Understanding and Predicting Drug Delivery from Hydrophilic Matrix Tablets Using the "Sequential Layer" Model

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Purpose. The objectives of this work were (i) to study and understand the physicochemical phenomena which are involved in the swelling and drug release from hydrophilic matrix tablets using the "sequential layer" model; and (ii) to predict the effect of the initial radius, height and size of the tablets on the resulting drug release profiles.
Methods. Tablets were prepared by direct compression, using hydroxypropyl methylcellulose (HPMC) grades with different average molecular weights as matrix-forming polymers. The in vitro release of chlorpheniramine maleate, propranolol HCl, acetaminophen, theophylline and diclofenac sodium was studied in phosphate buffer (pH 7.4) and 0.1 M HCl, respectively. The initial drug loading varied from 1 to 70%, while the radius and height of the tablets varied from 1 to 8 mm.
Results. The "sequential layer" model considers water and drug diffusion with non-constant diffusivities and moving boundary conditions, non-homogeneous polymer swelling, drug dissolution, and polymer dissolution. We showed that this model was able to predict the resulting drug release kinetics accurately in all cases.
Conclusions. The "sequential layer" model can be used to elucidate the swelling and drug release behavior from hydrophilic matrix tablets and to simulate the effect of the device geometry on the drug release patterns. Hence, it can facilitate the development of new pharmaceutical products.

Key words: hydrophilic matrix tablet; diffusion; swelling; release mechanism; modeling; hydroxypropyl methylcellulose (HPMC).

INTRODUCTION

An important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems is hydroxypropyl methylcellulose (HPMC) (1). One of its most important characteristics is its swellability, which has a pronounced effect on the release kinetics of an incorporated drug. On contact with biologic fluid water diffuses into the device, resulting in polymer chain relaxation with volume expansion (2). Then, the incorporated drug dissolves and diffuses out of the system. In a typical experimental dissolution vessel and depending on the type of substitution and chain length of the HPMC type used, the macromolecules disentangle more or less rapidly from the polymer. All these phenomena (water, drug and polymer diffusion, polymer swelling, and drug and polymer dissolution) can contribute to the control of drug release (3).

When designing a new oral controlled delivery system for a given drug, some of the major formulation parameters which can be varied to adjust the resulting release patterns include: (i) the type of matrix-forming polymer; (ii) the initial drug loading; and (iii) the geometry of the tablet (height, radius and size). The required composition, size and shape of the system to achieve a particular drug release profile may be found by experimental studies in combination with mathematical models which are able to predict the resulting release profiles as a function of the tablet design (3,4).

Various mathematical theories have been reported in the literature, quantifying the occurring mass transport phenomena in different types of controlled drug delivery systems (3,5,6). These theories can be classified according to the physicochemical phenomena they take into account (3). Roughly, models considering diffusion, swelling, and/or dissolution/erosion can be distinguished. The mathematical treatment is rather simple if only one release rate controlling mechanism is considered. Various pharmaceutical systems can successfully be described with these simple models (3,7). However, in many cases two different mechanisms have to be considered simultaneously. For example, in most biodegradable drug delivery systems, diffusional processes and polymer erosion must be taken into account at the same time (8,9). This renders the mathematical analysis more complex, as the application of the model becomes more difficult (9).

In the case of oral hydrophilic matrix tablets, three phenomena must be taken into account simultaneously: (i) the diffusion of water, drug and disentangled polymer chains; (ii) polymer swelling; and (iii) drug and polymer dissolution (10–12). Consequently, the mathematical treatment becomes very complex. Yet up to now, relatively few theoretical models have been reported in the literature describing this type of controlled drug delivery system (4,13–17).

The crucial point for the predictive power of these theories is the adequate consideration of all physicochemical phenomena. For example, it is essential to take into account that the diffusion coefficients of water and drug in hydrophilic matrix tablets are not constant. In dry systems the diffusion rates approach zero. Thus, the diffusivities of the components approach zero. In contrast, in fully swollen devices the mobilities of the molecules are comparable to those in aqueous solutions. Hence, the diffusion coefficients are of the same order of magnitude as in pure water. Furthermore, the mass transport process in a tablet is three-dimensional. Thus, Fick's second law of diffusion must be solved considering the cylindrical geometry of the device, and polymer swelling must be allowed to occur in all directions. Depending on the degree of substitution and chain length of the HPMC type used, the macromolecules disentangle more or less rapidly from the polymer above a critical water concentration and diffuse into the bulk fluid (16–18).

Polymer swelling and polymer dissolution both significantly complicate the solution of Fick's law of diffusion, leading to moving boundary conditions (4). In addition, also the physicochemical properties of the incorporated drug have to be considered. For example, drug dissolution must be taken into account in the case of poorly water-soluble drugs (solu-

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bility and dissolution rate) (12). If the drug concentration exceeds the solubility of the drug under the given conditions, dissolved and undissolved drug co-exist within the matrix. It is important to consider that only dissolved drug is available for diffusion.

We previously presented a new mathematical model (the "sequential layer" model) (12), which takes into account all these phenomena and which is much more comprehensive than any pre-existing model, our own ones included (10,11). Yet, the applicability of this theory to different drugs, polymers, release media and tablet compositions was not evaluated at that time. Only one theoretical prediction for one specific system was made and compared with independent experimental data. This was because the model requires several molecular/diffusional parameters that are difficult to calculate, even for "simple" excipients, especially cellulose excipients. The major aims of the present study were: (i) to evaluate the applicability of the "sequential layer" model to a broad range of hydrophilic matrix tablets; (ii) to use the model to understand the phenomena involved in swelling and drug release in these systems; (iii) to simulate the effect of the tablet design on the resulting drug release kinetics; and (iv) to show to the practitioner how he can use this model.

