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Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC)

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Abstract

The objective of this article is to review the spectrum of mathematical models that have been developed to describe drug release from hydroxypropyl methylcellulose (HPMC)-based pharmaceutical devices. The major advantages of these models are: (i) the elucidation of the underlying mass transport mechanisms; and (ii) the possibility to predict the effect of the device design parameters (e.g., shape, size and composition of HPMC-based matrix tablets) on the resulting drug release rate, thus facilitating the development of new pharmaceutical products. Simple empirical or semi-empirical models such as the classical Higuchi equation and the so-called power law, as well as more complex mechanistic theories that consider diffusion, swelling and dissolution processes simultaneously are presented, and their advantages and limitations are discussed. Various examples of practical applications to experimental drug release data are given. The choice of the appropriate mathematical model when developing new pharmaceutical products or elucidating drug release mechanisms strongly depends on the desired or required predictive ability and accuracy of the model. In many cases, the use of a simple empirical or semi-empirical model is fully sufficient. However, when reliable, detailed information are required, more complex, mechanistic theories must be applied. The present article is a comprehensive review of the current state of the art of mathematical modeling drug release from HPMC-based delivery systems and discusses the crucial points of the most important theories.

Keywords: Controlled drug delivery; HPMC; Hydrophilic matrices; Hydroxypropyl methylcellulose; Modeling; Release mechanism

Contents

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1. Introduction

Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems [1,2]. One of its most important characteristics is the high swellability, which has a significant effect on the release kinetics of an incorporated drug. Upon contact with water or biological fluid the latter diffuses into the device, resulting in polymer chain relaxation with volume expansion [3,4]. Then, the incorporated drug diffuses out of the system.

For the design of new controlled drug delivery systems which are based on HPMC and aimed at providing particular, pre-determined release profiles, it is highly desirable: (i) to know the exact mass transport mechanisms involved in drug release; and (ii) to be able to predict quantitatively the resulting drug release kinetics. The practical benefit of an adequate mathematical model is the possibility to simulate the effect of the design parameters of HPMC-based drug delivery systems on the release profiles [5]. In the ideal case, the required composition (type and amount of drug, polymer and additives) and geometry (size and shape) of the new controlled drug delivery system designed to achieve a certain drug release profile can be predicted theoretically. Thus, the number of necessary experiments can be minimized and the development of new pharmaceutical products significantly facilitated.

Diffusion, swelling and erosion are the most important rate-controlling mechanisms of commercially available controlled release products [6]. Diffusion can be described using Fick's second law [7–9]. There are various ways to apply the respective equations [10]. First of all, the considered geometry is important. Assuming one-dimensional transport in thin films results in rather simple mathematical expressions, but this approach is only valid for flat, planar devices. In the case of HPMC-based drug delivery systems three-dimensional, cylindrical geometries (tablets) are more relevant, but mathematically more difficult to treat. In addition, it is necessary to decide whether to assume constant or non-constant diffusivities. The mathematical treatment of constant diffusivity problems is much simpler, but only valid in the case of polymers that do not significantly swell upon contact with water (e.g., ethylcellulose). For HPMC tablets, the drug diffusion coefficients are strongly dependent on the water content of the system [11]. Here, the assumption of constant diffusivities leads to less realistic mathematical models. Depending on the degree of substitution and chain length of the HPMC type used, polymer dissolution might be observed during drug release. This will complicate the solution of Fick's second law of diffusion, leading to moving boundary conditions. In addition to the physicochemical properties of the polymer also the characteristics of the drug have to be considered. For example, drug dissolution has to be taken into account in case of poorly water-soluble drugs.

Depending on the complexity of the resulting system of mathematical equations describing diffusion, swelling and/or dissolution processes, analytical and/or numerical solutions can be derived. Analytical solutions have the major advantage of being more informative. The involved design and physicochemical parameters still appear in the equations.

In the case of explicit analytical solutions, we can obtain direct relationships between the dependent and independent variables. In the case of implicit analytical solutions, this dependence is not as obvious. However, compared to numerical solutions, it is still much easier to get an idea of the effect of certain independent variables on particular dependent variables. Thus, it is highly desirable to derive explicit analytical solutions. Unfortunately, this is only possible in the case of rather simple forms of the diffusion equations, e.g., assuming constant diffusivities. In general, physically more realistic models are mathematically more complex and very often it is difficult to find analytical solutions of the respective set of equations [12]. Three important methods to derive exact mathematical solutions can

be distinguished: (i) the method of reflection and superposition; (ii) the method of separation of variables; and (iii) the method of the Laplace transform. For a discussion of the advantages and disadvantages of these methods the reader is referred to other literature (e.g., [7,13,14]). Also a description of the principles of numerical analysis is beyond the scope of this review, but excellent textbooks are available (e.g., [7,13–15]). In contrast to analytical solutions, only approximate solutions are derived. The resulting error can be controlled using various different methods. Generally, cumbersome mathematical calculations are required to reduce the approximation error to an acceptable level (e.g. $<0.1\%$). The development of digital computers dramatically decreased the time necessary to perform the calculations, so that nowadays numerical methods have become economic even for routine use.

It is the scope of this article to review the most important mathematical models which have been developed to describe drug release from HPMC-based pharmaceutical systems. Simple and very comprehensive theories are presented and their advantages and limitations are discussed. For a better understanding of the described theories, first the most relevant physicochemical properties of HPMC and the major principles of the overall drug release mechanisms from HPMC-based delivery systems are presented. Due to the substantially high number of variables, no effort was made in this review to present a uniform picture of the different systems of notation defined by the respective authors. The original nomenclatures are used and only some cases are modified by using more common abbreviations to avoid misunderstandings.

2. Physicochemical characterization of HPMC

HPMC is a propylene glycol ether of methylcellulose; its chemical structure is illustrated in Fig. 1. The substituent R represents either a $-CH_3$, or a $-CH_2CH(CH_3)OH$ group, or a hydrogen atom. The physicochemical properties of this polymer are strongly affected by: (i) the methoxy group content; (ii) the hydroxypropoxy group content; and (iii) the molecular weight. The USP distinguishes four different types of HPMC, classified according to their

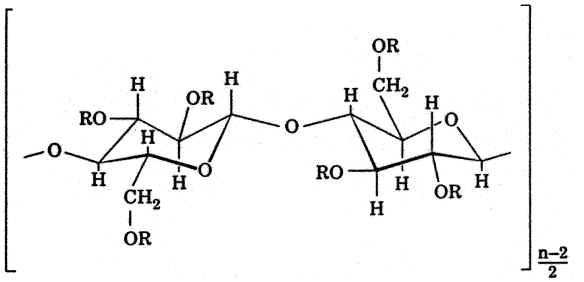

Fig. 1. Chemical structure of HPMC. The substituent R represents either a $-CH_3$, or a $-CH_2CH(CH_3)OH$ group, or a hydrogen atom.

relative $-OCH_3$ and $-OCH_2CH(CH_3)OH$ content: HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy-groups, the last two numbers the percentage of hydroxypropoxy-groups, determined after drying at 105°C for 2 h. The exact limits for the degree of substitution defining the respective HPMC types are given in Table 1. In addition, the USP describes a method to determine the apparent viscosity of an aqueous 2% solution of the polymer using a suitable viscosimeter of the Ubbelohde type. This apparent viscosity serves as a measure for the average chain length of the polymer. The measured value must lie within the 80.0 to 120.0% range of the viscosity stated on the label for HPMC types of 100 mPa s or less, and within the 75.0 to 140.0% range for HPMC types of higher viscosity.

