharm. Sci.* **85**:725–731 (1996).
4. A. R. Rajabi-Siahboomi, R. W. Bowtell, P. Mansfield, M. C. Davies, and C. D. Melia. Structure and behavior in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging. *Pharm. Res.* **13**:376–380 (1996).
5. C. A. Fyfe and A. I. Blazek. Investigation of hydrogel formation from hydroxypropylmethylcellulose (HPMC) by NMR spectroscopy and NMR imaging techniques. *Macromolecules* **30**:6230–6237 (1997).
6. R. Eyjolfsson. Hydroxypropyl methylcellulose mixtures: Effects and kinetics of release of an insoluble drug. *Drug Dev. Ind. Pharm.* **25**:667–669 (1999).
7. L. Maggi, E. O. Machiste, M. L. Torre, and U. Conte. Formulation of biphasic release tablets containing slightly soluble drugs. *Eur. J. Pharm. Biopharm.* **48**:37–42 (1999).
8. B.-J. Lee, S.-G. Ryu, and J.-H. Cui. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablets containing melatonin. *Drug Dev. Ind. Pharm.* **25**:493–501 (1999).
9. A. T. Pham and P. I. Lee. Probing the mechanisms of drug release from hydroxypropylmethyl cellulose matrices. *Pharm. Res.* **11**:1379–1384 (1994).
10. K. M. Picker. The influence of drug concentration on release from tablets made of carrageenans. *Proceed. Int'l. Symp. Control. Rel. Bioact. Mater.* **26**:992–993 (1999).
11. J. W. Skoug, M. V. Mikelsons, C. N. Vigneron, and N. L. Stemm. Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release. *J. Control. Rel.* **27**:227–245 (1993).
12. P. Colombo, R. Bettini, P. Santi, A. De Ascentiis, and N. A. Peppas. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. *J. Control. Rel.* **39**:231–237 (1996).
13. R. T. C. Ju, P. R. Nixon, and M. V. Patel. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. *J. Pharm. Sci.* **84**:1455–1463 (1995).
14. R. T. C. Ju, P. R. Nixon, M. V. Patel, and D. M. Tong. Drug release from hydrophilic matrices. 2. A mathematical model based on the polymer disentanglement concentration and the diffusion layer. *J. Pharm. Sci.* **84**:1464–1477 (1995).
15. P. Gao, P. R. Nixon, and J. W. Skoug. Diffusion in HPMC gels. II. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. *Pharm. Res.* **12**:965–971 (1995).
16. P. Gao, J. W. Skoug, P. R. Nixon, T. R. Ju, N. L. Stemm, and K.-C. Sung. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. *J. Pharm. Sci.* **85**:732–740 (1996).
17. R. T. C. Ju, P. R. Nixon, and M. V. Patel. Diffusion coefficients of polymer chains in the diffusion layer adjacent to a swollen hydrophilic matrix. *J. Pharm. Sci.* **86**:1293–1298 (1997).
18. I. Katzhendler, A. Hoffman, A. Goldberger, and M. Friedman. Modeling of drug release from erodible tablets. *J. Pharm. Sci.* **86**:110–115 (1997).
19. J. Siepmann, K. Podual, M. Sriwongjanya, N. A. Peppas, and R. Bodmeier. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. *J. Pharm. Sci.* **88**:65–72 (1999).
20. J. Siepmann, H. Kranz, R. Bodmeier, and N. A. Peppas. HPMC-matrices for controlled drug delivery: A new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics. *Pharm. Res.* **16**:1748–1756 (1999).
21. J. Siepmann, H. Kranz, N. A. Peppas, and R. Bodmeier. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. *Int. J. Pharm.,* **201**:151–164 (2000).
22. J. Crank. *The Mathematics of Diffusion,* 2nd ed., Clarendon Press, Oxford, 1975.
23. H. Fujita. Diffusion in polymer-diluent systems. *Fortschr. Hochpolym.-Forsch.* **3**:1–47 (1961).
24. B. Narasimhan and N. A. Peppas. Disentanglement and reptation during dissolution of rubbery polymers. *J. Polym. Sci., Polym. Phys.* **34**:947–961 (1996).
25. B. Narasimhan and N. A. Peppas. On the importance of chain reptation in models of dissolution of glassy polymers. *Macromolecules* **29**:3283–3291 (1996).
26. B. Narasimhan and N. A. Peppas. Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. *J. Pharm. Sci.* **86**:297–304 (1997).
27. A. A. Noyes and W. R. Whitney. Über die Auflösungsgeschwindigkeit von festen Stoffen in ihren eigenen Lösungen. *Z. physikal. Chem.* **23**:689–692 (1897).
28. R. Bodmeier and O. Paeratakul. Process and formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes. *Int. J. Pharm.* **70**:59–68 (1991).
29. R. Bodmeier and H. Chen. Evaluation of biodegradable poly(lactide) pellets prepared by direct compression. *J. Pharm. Sci.* **78**: 819–822 (1989).
30. L. T. Fan and S. K. Singh. *Controlled release: A quantitative treatment,* Springer-Verlag, Berlin, 1989.