EXPERIMENTAL SECTION

Materials

The following materials were obtained from commercial suppliers and used as received: acetaminophen and theophylline anhydrous (both from Synopharm GmbH, Barsbüttel, Germany), chlorpheniramine maleate (CPM; ICN Biomedicals Inc., Aurora, Ohio), diclofenac sodium (Kraemer & Martin Pharma Handels-GmbH, Krefeld, Germany), propranolol HCl (Knoll AG, Ludwigshafen, Germany), hydroxypropyl methylcellulose (HPMC; Methocel® K4M, K15M and K100M, 100% < 30 mesh screen, 99% < 40 mesh screen, Colorcon Ltd., Orpington, United Kingdom).

Methods

Drug-free and drug-loaded (1–70% w/w initial drug content) HPMC tablets were prepared by direct compression. The drug and polymer powders were blended thoroughly with a pestle and mortar. Then, 400 mg (drug-containing tablets) or 500 mg (drug-free tablets) were weighed and manually fed into the die of a single-punch tableting machine (EK0, Korsch, Berlin, Germany) to produce tablets using flat-faced punches (2, 8, 10, 12, 13, 14, or 16 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 M HCl] was used to study the *in vitro* drug release kinetics. At predetermined time intervals, 2 mL samples (which were replaced with fresh medium) were withdrawn, filtered and assayed spectrophotometrically (UV-2101 PC, Shimadzu Scientific Instruments Inc., Columbia, Maryland) at the following wavelengths: acetaminophen, λ = 244 nm; chlorpheniramine maleate, λ = 264 nm; diclofenac sodium, λ = 275 nm; propranolol HCl, λ = 291 nm; theophylline, λ = 270 nm. All experiments were conducted in triplicate.

Tablet weight loss studies were performed as follows: pure HPMC tablets (500 mg, 12 mm diameter, 80 N hardness) were treated as described above. They were weighed at time t = 0 (initial weight). At predetermined time intervals (1, 2, 3, 4, 5, 6, 7, 8, 24, and 32 h) tablets were withdrawn from the release medium [0.1 M HCl or phosphate buffer (pH 7.4), respectively], and dried in an oven at 50°C to constant weight (dry weight).

MATHEMATICAL ANALYSIS

A detailed description of the mathematical analysis was presented before by Siepmann *et al.* (10–12). Briefly, the "sequential layer" model considers the following physicochemical phenomena occurring during drug release from hydrophilic matrix tablets:

(i) At early times, significant water concentration gradients are formed at the matrix/water interface leading to water imbibition into the system. This process is taken into account considering: (i) the exact geometry of the tablet; (ii) the axial and radial direction of the mass transport; and (iii) the significant dependence of the water diffusion coefficient on the matrix swelling ratio (19,20).

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

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

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

(v) In the case of poor water-solubility, dissolved and undissolved drug co-exist within the polymer matrix. Undissolved drug is not available for diffusion.

(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 on drug depletion.

(vii) Depending on the chain length and degree of substitution of the hydrophilic polymer used, the polymer itself dissolves more or less rapidly.

With these phenomena in mind, polymer dissolution was taken into account based on the reptation theory (21–23). A dissolution rate constant, k_{diss}, was considered characterizing the polymer mass loss velocity normalized to the actual surface area of the system:

$$M_{pt} = M_{p0} - k_{diss} A_t t \tag{1}$$

Here, M_{pt} and M_{p0} are the dry polymer matrix mass at time t, and t = 0, respectively; A_t denotes the surface area of the device at time t. Water and drug diffusion were described using Fick's second law of diffusion (24):

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\} \tag{2}$$

Here, c_k and D_k are the concentration and diffusion coefficient of the diffusing species (k = 1 for water, k = 2 for the drug), respectively; r denotes the radial coordinate, z is the axial coordinate, θ is the angular coordinate, and t represents time. According to the free volume theory of diffusion, a Fujita-type (25) exponential dependence of the diffusion co-

efficients on the water content of the system was taken into account:

$$D_k = D_{kcrit} \exp\left\{-\beta_k\left(1 - \frac{c_1}{c_{1crit}}\right)\right\} \quad (3)$$

where β_1 and β_2 are dimensionless constants characterizing this concentration-dependence. 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 (21–23).

Ideal mixing was assumed (no volume contraction on mixing drug, polymer and water), and the total volume of the system at any instant was given by the sum of the volumes of the single components. The calculation of the new matrix dimensions was based on a mass balance considering drug, polymer and water. The initial conditions reflected the fact that the matrix is dry and the drug uniformly distributed throughout the device at t = 0. For the definition of the boundary conditions the water concentration at the surface of the matrix, c_{1crit}, was calculated from the polymer disentanglement concentration (21–23), and the drug concentration at the surface of the matrix was assumed to be equal to zero (perfect sink conditions). Throughout the experiments the tablet hardness was kept constant at 80 N, but the model allows taking into account the influence of this parameter if it significantly affects the water, drug and/or polymer transport (by the system characteristic parameters). To minimize computation time, the origin of the coordinate system was placed at the center of the matrix, resulting in two symmetry planes for the drug and water concentration profiles. Thus, only the concentration profiles within a quarter of the cylindrical matrix had to be calculated. Owing to the concentration dependence of the diffusion coefficients and to the time-variant composition and dimensions of the system, the described set of partial differential equations was solved numerically, using finite differences. More details on the mathematical analysis are given in the appendix and in the literature (10–12).