Interestingly, Dahl et al. [16] reported broad variations concerning important characteristics of seven batches HPMC 2208 with a labeled viscosity of 15,000 mPa s, provided by two different manufacturers. All samples had similar viscosities, except one batch which was outside the USP specifications. The methoxy-group content was uniformly high and

Table 1
USP specifications for different types of HPMC, classified according to their degree of methoxy- and hydroxypropoxy-substitution

Substitution type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

three batches fell outside the USP limits of 19.0 to 24.0%. The hydroxypropoxy-group content (although within the USP specifications of 4.0 to 12.0%), varied relatively more than the methoxy group content. These variations lead to significant differences concerning the resulting release rate of naproxen from compressed matrix tablets in vitro. The authors concluded that each batch (even from the same manufacturer) should be carefully controlled and that the specifications of the USP and other pharmacopoeas might have to be reinforced.

The glass transition temperature, T_g, of a polymer is an important characteristic constant, in particular with respect to applications in the field of controlled drug delivery. Below the T_g the mobility of the macromolecules is very low. The material is in its glassy state resulting in extremely small diffusion rates [10]. In contrast, above the glass transition temperature the mobility of the polymer chains is markedly increased (rubbery state), leading to much higher mass transfer rates of water and drug. Thus, we must know the T_g of the polymer when modeling drug release from controlled delivery systems. A good summary of work that has been done to determine the T_g of HPMC has been provided by Doelker [17]. He compares the results of various researchers [18–26] and lists values ranging from 154 to 184°C (Table 2). Various techniques have been used to determine the glass transition temperature: differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermomechanical analysis (TMA), torsional braid analysis (TBA) and dynamic mechanical analysis (DMA). Different methods often lead to different T_g-values, and usually only the results achieved with one special method can be compared directly. In addition, the variation of the degree of substitution and the molecular weight plays a role in the observed variance of the T_g. Furthermore, a 57°C-value was reported by Conte et al. [26], which seems to correspond to a low-energy secondary transition. The relevance of this low-temperature transition is yet unknown, but could be of significance in the diffusion of oxygen and water.

Numerous studies have been reported in the literature investigating the drug release kinetics from HPMC-based delivery systems [27–31]. Various techniques have been used to elucidate the physical processes involved. For example, Melia and coworkers [32–35] characterized the water mobility in the gel layer of hydrating HPMC matrices using NMR imaging. It has been shown that there is a diffusivity gradient across this layer and that it is affected by the degree of substitution of the polymer. Also Fyfe and Blazek [36] investigated the HPMC hydrogel formation by NMR spectroscopy pointing out the complications due to the presence of trapped gas [37]. Recently, they studied the release behavior of two model drugs, triflupromazine–HCl and 5-fluorouracil from HPMC tablets [38]. The tablet swelling was restricted to one dimension and distributions of the water and model drugs were obtained by ^{1}H and ^{19}F imaging. The distributions of triflupromazine–HCl and HPMC paralleled each other and the drug was only released at the eroding edge of the tablet where the HPMC concentration dropped below 10%. In contrast, 5-fluorouracil was released much more rapidly from the tablet and appeared to escape by diffusion from regions as high as 30% HPMC. They also developed a system for performing NMR imaging experiments on drug delivery devices within a flow-through dissolution apparatus, USP Apparatus 4 [39].

Ford and coworkers [40–42] used DSC techniques to study the distribution and amount of water in

Table 2
Reported glass transition temperatures for HPMC (adapted from Doelker [17], with permission from Springer–Verlag)

Material	Method	T_g (°C)	Ref.
HPMC Type 2910			
Methocel® E15	TMA	172–175[a]	[18]
Pharmacoat® 606	DSC	177	[19]
Pharmacoat® 606	DSC	155	[20]
Pharmacoat® 606	DSC	180	[21]
Pharmacoat® 606	DTA	169–174	[21]
Pharmacoat® 606	TBA	153.5, 158.5	[21]
Pharmacoat® 606	DSC	155.8	[22]
Pharmacoat® 606	TMA	163.8, 174.4	[22]
Pharmacoat® 603	DMA	160	[23]
Pharmacoat® 606	DMA	170	[23]
Pharmacoat® 615	DMA	175	[23]
Pharmacoat® 606	DMA	154	[24]
HPMC Type 2208			
Methocel® K4M	DSC	184	[25]
Methocel® K4M	DSC	(57)	[26]

[a] The values obtained by TMA in the penetration mode have been reported by the authors as softening temperatures.

HPMC gels. Water loosely bound to the polymer was detected as one or more events appearing at the low-temperature side of the main endotherm for the melting of free water in the DSC scans. The HPMC molecular weight, HPMC substitution type, gel storage time, and added drug influenced the appearance of these melting events [43,44]. Pham and Lee [28] designed a new flow-through cell to provide well-defined hydrodynamic conditions during the experimental studies and to allow precise measurements of dissolution and swelling front positions versus time. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release were found to increase with either higher levels of drug loading or lower viscosity grades of HPMC. Gao and Meury [45] developed an optical image analysis method to examine the dynamic swelling behavior of HPMC-based matrix tablets in situ. In addition to providing precise determinations of the apparent gel layer thickness and the tablet dimensions, this method is also capable of estimating the HPMC concentration profile across the gel layer. They used this technique to characterize the effect of the HPMC/lactose ratio and HPMC viscosity grade (molecular weight) on the swelling of the matrix [46]. For all formulations tested it was found that (i) swelling is anisotropic with a preferential expansion in the axial direction; and (ii) swelling is isotropic with respect to the gel layer thickness and composition in both, axial and radial directions.

The modification of the surface area of HPMC tablets in order to achieve a desired release rate has been studied by Colombo et al. [47,48]. Different surface portions of an HPMC matrix tablet were covered with an impermeable coating. They investigated the drug release mechanisms and studied the influence of the type of coating on the resulting release rate. In order to facilitate the industrial production, the manual film-coating process can be avoided using press-coating techniques [49].

3. Overall drug release mechanism from HPMC-based systems

The overall drug release mechanism from HPMC-based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. The following phenomena are involved:

(i) At the beginning of the process, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. To describe this process adequately, it is important to consider (i) the exact geometry of the device; (ii) in case of cylinders, both, axial and radial direction of the mass transport; and (iii) the significant dependence of the water diffusion coefficient on the matrix swelling ratio [50,51]. 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. Water acts as a plasticizer and reduces the glass transition temperature of the system. Once the T_g equals the temperature of the system, the polymer chains undergo the transition from the glassy to the rubbery state.

(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) Upon 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 non-dissolved drug coexist within the polymer matrix. Non-dissolved 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 upon drug depletion.

(vii) Depending on the chain length and degree of substitution of the HPMC type used, the polymer itself dissolves more or less rapidly. In certain cases this phenomenon is negligible, for example if all drug has already been released before polymer dissolution becomes important.

As a result of conditions (i), (ii), (iv), (vi), and (vii) the mathematical description of the diffusional processes requires strongly time-dependent terms.

From the aforementioned possible phenomena it is obvious that there is no universal drug release mechanism that is valid for all kinds of HPMC-based systems. In contrast, there are many devices that

exhibit various mechanisms that control drug release, mechanisms such as polymer swelling, drug dissolution, drug diffusion or combinations of the above. The physicochemical characteristics and geometry of each device determine the resulting governing processes. Concerning the mathematical modeling of drug release from HPMC-based systems, one must identify the most important transport phenomenon for the investigated device and neglect the other processes, otherwise the mathematical model becomes too complex for facile use.

4. Empirical and semi-empirical mathematical models

4.1. Higuchi equation

In 1961, Higuchi [52] published the probably most famous and most often used mathematical equation to describe the release rate of drugs from matrix systems. Initially valid only for planar systems, it was later modified and extended to consider different geometries and matrix characteristics including porous structures [53–57]. We have pointed out in the past [9] that the classical Higuchi equation [52] was derived under pseudo-steady state assumptions and generally cannot be applied to 'real' controlled release systems.

The basic equation of the Higuchi model is:

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \qquad \text{for } c_0 > c_s \tag{1}$$

where M_t is the cumulative absolute amount of drug released at time t, A is the surface area of the controlled release device exposed to the release medium, D is the drug diffusivity in the polymer carrier, and c_0 and c_s are the initial drug concentration, and the solubility of the drug in the polymer, respectively. Clearly, Eq. (1) can be expressed as:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \tag{2}$$

where M_∞ is the absolute cumulative amount of drug released at infinite time (which should be equal to the absolute amount of drug incorporated within the system at time $t=0$), and K is a constant reflecting the design variables of the system. Thus, the fraction of drug released is proportional to the square root of time. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time.

An important advantage of these equations is their simplicity. However, when applying them to controlled drug delivery systems, the assumptions of the Higuchi derivation should carefully be kept in mind:

(i) The initial drug concentration in the system is much higher than the solubility of the drug. This assumption is very important, because it provides the basis for the justification of the applied pseudo-steady state approach. The resulting concentration profiles of a drug initially suspended in an ointment are illustrated in Fig. 2. The solid line represents the drug concentration profile after exposure of the ointment to perfect sink for a certain time t.

As can be seen there is a sharp discontinuity at distance h from the surface. For this distance h above the absorbing surface the concentration gradient is essentially constant, provided, the initial drug concentration within the system, c_0, is much greater than the solubility of the drug ($c_0 >> c_s$). After an additional time interval, Δt, the new concentration profile of the drug is given by the broken line. Again, a sharp discontinuity and otherwise linear concentration profiles result. Under these particular conditions Higuchi derived the very simple relationship between the release rate of the drug and the square root of time.

(ii) Mathematical analysis is based on one-dimen-

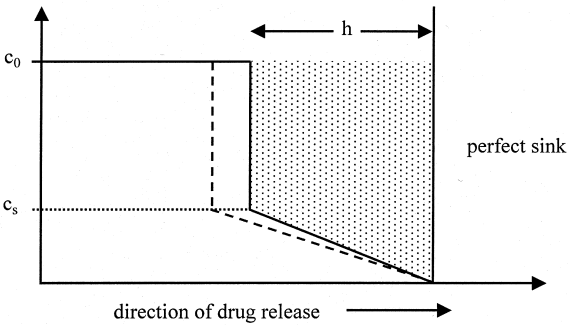

Fig. 2. Pseudo-steady state approach applied for the derivation of the classical Higuchi equation. Theoretical concentration profile existing in an ointment containing suspended drug and in contact with a perfect sink (adapted from [52] with permission from Wiley & Sons).

sional diffusion. Thus, edge effects must be negligible.

(iii) The suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the system.

(iv) Swelling or dissolution of the polymer carrier is negligible.

(v) The diffusivity of the drug is constant.

(vi) Perfect sink conditions are maintained.

It is evident that these assumptions are not valid for most controlled drug delivery systems based on HPMC. However, due to the extreme simplicity of the classical Higuchi equation (Eq. (1)), the latter is often used to analyze experimental drug release data to get a rough idea of the underlying release mechanism. But the information obtained should be viewed with caution. The superposition of various different effects, such as HPMC swelling, transition of the macromolecules from the glassy to the rubbery state, polymer dissolution, concentration-dependent water and drug diffusion etc. might also result in an apparent square root of time kinetics. In addition, a proportionality between the fractional amount of drug released and the square root of time can as well be derived from an exact solution of Fick's second law of diffusion for thin films of thickness δ under perfect sink conditions, uniform initial drug concentration with $c_0 < c_s$ (monolithic solutions) and assuming constant diffusivities ([7,58,59]):

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{1/2}\left\{\pi^{-1/2} + 2\sum_{n=1}^{\infty}(-1)^n \text{ierfc}\frac{n\delta}{2\sqrt{Dt}}\right\} \quad (3)$$

Here, M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; D represents the diffusivity of the drug within the polymeric system. As the second term in the second brackets vanishes at short times, a sufficiently accurate approximation of Eq. (3) for $M_t/M_\infty < 0.60$ can be written as follows:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2} = k'\sqrt{t} \quad (4)$$

where k' is a constant.

Thus, a proportionality between the fraction of drug released and the square root of time can also be based on these physical circumstances which are substantially different from those studied by Higuchi for the derivation of his classical equation (monolithic solutions versus monolithic dispersions). However, in both cases diffusion is the dominating mechanism and hence a proportionality between the cumulative amount of drug released and the square root of time is commonly regarded as an indicator for diffusion-controlled drug release.

Various researchers used the Higuchi equation to interpret their experimental drug release data. For example, Sung et al. [60] investigated the effect of formulation variables (HPMC/lactose ratio and HPMC viscosity grade) on the resulting Higuchi rate constants of a water-soluble model drug, adinazolam mesylate. For HPMC K15M and HPMC K100M they found similar values, whereas for HPMC K4M and HPMC K100LV and various HPMC/lactose ratios significantly different constants were obtained. This study is a good example for the use of the Higuchi equation for HPMC-based drug delivery systems, because although good fittings were obtained, the authors make clear that additional mathematical analysis is needed to make definitive mechanistic conclusions. Talukdar and Kinget [61] not only determined Higuchi constants, but used Eq. (1) to obtain the diffusivities of three model drugs (indometacin, indometacin sodium and caffeine) in hydrated HPMC and xanthan gum gels. In addition, they used a special apparatus for the experimental studies, restricting drug release to one surface only.

4.2. Power law

A more comprehensive, but still very simple, semi-empirical equation to describe drug release from polymeric systems is the so-called power law:

$$\frac{M_t}{M_\infty} = kt^n \quad (5)$$

Here, M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant incorporating structural and geometric characteristics of the device, and n is the release exponent, indicative of the mechanism of drug release.