For theoretical predictions, the structural and diffusional parameters given in Table I, characterizing a particular polymer-drug-release medium combination are required. These parameters were either already known (10–12) or determined by fitting the model to experimental data (k_{diss}: dry matrix weight data, D_{2crit}: drug release data). To provide an accurate determination, only one or maximal two parameters were/had been determined at the same time by fitting the model to a set of at least twelve experimental data points (12). The fitting procedure was based on the minimization of the resulting differences between experimental and theoretical values (least squares method, combined with a modified simplex method: Nelder-Mead-method).

Table I. Structural and Diffusional Parameters Characterizing a Particular Polymer-Drug-Release Medium Combination

Abbreviation	Parameter
c_{1crit}	Critical water concentration at the interface matrix/release medium
D_{1crit}	Diffusion coefficient of water at c_{1crit}
D_{2crit}	Diffusion coefficient of the drug at c_{1crit}
β_1	Constant characterizing the dependence of D_1 on the water concentration
β_2	Constant characterizing the dependence of D_2 on the water concentration
k_{diss}	Dissolution rate constant of the polymer
c_s	Solubility of the drug in the release medium

RESULTS AND DISCUSSION

Polymer Dissolution

Polymer dissolution studies were conducted with pure HPMC K4M, K15M and K100M tablets (500 mg, initial radius = 6 mm). The viscosities of 2% aqueous solutions (20°C) of these polymer grades are equal to 4,000, 15,000, and 100,000 cps, respectively. The increasing viscosity indicates an increase in the average molecular weight of the polymers [96, 134, and 267 kDa according to (16)].

Figure 1a shows the change in the dry tablet matrix weights as a function of time, on exposure to 0.1 M HCl (constant temperature of 37°C). It was observed that the average molecular weight of the polymer affected its dissolution rate. This can be explained as follows. On water imbibition

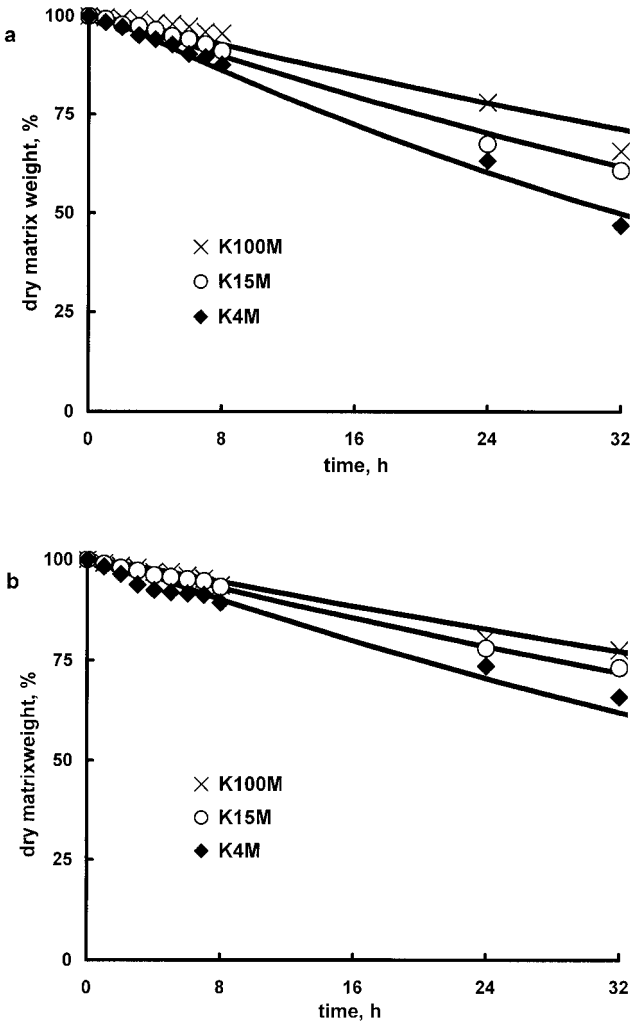

Fig. 1. Effect of the average molecular weight of the polymer on the dissolution kinetics of pure HPMC tablets (500 mg, initial radius = 6 mm). Dry matrix weight vs. time on exposure to (a) 0.1 M HCl; and (b) phosphate buffer (pH 7.4), respectively (37°C, symbols: experimental results, curves: fitted values).

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. Once the macromolecules are disentangled, they diffuse through the unstirred layer surrounding the device, which is characterized by a distinct polymer concentration gradient. With increasing polymer molecular weight the degree of entanglement of the macromolecules increases. Thus, the critical water concentration above which disentanglement occurs increases (16–18). In addition, the diffusion coefficient of the disentangled polymer chains through the unstirred layer surrounding the device decreases with increasing molecular weight (3,16–18).

The "sequential layer" model considers both, the increased critical water concentration and the decreased diffusion coefficient through the unstirred layer with increasing polymer molecular weight. Good agreement between theory and experiment was found when fitting the model to the experimental data (Fig. 1a, the curves represent the theoretical data). The determined polymer dissolution rate constants decreased from 20.5×10^{-5} to 9.9×10^{-5} mg/(s·cm^2) for HPMC K4M to K100M (Table II). Once knowing these parameters, the dissolution kinetics (amount of dissolved and undissolved polymer vs. time) of tablets based on these hydrophilic matrix formers could be calculated at any time step and for any tablet geometry.