As can be seen, the classical Higuchi equation (Eq. (1)) as well as the above described short time

approximation of the exact solution of Fick's second law for thin films (Eq. (4)) represent the special case of the power law where $n=0.5$. Peppas and co-workers [62,63] were the first to give an introduction into the use and the limitations of this equation. The power law can be seen as a generalization of the observation that superposition of two apparently independent mechanisms of drug transport, a Fickian diffusion and a case-II transport [64,65], describes in many cases dynamic swelling of and drug release from glassy polymers, regardless of the form of the constitutive equation and the type of coupling of relaxation and diffusion [66].

It is clear from Eq. (5) that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics. For slabs, the mechanism that creates the zero-order release is known among polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring upon water imbibition into the system is the rate-controlling step. Water acts as a plasticizer and decreases the glass transition temperature of the polymer. Once the T_g equals the temperature of the system, the polymer chains undergo the transfer from the glassy to the rubbery state, with increasing mobility of the macromolecules and volume expansion.

Thus, Eq. (5) has two distinct physical realistic meanings in the two special cases of $n=0.5$ (indicating diffusion-controlled drug release) and $n=1.0$ (indicating swelling-controlled drug release). Values of n between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent n, 0.5 and 1.0, are only valid for slab geometry. For spheres and cylinders different values have been derived [67,68], as listed in Table 3. Unfortunately, this fact is not always taken into account, leading to misinterpretations of experimental results.

In the case of HPMC-based systems it has to be pointed out that the application of the power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion-controlled drug release mechanism, this is not automatically valid for HPMC. The derivation of the Higuchi equation and the above described short time approximation of Fick's second law for slab geometry assume constant diffusivities and constant dimensions of the device during drug release. However, HPMC swells to a significant extend, the diffusion coefficients of water and incorporated drugs are strongly concentration dependent [69], and HPMC itself dissolves more or less rapidly. An apparent square root of time release kinetics can thus result from the superposition of various effects, and is not necessarily based on a simple drug diffusion-control. As in the case of the Higuchi equation the information obtained should be viewed with caution. However, the power law is already more comprehensive than the Higuchi equation.

Conte et al. [70] used the power law to describe drug release from HPMC-based multi-layer matrix tablets. The effect of the addition of one or two barrier layer(s) added to the planar surface(s) of a drug-containing HPMC core was studied. These additional barrier layers limit the core hydration process by maintaining the planar surfaces of the tablet covered during drug release. Moreover, the barrier layers reduce the surface area of the drug-containing core directly exposed to the release medium. As a result, the release rate was decreased and the kinetics shifted towards constant drug release. Trapidil and sodium diclofenac were used as model drugs. Recently, Rekhi et al. [71] applied the power law to gain information about the release

Table 3
Exponent n of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry

Exponent, n			Drug release mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
$0.5<n<1.0$	$0.45<n<0.89$	$0.43<n<0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

mechanism of Methocel K100LV-based tablets containing metoprolol tartrate. The overall aim of their study was to examine the influence of critical formulation and processing variables as described in the AAPS/FDA Workshop II report on scale-up of oral extended-release dosage forms. They found values for the exponent n ranging from 0.46 to 0.59 and concluded that the release seemed to be predominantly diffusion-controlled and that the investigated formulation and processing variables did not alter the drug release mechanism. Also recently, Colombo and co-workers [72] applied the power law to experimental drug release data of a very water-soluble drug, buflomedil pyridoxal phosphate from HPMC-based matrix tablets. They found a value of 0.73 for the exponent n, indicating anomalous drug transport from the swellable matrix. As evident from these examples [70–72], the entire range of values for the exponent n can be obtained from HPMC-based controlled release dosage forms, corresponding to a wide range of possible dominating drug release mechanisms.

4.3. Other empirical and semi-empirical models

Another interesting model was developed by Peppas and Sahlin [73]:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{6}$$

where k_1, k_2 and m are constants. The first term on the right hand side represents the Fickian diffusional contribution, F, whereas the second term the case-II relaxational contribution, R. The ratio of both contributions can be calculated as follows:

$$\frac{R}{F} = \frac{k_2 t^m}{k_1} \tag{7}$$

Bettini et al. [74] applied these equations to investigate the effect of the molecular weight of the HPMC type used and the addition of partial impermeable coatings to HPMC matrix tablets containing buflomedil pyridoxal phosphate. No significant effect on the resulting R/F-ratios was found with the investigated different viscosity grades of HPMC, whereas the addition of the impermeable coatings significantly affected the governing release mechanism (Fig. 3). Uncoated matrix tablets showed very low, and partially coated systems much higher R/F-ratios. The authors concluded that the importance of the relaxational contribution for drug release is more pronounced in the case of partially coated HPMC matrix tablets.

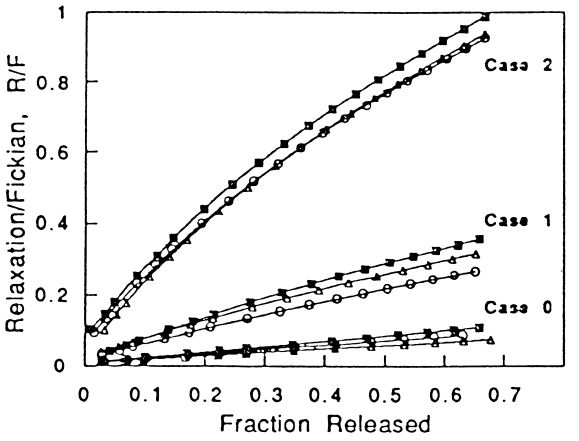

Fig. 3. Use of the Peppas–Sahlin model to investigate the effect of the polymer molecular weight and addition of impermeable coatings on the release rate of buflomedil pyridoxal phosphate from HPMC tablets. Case 0, uncoated matrix; case 1, one base of the cylinder covered; case 2, two bases of the cylinder covered; open triangles, Methocel K4M; open circles, Methocel K15M; and filled squares, Methocel K100M. (Reprinted from [74] with permission from Elsevier).

5. Comprehensive mechanistic theories

Fu and co-workers [75] described an analytical solution of Fick's second law for cylindrical geometry, considering mass transfer in three dimensions:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{h^2 r^2} \sum_{m=1}^{\infty} \alpha_m^{-2} \exp(-D\alpha_m^2 t) \times \sum_{n=1}^{\infty} \beta_n^{-2} \exp(-D\beta_n^2 t) \tag{8}$$

with

$$J_0(r\alpha) = 0 \tag{9}$$

and

$$\beta_n = \frac{(2n+1)\pi}{2h} \tag{10}$$

Here, M_t and M_∞ are the amount of drug released at time t and infinite time, respectively; h denotes the half-length and r the radius of the cylinder. The constant diffusion coefficient is represented by D, t is the time, α and β are defined by the above given equations, with J_0 being a zero-order Bessel function; m and n are integers. This model is applicable to tablets that range from the shape of a flat disk (radius>thickness) to that of a cylindrical rod (radius<thickness), the drug being homogeneously distributed within the system. But they did not consider the volume expansion of the system and assumed constant diffusion coefficients.

Peppas et al. [76] presented a drug diffusion model for the case of diffusion of an initially uniformly distributed drug through a polymeric matrix. Drug diffusion from a single surface is analyzed for the case of countercurrent diffusion of a solvent which is thermodynamically compatible with the polymer. Due to swelling, considerable volume expansion is observed leading to a moving boundary diffusion problem. Drug concentration profiles within the polymer and drug release rates can be determined. The results are in good agreement with experimental data obtained for the system of KCl distributed in HPMC matrix tablets (Fig. 4). Singh and Fan [77] developed a generalized mathematical model for the simultaneous transport of a drug and a solvent in a planar glassy polymer matrix. The drug diffuses out of the matrix which is undergoing macromolecular chain relaxation and volume expansion due to solvent absorption from the environment into the matrix. The swelling behavior of the polymer is characterized by a stress-induced drift velocity term 'v' corresponding to the so-called case-II velocity. The change of volume due to the relaxation phenomenon is assumed instantaneous. The model incorporates convective transport of the two species induced by volume expansion and by stress gradient. However, it was developed for planar systems, not for cylindrical matrices. Cohen and Erneux [78,79] 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 into the polymer. But also their theory was developed for thin films, and not for cylindrical tablets.

Korsmeyer et al. [80,81] developed a model, describing the diffusion of a penetrant and a solute in a swellable polymer slab. The model was applied to the case of a hydrophilic polymer containing a water-soluble drug, in which the penetrant (water) is sorbed and the drug is desorbed. The model allows the incorporation of any appropriate form of the diffusion coefficients. A Fujita-type exponential dependence on penetrant concentration was chosen [82] and shown to be adequate for the prediction of a range of transport behavior. Dimensional changes in the sample are predicted by allowing each spatial increment to expand according to the amount of penetrant sorbed. During the initial period of drug release, the swelling is restricted to one dimension by the glassy core of the sample. At a later point in the process, when the center of the sample has sorbed enough penetrant to plasticize it, the sample relaxes to an isotropically swollen state; thereafter, swelling is three-dimensional. The process is modeled as a two-component diffusion in a continuous medium. For the penetrant (water, subscript 1), the following equations are applied:

$$\frac{\partial c_1}{\partial \tau} = \frac{\partial}{\partial \xi}\left(D_1 \frac{\partial c_1}{\partial \xi}\right) \tag{11}$$

where D_1 is the diffusion coefficient of the penetrant, and c_1 is the normalized concentration of the penetrant:

$$c_1 = \frac{c_w}{c_{w,e}} \tag{12}$$

Here, c_w is the penetrant concentration in the polymer, and $c_{w,e}$ is the equilibrium concentration of the penetrant in the polymer. Time t is scaled according to the diffusion coefficient of water in the fully swollen polymer, $D_{1,s}$, and the dry thickness of the slab, L_0:

$$\tau = \frac{tD_{1,s}}{L_0^2} \tag{13}$$

The spatial coordinate x is normalized with respect to the dry thickness of the slab:

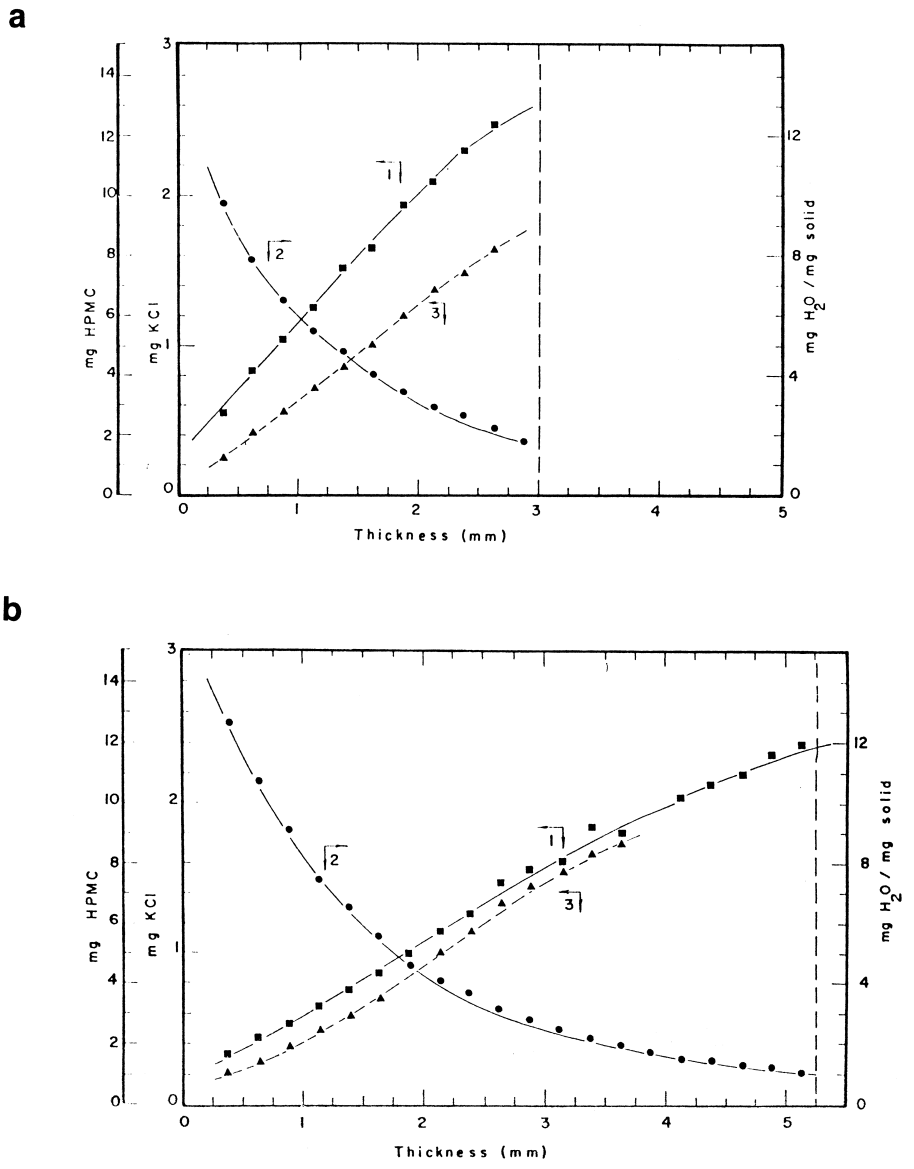

Fig. 4. Use of a comprehensive mechanistic diffusion model [76] to elucidate the involved transport processes from KCl-loaded HPMC tablets. Calculated (curves) and experimentally measured (symbols) concentration profiles of (1) KCl, (2) water, and (3) HPMC 2208 in the gel phase of swollen polymer tablets after (a) 5 h, and (b) 6 h, respectively. The vertical broken line corresponds to the swelling front (reprinted from [76], with permission from Elsevier).

$$\xi = \frac{x}{L_0} \tag{14}$$

To describe drug diffusion (subscript 2) through the polymer, the following equations are used:

$$\frac{\partial c_2}{\partial \tau} = \frac{\partial}{\partial \xi}\left(D_2 \frac{\partial c_2}{\partial \xi}\right) \tag{15}$$

where D_2 is the diffusion coefficient of the drug, and c_2 is the normalized concentration of the drug:

$$c_2 = \frac{c_s}{c_{s,i}} \tag{16}$$

Here, c_s is the drug concentration in the polymer, and $c_{s,i}$ denotes the initial concentration of the drug in the polymer. The following boundary conditions are applied:

$$c_1(0,\tau) = c_1(\xi,\tau) = 1 \tag{17}$$

and

$$c_2(0,\tau) = c_2(\xi,\tau) = 0 \tag{18}$$

where 0 and ξ are the two surfaces of the slab. It has to be emphasized that ξ describes the continuously moving outside surface of the slab. The initial conditions are:

$$c_1(\xi,0) = 0 \tag{19}$$

and

$$c_2(\xi,0) = 1 \tag{20}$$

These sets of differential equations are solved numerically. However, their theory was developed for thin films, not for cylindrical tablets.