In phosphate buffer (pH 7.4), the same tendency in the weight loss of pure HPMC tablets was observed as in 0.1 M HCl (Fig. 1b): with increasing polymer molecular weight the dissolution rate decreased (symbols represent experimental data). Interestingly, all polymer grades dissolved more slowly in phosphate buffer (pH 7.4) than in 0.1 M HCl (Fig. 1b vs. 1a). Due to the complexity of the system, it is difficult to identify the exact reasons for this phenomenon. It might be related to the different osmolalities of the release media and/or to charge effects resulting in different water penetration rates into the devices. An exact analysis of this aspect is beyond the scope of this work. Fitting the "sequential layer" model to the weight loss data lead to good agreement between theory and experiment in both release media (Fig. 1, curves show calculated values). The determined dissolution rate constants are listed in Table II and can be used to calculate the exact amount of polymer dissolved for any tablet geometry at any time point.

Table II. Polymer Dissolution Rate Constant, k_{diss}, and Diffusion Coefficient of Acetaminophen at the Matrix/Release Medium Interface, D_{2crit}, for Different HPMC Grades in 0.1 M HCl and Phosphate Buffer (pH 7.4), Respectively

Polymer	Release medium	$k_{diss} \times 10^5$ mg/(s · cm^2)	$D_{2crit} \times 10^6$ cm^2/s
HPMC K4M	0.1 M HCl	20.5	19.0
	Phosphate buffer (pH 7.4)	14.4	17.0
HPMC K15M	0.1 M HCl	15.1	15.5
	Phosphate buffer (pH 7.4)	10.7	13.8
HPMC K100M	0.1 M HCl	9.9	12.4
	Phosphate buffer (pH 7.4)	7.7	9.6

Effect of the Polymer Grade

For the practical importance of the "sequential layer" model, it was essential to test whether the theory was able to describe drug release for more than only one specific polymer grade. In Fig. 2a the release kinetics of acetaminophen from HPMC K4M, K15M, and K100M-based tablets (200 mg drug, 200 mg polymer, initial radius = 6 mm) in 0.1 M HCl are illustrated. With decreasing polymer molecular weight the degree of entanglement of the macromolecules decreases. Thus, the mobility of the polymer chains on water imbibition increases. According to the free volume theory of diffusion, the probability for a diffusing molecule to jump from one cavity into another consequently increases (3). This leads to in-

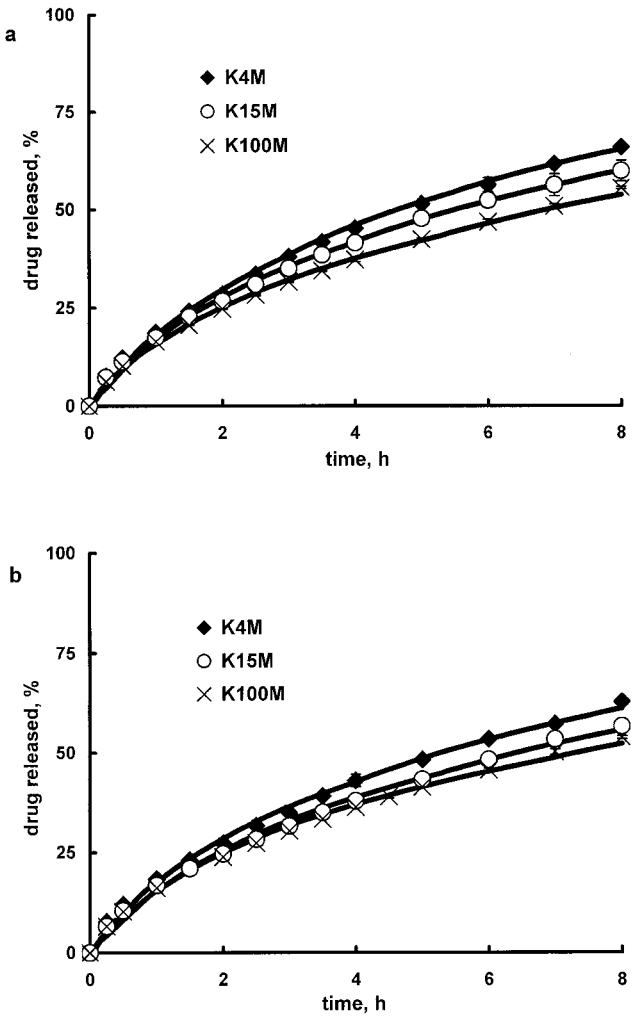

Fig. 2. Effect of the polymer grade on drug release from hydrophilic matrix tablets. Acetaminophen release from HPMC K4M, K15M, and K100M-based tablets in (a) 0.1 M HCl; and (b) phosphate buffer (pH 7.4), respectively (37°C, 200 mg drug, 200 mg polymer, initial radius = 6 mm) (symbols: experimental results, curves: fitted values).

creased water and drug diffusion coefficients and increased drug release rates. In addition, the polymer dissolution rate increased with decreasing molecular weight (as shown above). Importantly, the "sequential layer" model takes these effects into account and accurately describes the experimental data (Fig. 2a). The determined diffusion coefficient of acetaminophen at the matrix/release medium interface decreased from 19.0×10^{-6} to 12.4×10^{-6} cm^2/s with increasing polymer molecular weight (Table II). In phosphate buffer (pH 7.4), the same tendencies were observed. The release rate and diffusion coefficients decreased in the rank order HPMC K4M > K15M > K100M (Fig. 2b and Table II).