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 was developed by Gao et al. [83,84]. It is based on the steady state approximation to Fick's law for the release of drugs from solid matrices [52], modified by Lapidus and Lordi [57]:

$$M_t = M_0 \frac{S}{V}\left(\frac{D't}{\pi}\right)^{0.5} \tag{21}$$

where M_t denotes the amount of drug released at time t, M_0 is the initial amount of drug within the tablet; S represents the surface area and V the volume available for release, D' is the effective diffusion coefficient, defined by:

$$D' = \frac{D}{\tau} \tag{22}$$

Here, D is the true self-diffusion coefficient of the drug in the pure release medium and τ is the tortuosity of the diffusing matrix. However, the swelling of the system is not taken into account and the mathematical analysis reduced to one dimension.

Ju and co-workers [85–87] developed a comprehensive mathematical model to describe the swelling/dissolution behaviors and drug release from HPMC matrices. The major thrust of this model is to employ an important physical property of the polymer, the polymer disentanglement concentration, $\rho_{p,dis}$, the polymer concentration below which polymer chains detach of the gelled matrix. Furthermore, matrix dissolution is considered similar to the dissolution of an object immersed in a fluid. As a result, a diffusion layer separating the matrix from the bulk solution is incorporated into the transport regime. In addition, an anisotropic expansion model is introduced to account for the anisotropic expansion of the matrix, the surface area in the radial direction dominating over the surface area in the axial direction. They predicted that the overall tablet size and characteristic swelling time correlate with $\rho_{p,dis}$ qualitatively. Two scaling laws were established for the fractional polymer $[M_p(t)/M_p(\text{infinity})]$ and drug $[M_d(t)/M_d(\text{infinity})]$ released as $M_p(t)/M_p(\text{infinity}) \propto M^{-1.05}$ and $M_d(t)/M_d(\text{infinity}) \propto M^{-0.24}$, which is consistent with the limiting polymer molecular weight effect on drug release.

The mathematical analysis is based on the following equation:

$$\left(\frac{\partial \rho_i}{\partial t}\right) = -\frac{\partial \rho_i}{\partial r}\frac{\mathrm{d}r}{\mathrm{d}t} + \frac{1}{r}\frac{\partial}{\partial r}\left(rD_i\rho_t\frac{\partial w_i}{\partial r}\right) - \rho_i\frac{\mathrm{d}V/V}{\mathrm{d}t} \tag{23}$$

Here, ρ_i and D_i are the mass concentration and diffusivity of the species i; w_i represents the respective weight fraction, r and t radial position and time; V denotes the volume of the matrix. As can be seen, they restricted the mathematical analysis to radial mass transfer only, neglecting processes in axial direction. The first term on the right hand side is a convection term, arising from the moving boundary. It can also be considered as the interpolation term for calculating the concentrations at each new time step. Muray and Landis [88] assumed a grid point at r to move with a velocity $\mathrm{d}r/\mathrm{d}t$. The second term accounts for the Fickian diffusion of the species i, with the diffusivity D_i and the local overall mass concentration ρ_t. The presence of the second term also

implies that the time scale for drug dissolution is much faster than that for drug diffusion, e.g., diffusion (instead of dissolution) of drug molecules is the controlling mechanism of drug release. This assumption is only valid for water-soluble drugs. For poorly water-soluble drugs, a dissolution term needs to be incorporated into the governing equation. The third term is the source term, which considers concentration changes resulting from matrix volume changes. Based on NMR measurements of Gao and Fagerness [83], the following concentration dependencies of the diffusivities are assumed:

$$\frac{D_{s,w}}{D_{w,0}} = k'_w \exp(k_w w_w) \tag{24}$$

$$\frac{D_d}{D_{d,0}} = \exp(-k_{d,p} w_p - k_{d,1} w_1 - k_{d,d} w_d) \tag{25}$$

with $D_{s,w}$ and D_d being the self-diffusion coefficient of water and the mutual diffusion coefficient of the drug. The subscripts w, d and p refer to water, drug and polymer, respectively. The diffusivity of the species i in a dilute solution is denoted by D_{i0}; and k'_w, k_w, and $k_{d,i}$ are the prefactor, and the weighting factors, respectively. For water and polymer, the mutual diffusion coefficient, D_w, is related to the self-diffusion coefficient of water, $D_{s,w}$ and polymer, $D_{s,p}$, as follows [89]:

$$D_w = D_{s,w}\phi_p + D_{s,p}\phi_w \cong D_{s,w}\phi_p \tag{26}$$

where ϕ_i is the volume fraction of the species i. For HPMC they found the following relationship between the polymer disentanglement concentration, $\rho_{p,dis}$, and the polymer molecular weight, M:

$$\rho_{p,dis} = 0.05(M/96000)^{-0.8} \tag{27}$$

This relationship is also illustrated in Fig. 5. At lower polymer molecular weights the variation of $\rho_{p,dis}$ is much more pronounced than at higher molecular weights. For example, $\rho_{p,dis}$ decreases from 0.13 to 0.05 g/ml as the molecular weight increases from 30 to 100 kDa. However, a further increase in molecular weight from 100 to 300 kDa causes a decrease in $\rho_{p,dis}$ by only less than 0.03 g/ml. This observation suggests that the extend of polymer chain entanglement gradually reaches a limit at high polymer molecular weights. Rather

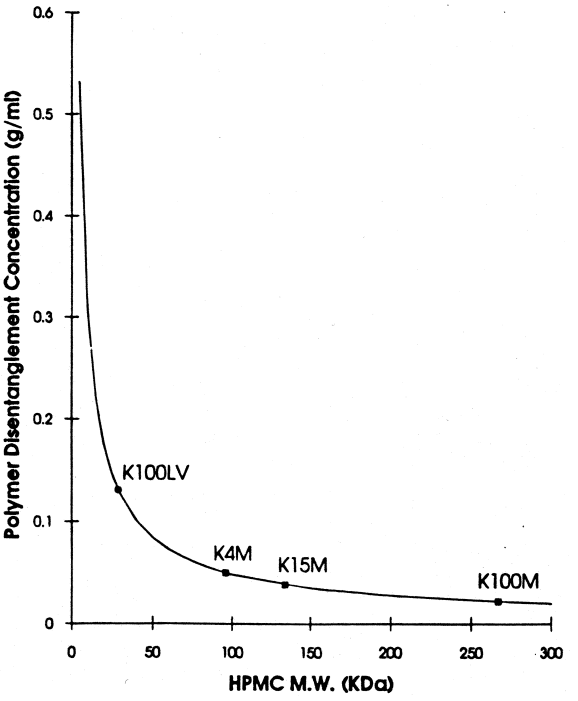

Fig. 5. Dependence of the polymer disentanglement concentration, $\rho_{p,dis}$, for HPMC on the molecular weight of the polymer, according to Ju and co-workers [86]. The filled circle corresponds to $\rho_{p,dis}$ for HPMC K100LV, while the filled squares correspond to $\rho_{p,dis}$ for HPMC K4M, K15M, and K100M, respectively (reprinted from [86], with permission from Wiley & Sons).

good agreement between model predictions for polymer and drug release and experimental data was found (within 15% error, Fig. 6). However, mathematical analysis of mass transport is restricted to radial processes only, ignoring axial transport phenomena.

Recently ([5,11,69,90]), a new comprehensive mathematical model has been developed describing drug release from HPMC-based matrix tablets, taking into account the diffusion of water and drug, non-constant diffusivities, moving boundary conditions, the swelling of the system, polymer and drug dissolution, and radial and axial mass transfer in cylindrical geometries. This model is valid for various kinds of HPMC types (even for derivatives, such as hydroxypropyl methylcellulose acetate succinate, HPMCAS [91]), freely and poorly water-soluble drugs and a wide range of initial drug loadings. It has successfully been used to describe the effect of

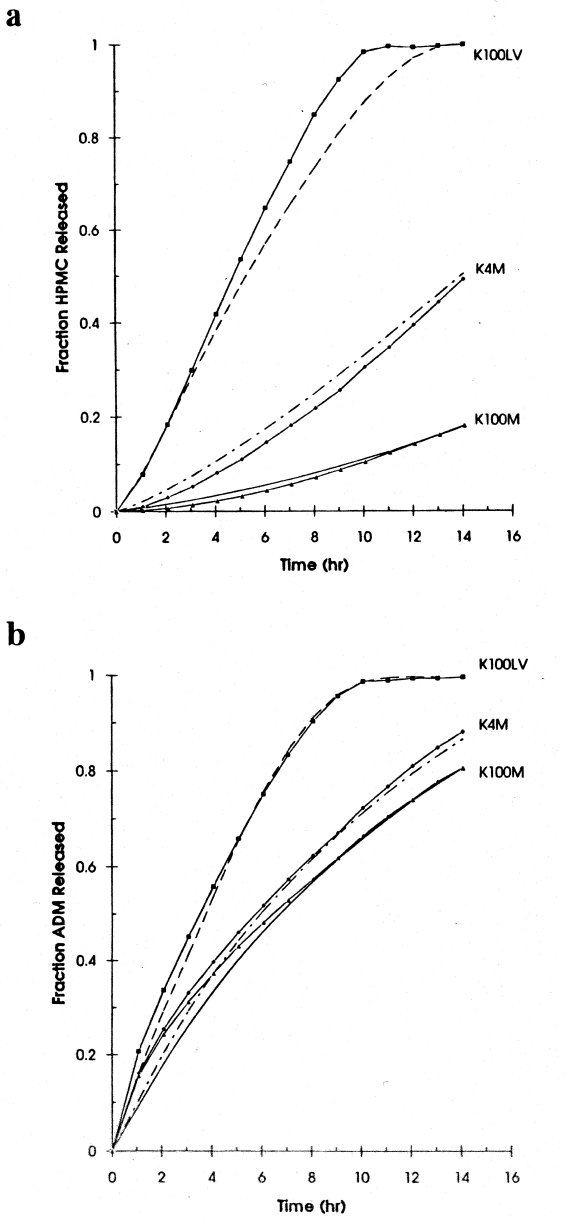

Fig. 6. Comparison of model predictions (broken curves) and experimental data (solid curves) for fractional (a) HPMC, and (b) adinazolam mesylate (ADM) release from HPMC-based matrices. Each tablet weights 500 mg, with a radius and thickness of 3.85 mm and 7.7 mm, respectively. The composition of each tablet is as follows: 35% HPMC, 62% lactose, 2.5% adinazolam mesylate, and 0.5% magnesium stearate (reprinted from [86], with permission from Wiley & Sons).

the design parameters of HPMC-based controlled release systems, such as size and shape of matrix tablets and composition of the device (type and amount of drug and type and amount of polymer).

Polymer dissolution is taken into account using the reptation theory [92–94]. Above a certain critical water concentration, c_{1crit}, the polymer chains at the surface of the system start to disentangle and diffuse through the unstirred layer into the bulk fluid. A dissolution rate constant, k_{diss}, is considered characterizing the polymer mass loss velocity normalized to the actual surface area of the system:

$$M_{pt} = M_{p0} - k_{diss} A_t t \tag{28}$$

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 are described using Fick's second law of diffusion for cylindrical geometry, taking into account axial and radial mass transport and concentration-dependent diffusivities [7]:

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\} \tag{29}$$

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 (Fig. 7). According to the free volume theory of diffusion, a Fujita-type [82] exponential dependence of the diffusion coefficients on the water content of the system is taken into account:

$$D_k = D_{kcrit}\exp\left\{-\beta_k\left(1-\frac{c_1}{c_{1crit}}\right)\right\} \tag{30}$$

where β_1 and β_2 are dimensionless constants characterizing this concentration-dependence. Also D_{1crit} and D_{2crit} denote the diffusion coefficients of water and drug at the interface matrix/release medium, where polymer chain disentanglement occurs [85,86,92–94]. Ideal mixing is assumed (no volume contraction upon mixing drug, polymer and water), and the total volume of the system at any instant is given by the sum of the volumes of the single

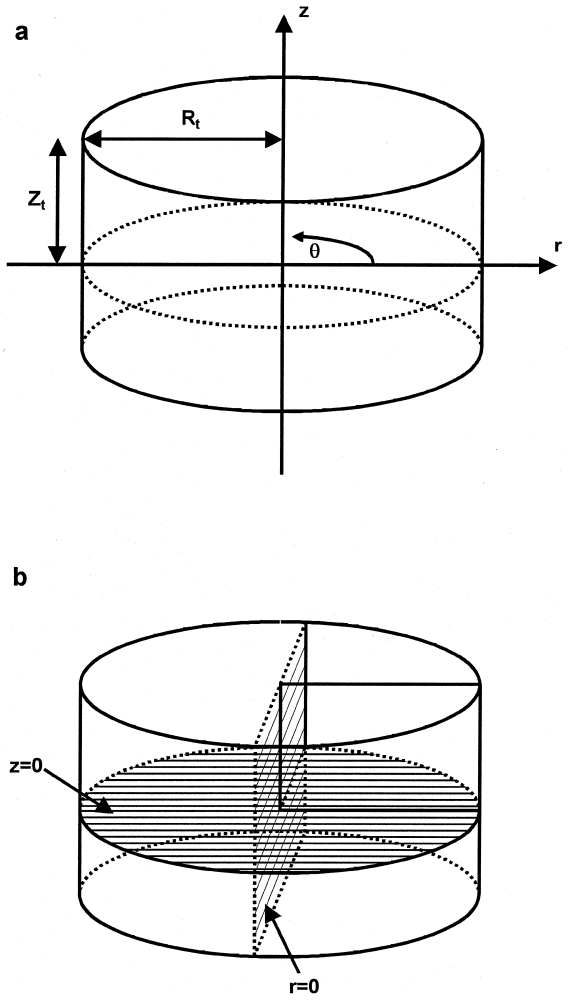

Fig. 7. (a) Schematic of an HPMC matrix tablet for the mathematical analysis of a comprehensive mechanistic model [5,11,69,90], with (b) symmetry planes in axial and radial direction for the water and drug concentration profiles (R_t and Z_t represent the time-dependent radius and half-height of the cylindrical matrices, respectively).