Drug release in phosphate buffer (pH 7.4) was slightly slower than in 0.1 M HCl (Fig. 2b vs. 2a). This might be attributed to the different drug solubilities, polymer dissolution rates and drug diffusion coefficients in these media. The solubility of acetaminophen at 37°C in 0.1 M HCl is 20.2 mg/mL compared to 19.6 mg/mL in phosphate buffer (pH 7.4) (26). Thus, the resulting concentration gradients, which are the driving forces for diffusion, are slightly higher in 0.1 M HCl compared to phosphate buffer (pH 7.4). In addition, the matrix-forming polymer dissolves faster in 0.1 M HCl than in phosphate buffer (pH 7.4) (as shown above), resulting in shorter diffusion pathways. Thirdly, the mobility of the drug molecules within the device is increased in 0.1 M HCl, as indicated by the higher diffusion coefficients (Table II).

Effect of the Type of Drug

For the practical importance of the "sequential layer" model, it was also essential to test whether the theory was applicable to different types of drugs. Figure 3a and 3b show the experimentally determined release (symbols) of chlorpheniramine maleate, propranolol HCl, acetaminophen, theophylline and diclofenac sodium from HPMC K4M-based matrix tablets in 0.1 M HCl and phosphate buffer (pH 7.4), respectively. The resulting release profile depended on the type of drug and release medium. Various factors contribute to the overall control of drug release, such as the solubility of the drug within the bulk fluid, the size of the drug molecule and its mobility within the swollen polymeric network, the dissolution rate of the polymer and polymer-drug interactions. As can be seen in Fig. 3a and 3b good agreement between theory and experiment was obtained in all cases (curves represent calculated values). Some of the above-mentioned factors are directly considered in the theory (e.g., solubility of the drug in the release medium), others are indirectly considered (e.g., polymer-drug interactions).

Effect of the Initial Drug Loading

The initial drug content of oral controlled delivery systems significantly varies, depending on the pharmacokinetic properties of the incorporated drug and the required concentrations at the target site. We previously showed that the "sequential layer" model was able to describe the effect of the initial drug loading on the release patterns in the case of HPMC K15M-based matrix tablets (12). The model considers the co-existence of dissolved and undissolved drug within the system whenever the drug concentration at a particular position exceeds the solubility of the drug in the amount of water present at this position. To verify the validity of the "sequential layer" model for other HPMC grades than K15M, we tested its ability to quantify the release rate of acetaminophen from HPMC K100M-based tablets, varying the initial drug loading from 1 to 70% (w/w).

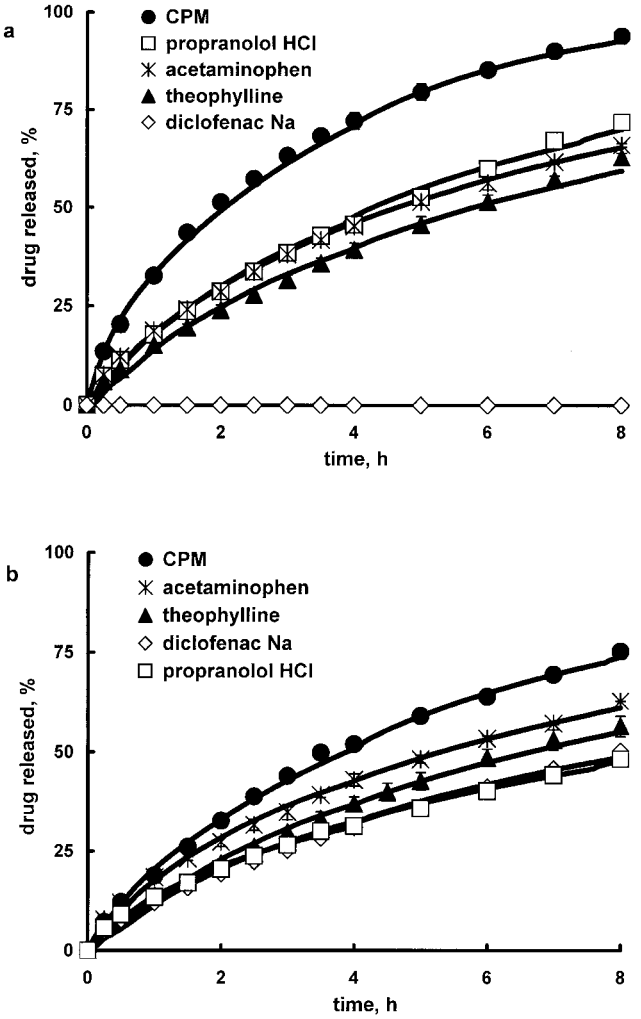

Fig. 3. Effect of the type of drug on the release patterns from HPMC K4M-based matrix tablets. Chlorpheniramine maleate, propranolol HCl, acetaminophen, theophylline and diclofenac sodium release in (a) 0.1 M HCl; and (b) phosphate buffer (pH 7.4), respectively (37°C, 200 mg drug, 200 mg polymer, initial radius = 6 mm) (symbols: experimental results, curves: fitted values).

Figure 4a and 4b illustrate the experimentally determined absolute cumulative amount of drug released vs. time in 0.1 M HCl and phosphate buffer (pH 7.4), respectively (symbols). The absolute and relative (data not shown) release rate of the drug increased in both media with increasing initial drug loading due to the increased porosity of the polymeric network on drug depletion. Figure 4a and 4b also show the fitted, theoretical drug release rates in these media (curves). As can be seen, good agreement was obtained in all cases.