components. The calculation of the new matrix dimensions is based on a mass balance considering drug, polymer and water. The initial conditions reflect 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}, is calculated from the polymer disentanglement concentration [85,86,92–94], and the drug concentration at the surface of the matrix is assumed to be equal to zero (perfect sink condition). To minimize computation time, the origin of the coordinate system is placed at the center of the matrix, resulting in two symmetry planes for the drug and water concentration profiles (Fig. 7). Thus, only the concentration profiles within a quarter of the cylindrical matrix have 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 is solved numerically, using finite differences.

A practical application of this model is shown in Fig. 8. The effect of the initial theophylline loading on the resulting absolute and relative release rates from HPMC tablets is illustrated in phosphate buffer pH 7.4 (Figs. 8a and c), and 0.1 N HCl (Figs. 8b and d), 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. This phenomenon can be explained as follows. With increasing initial drug loading the porosity of the matrix upon drug depletion increases. Thus, the resistance for further drug diffusion decreases. This effect leads to increased absolute drug transfer rates. However, 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, whereas the resulting drug concentration gradient (being the driving force for diffusion) not increases. Thus, the absolute amount of drug released within a certain time period remains constant, while the 100%-reference value increases. In consequence, the relative drug release rate decreases. This non-dissolved drug effect can overcompensate the above described porosity effect, as illustrated in Figs. 8a and b. 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

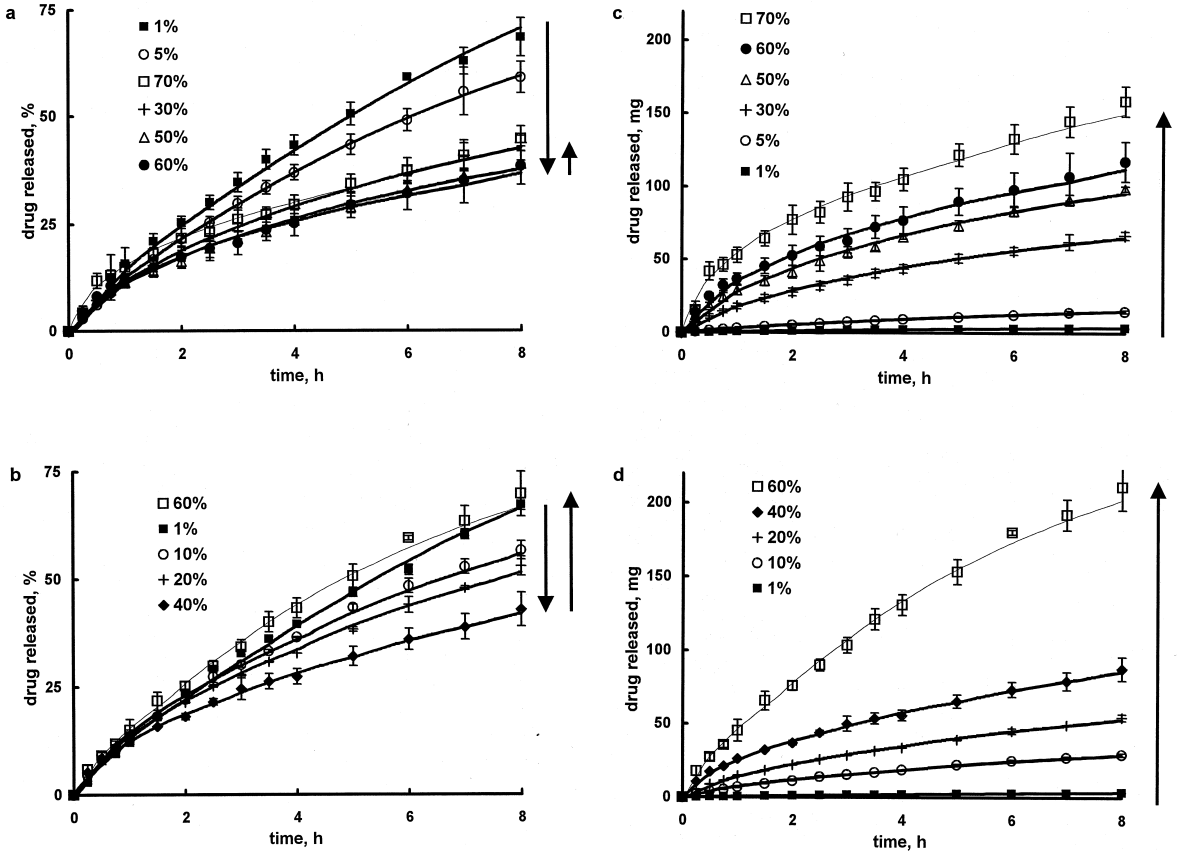

Fig. 8. Practical application of a comprehensive mechanistic model to experimental drug release data. Effect of the initial theophylline loading on the resulting release kinetics from HPMC tablets in (a) phosphate buffer (pH 7.4), relative values (■ 1%, ○ 5%, □ 70%, + 30%, △ 50%, ● 60%), (b) 0.1 N HCl, relative values (□ 60%, ■ 1%, ○ 10%, + 20%, ♦ 40%), (c) phosphate buffer (pH 7.4), absolute values (□ 70%, ● 60%, Δ 50%, + 30%, ○ 5%, ■ 1%), (d) 0.1 N HCl, absolute values (□ 60%, ♦ 40%, + 20%, ○ 10%, ■ 1%) (500 mg tablets, initial radius = 0.6 cm, 37°C, curves: calculated values, symbols: experimental results).

mathematical model to consider these aspects and to predict precisely the resulting drug release rates.

6. Conclusions

A large spectrum of mathematical models describing drug release from HPMC-based controlled release devices has been developed. The choice of the appropriate model for a particular purpose depends on various aspects. Of course, certain device design parameters, such as the geometry of the system or the amount and water-solubility of the incorporated drug already exclude some of the models. But probably the most important aspect when developing new pharmaceutical products or elucidating drug release mechanisms is the desired/required predictive ability and accuracy of the model. In many cases, the use of simple empirical or semi-empirical models is fully sufficient. However, when reliable, detailed information are required, more complex, mechanistic theories must be applied.

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