Effect of the Tablet Height (Constant Radius)

Figure 5a shows the theoretically predicted relative amount of theophylline released from HPMC K15M-based matrix tablets into phosphate buffer (pH 7.4). The initial tablet radius was kept constant at 4 mm, whereas the initial tablet

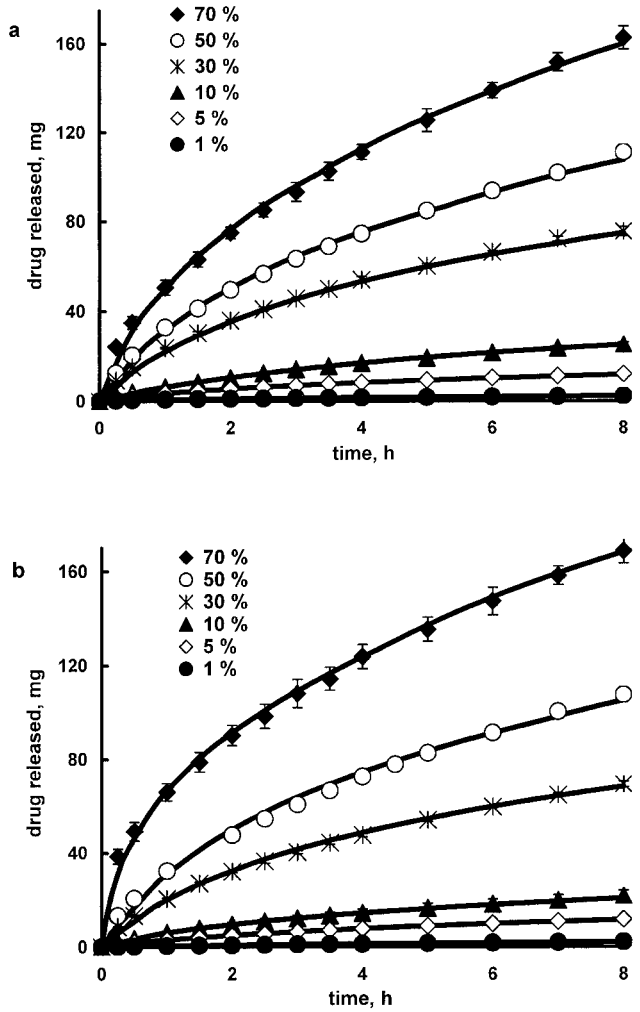

Fig. 4. Effect of the initial drug loading on the release patterns from HPMC K100M-based matrix tablets. Acetaminophen release for 70, 50, 30, 10, 5, and 1% w/w initial drug loading in (a) 0.1 M HCl; and (b) phosphate buffer (pH 7.4), respectively (37°C, 400 mg tablet weight, initial radius = 6 mm) (symbols: experimental results, curves: fitted values).

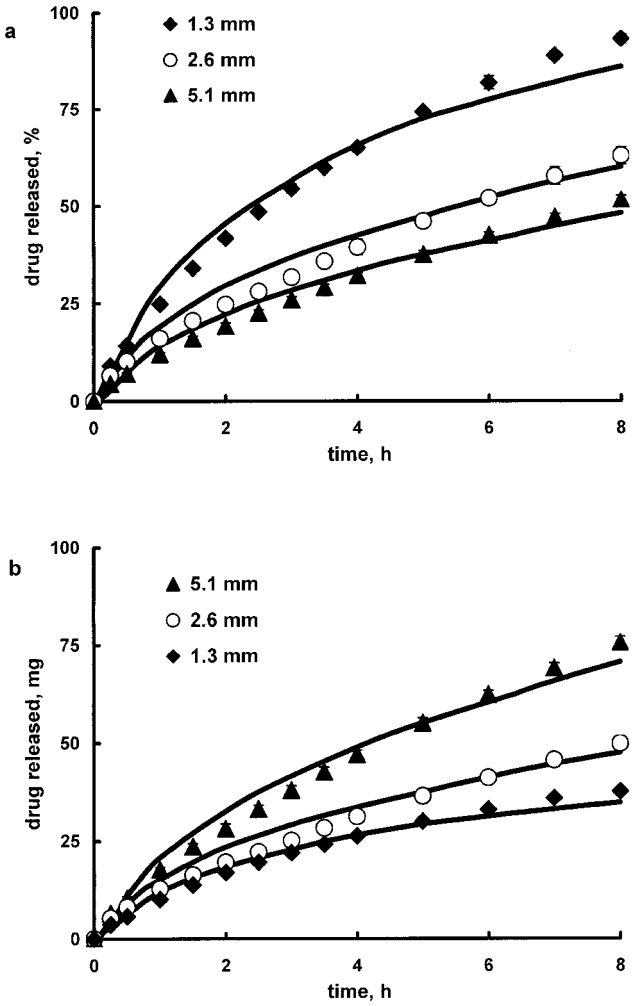

Fig. 5. Effect of the initial tablet height on the release patterns of theophylline from HPMC K15M-based matrix tablets in phosphate buffer (pH 7.4): (a) relative amount of drug released; and (b) absolute amount of drug released vs. time (37°C, initial tablet radius = 4 mm, initial tablet height indicated in the figure legend, 50% w/w initial drug loading) (curves: predicted values, symbols: independent experimental data).

height was varied from 1.3 to 5.1 mm. Also the initial drug loading was kept constant (50% w/w). As can be seen the model predicts a substantial increase in drug release with decreasing initial tablet height (which can probably be attributed to the increasing relative surface area of the system). The curves in Fig. 5a represent the theoretically predicted drug release rates.

It is important that this substantial increase in drug release was confirmed by the independent experimental studies (Fig. 5a, the symbols represent the experimental results), proving the predictive power of the "sequential layer" model. It has to be pointed out that Fig. 5a shows the *relative* drug release rates, the respective *absolute* release rates are illustrated in Fig. 5b. Obviously, the effect of the initial tablet height is inversed: with increasing tablet height, the absolute drug release rate increases due to the increased total amount of drug available for diffusion. Thus, the "total drug amount" effect overcompensates the "relative surface area" effect. From a tablet designer's point of view, to achieve a certain shape of release profile, the relative amounts of drug released are a priori more important. The respective absolute amounts of drug released, which determine the resulting drug concentrations at the site of action, can be adjusted by either varying the number of administered devices or by varying the drug loading of the system.

Effect of the Tablet Radius (Constant Height)

The "sequential layer" model was also used to predict the effect of the initial tablet radius of theophylline-loaded (50% w/w), HPMC K15M-based tablets in phosphate buffer (pH 7.4). The initial tablet height was kept constant at 2.6 mm, while the radius was varied from 1 to 6.5 mm. Figure 6a and 6b show the respective relative and absolute amounts of drug released vs. time (curves represent theoretical predictions). Clearly, the initial radius had a pronounced effect on both types of release profiles. With increasing initial tablet radius, the relative surface area decreases, thus, the relative release rate decreases. In contrast, the absolute amount of drug available for diffusion increases and this effect again

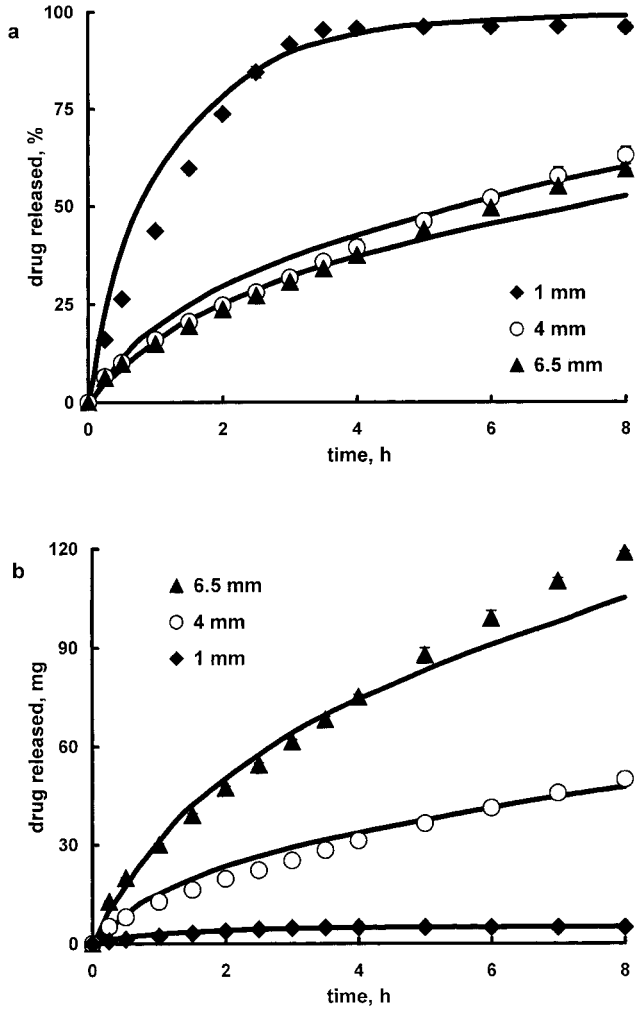

Fig. 6. Effect of the initial tablet radius on the release patterns of theophylline from HPMC K15M-based matrix tablets in phosphate buffer (pH 7.4): (a) relative amount of drug released; and (b) absolute amount of drug released vs. time (37°C, initial tablet height = 2.6 mm, initial tablet radius indicated in the figure legend, 50% w/w initial drug loading) (curves: predicted values, symbols: independent experimental data).

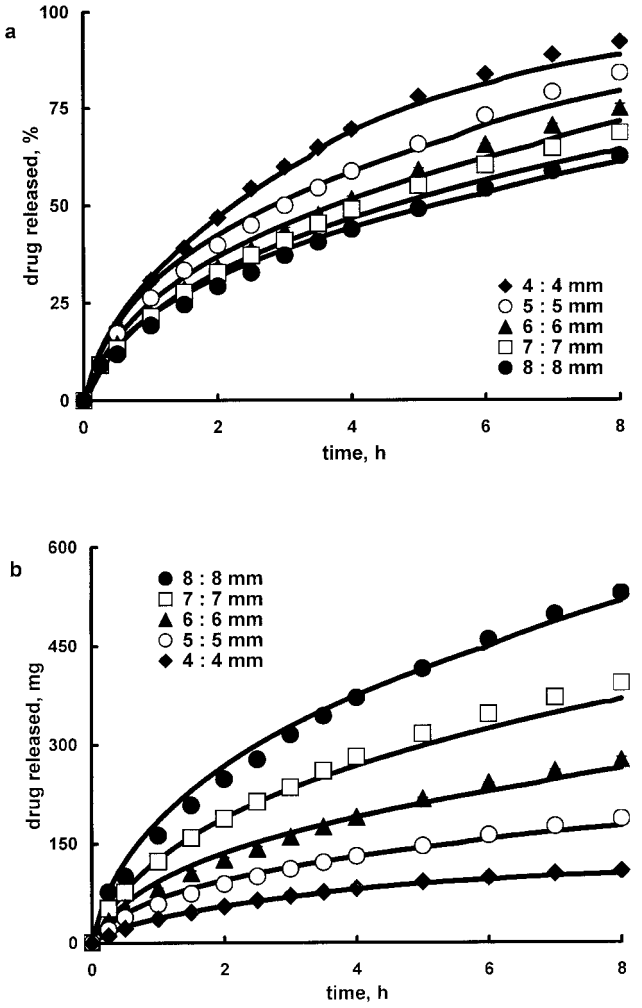

Fig. 7. Effect of the initial tablet size on the release patterns of chlorpheniramine maleate from HPMC K15M-based matrix tablets in 0.1 M HCl: (a) relative amount of drug released; and (b) absolute amount of drug released vs. time (curves: predicted values, symbols: independent experimental data).

overcompensates the effect of the decreased relative surface area, resulting in increased absolute drug release rates (Fig. 6b). Importantly, these theoretically predicted tendencies were both verified by the independent experimental studies (Fig. 6a and 6b, symbols represent experimental data), demonstrating the validity of the "sequential layer" model and its predictive power to facilitate the design of new oral controlled drug delivery systems.

Effect of the Tablet Size (Constant Ratio "Height : Radius")

Finally, the "sequential layer" model was used to predict the effect of the initial tablet size on the resulting release kinetics of chlorpheniramine maleate from HPMC K15M-based matrix tablets in 0.1 M HCl. The ratio "initial tablet height : initial tablet radius" was kept constant (1 : 1). The height was varied from 4 to 8 mm, and the model predicted fundamental differences in the resulting relative and absolute drug release rates (Fig. 7a and 7b). With increasing tablet size the relative drug release rate decreased, whereas the absolute release rate increased for analogous reasons as discussed above. Thus, also varying the tablet size is an effective tool to adjust the resulting drug release patterns. Again, these theoretical predictions of the "sequential layer" model (curves) were confirmed by the independent experimental studies (symbols).

CONCLUSIONS

The predictive power of the "sequential layer" model to describe drug release from hydrophilic matrix tablets has been demonstrated. The model is applicable to a wide range of polymers, drugs, release media and tablet compositions, and can be used to understand the effect of the tablet design (e.g., initial radius, height and size) on the resulting drug release patterns. The importance of the relative surface area of the device available for diffusion as well as of the total amount of drug present in the tablet was illustrated. The observed phenomena when varying the device geometry are not

straightforward and have to be accurately taken into account when designing new oral controlled drug delivery systems.

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APPENDIX

Initial Condition

At $t = 0$ the tablet 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:

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

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

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

Boundary Conditions

According to the theory of polymer dissolution (21–23), the water concentration at the interface matrix/release medium, c_{1crit}, can be calculated from the polymer disentanglement concentration. Thus, the corresponding boundary conditions can be written as follows:

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

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

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):

$$t > 0 \qquad c_2 = 0 \qquad 0 \le r \le R_t \qquad z = Z_t \quad (8)$$

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

As the origin of the coordinate system is placed at the center of the matrix, there are two symmetry planes for the drug and water concentration profiles:

$$t > 0 \qquad \frac{\partial \mathbf{c}_1}{\partial \mathbf{z}} = \mathbf{0} \qquad 0 \le r \le R_t \qquad z = 0 \quad (10)$$

$$t > 0 \qquad \frac{\partial \mathbf{c}_1}{\partial \mathbf{r}} = \mathbf{0} \qquad 0 \le z \le Z_t \qquad r = 0 \quad (11)$$

$$t > 0 \qquad \frac{\partial \mathbf{c}_2}{\partial \mathbf{z}} = \mathbf{0} \qquad 0 \le r \le R_t \qquad z = 0 \quad (12)$$

$$t > 0 \qquad \frac{\partial \mathbf{c}_2}{\partial \mathbf{r}} = \mathbf{0} \qquad 0 \le z \le Z_t \qquad r = 0 \quad (13)$$

As the polymer is swellable and the drug and polymer are water-soluble, the interface matrix/release medium is not stationary (R_t and Z_t are time-dependent), the boundaries are moving.

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. "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. The time is divided into g time intervals Δt (for most of the simulations $I = J = 50$ and $g = 500{,}000$ have been chosen). Using Eqs. 2,3 and Eqs. 6 to 13, the concentration profiles of water and drug for a new time step ($t = t_0+\Delta t$) can be calculated, when the concentration profile is known at the previous time step ($t = t_0$). The concentration at a certain inner grid point [i][j] for the new time step ($t = t_0+\Delta t$) is calculated from the concentrations at the same grid point [i][j] and its four direct neighbors [i-1][j]; [i][j-1]; [i][j+1]; [i+1][j] 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. 6 to 13). At time $t = 0$ the concentration profile of the drug and water are given by the initial conditions (Eqs. 4,5). Hence, the concentration profiles of drug and water at $t = 0+\Delta t$, $t = 0+2\Delta t$, $t = 0+3\Delta t, \ldots, t = 0+g\Delta t$ can be calculated sequentially.

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

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