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Review

Mathematical modeling of drug delivery

J. Siepmann*, F. Siepmann

College of Pharmacy, JE 2491, University of Lille, 3 rue du Professeur Laguesse, 59006 Lille, France

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ABSTRACT

Due to the significant advances in information technology mathematical modeling of drug delivery is a field of steadily increasing academic and industrial importance with an enormous future potential. The *in silico* optimization of novel drug delivery systems can be expected to significantly increase in accuracy and easiness of application. Analogous to other scientific disciplines, computer simulations are likely to become an integral part of future research and development in pharmaceutical technology. Mathematical programs can be expected to be routinely used to help optimizing the design of novel dosage forms. Good estimates for the required composition, geometry, dimensions and preparation procedure of various types of delivery systems will be available, taking into account the desired administration route, drug dose and release profile. Thus, the number of required experimental studies during product development can be significantly reduced, saving time and reducing costs. In addition, the quantitative analysis of the physical, chemical and potentially biological phenomena, which are involved in the control of drug release, offers another fundamental advantage: The underlying drug release mechanisms can be elucidated, which is not only of academic interest, but a pre-requisite for an efficient improvement of the safety of the pharmaco-treatments and for effective trouble-shooting during production. This article gives an overview on the current state of the art of mathematical modeling of drug delivery, including empirical/semi-empirical and mechanistic realistic models. Analytical as well as numerical solutions are described and various practical examples are given. One of the major challenges to be addressed in the future is the combination of mechanistic theories describing drug release out of the delivery systems with mathematical models quantifying the subsequent drug transport within the human body in a realistic way. Ideally, the effects of the design parameters of the dosage form on the resulting drug concentration time profiles at the site of action and the pharmacodynamic effects will become predictable.

Contents

* Corresponding author. Tel.: +33 3 20964708; fax: +33 3 20964942.
E-mail address: juergen.siepmann@univ-lille2.fr (J. Siepmann).

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1. Introduction

Mathematical modeling of drug delivery and predictability of drug release is a field of steadily increasing academic and industrial importance with an enormous future potential. Due to the significant advances in information technology, the *in silico* optimization of novel drug delivery systems can be expected to significantly improve in accuracy and easiness of application. Analogous to other scientific disciplines (e.g., aviation and aerospace), computer simulations are likely to become an integral part of future research and development in pharmaceutical technology. It is only a question of time when mathematical programs will be routinely used to help optimizing the design of novel dosage forms. Considering the desired type of administration, drug dose to be incorporated and targeted drug release profile, mathematical predictions will allow for good estimates of the required composition, geometry, dimensions and preparation procedure of the respective dosage forms. Thus, one of the major driving forces for the use of mathematical modeling in drug delivery is to save time and to reduce costs: The number of required experimental studies to develop a new and/or optimize an existing drug product can significantly be reduced.

In addition, the quantitative analysis of the physical, chemical and potentially biological phenomena, which are involved in the control of drug release, offers another fundamental advantage: The underlying drug release mechanisms can be elucidated. This knowledge is not only of academic interest, but a pre-requisite for an efficient improvement of the safety of new pharmaco-treatments. This is particularly true for highly potent drugs with narrow therapeutic windows. Furthermore, potential challenges encountered during production (trouble-shooting) can be much more efficiently addressed if the system is not treated as a "black box", but if there is a thorough understanding of how drug released is controlled. It is decisive to know which device properties are crucial to provide the desired system performance.

Up to date, numerous mathematical theories have been described in the literature (Siepmann and Peppas, 2001; Siepmann and Goepferich, 2001; Arifin et al., 2006; Lin and Metters, 2006), but most of them still lack in accuracy and/or easiness of application. The "father" of mathematical modeling of drug delivery is Professor Takeru Higuchi. In 1961, he published his famous equation allowing for a surprisingly simple description of drug release from an ointment base exhibiting a considerable initial excess of non-dissolved drug within an inert matrix with film geometry (Higuchi, 1961a,b). This was the beginning of the quantitative treatment of drug release from pharmaceutical dosage forms. Numerous models have been proposed since then, including *empirical*/*semi-empirical* as well as *mechanistic realistic* ones. In the first case, the mathematical treatment is (at least partially) purely descriptive and not based on real physical, chemical and/or biological phenomena. Consequently, no or very limited insight into the underlying drug release mechanisms can be gained. Furthermore, the predictive power of *empirical*/*semi-empirical* models is often low. This type of theories might for instance be useful if different types of drug release profiles are to be compared using a specific parameter (e.g., an apparent release rate constant for experimental design analysis). But great caution must be paid if mechanistic conclusions are drawn or quantitative predictions made. An exception are approaches based on artificial neural networks (ANNs), which can show good predictive power.

In contrast, *mechanistic* mathematical theories are based on real phenomena, such as diffusion, dissolution, swelling, erosion, precipitation and/or degradation (Siepmann et al., 1998; Narasimhan, 2001; Frenning and Stromme, 2003; Lemaire et al., 2003; Zhou and Wu, 2003; Frenning et al., 2005; Raman et al., 2005). This type of models allows for the determination of system-specific parameters that can offer deeper insight into the underlying drug release mechanisms. For instance, the relative importance of several processes that are involved (e.g., drug diffusion and polymer swelling) can be estimated. The dosage form is not treated as a "black box", but as a real drug delivery system the mechanisms of which can be understood. During product development such mechanistic realistic mathematical models allow for the quantitative prediction of the effects of formulation and processing parameters (e.g., the initial tablet height and radius) on the resulting drug release kinetics. Thus, the required composition, size, shape and preparation procedure of a novel dosage form with desired properties become theoretically predictable. In addition, challenges encountered during production are much easier to address when having a clear idea of how the system works.

When using and/or developing mathematical theories to quantify drug release from pharmaceutical dosage forms, the following aspects should carefully be taken into account:

(i) The accuracy of a mathematical theory generally increases with increasing model complexity: The more phenomena are taken into account, the more realistic the theory becomes. However, caution must be paid because too complex models are cumbersome to use. Too many system-specific parameters are required to allow for quantitative predictions. Thus, when developing a new mathematical theory for a particular drug delivery system great care must be taken to consider only the *dominant* physical, chemical and/or biological processes. If for instance several mass transport steps take place sequentially and if one of these processes is much slower than all others, only this step needs to be considered in the model.

(ii) Theoretical calculations should always be compared to experimental results. Importantly, there are two different types of comparisons: The theory can either be *fitted* to experimental data, or theoretical *predictions* can be compared with *independent* experimental results. In the first case, one or more model parameters are optimized in such a way that the differences between the experimental results and the theoretical calculations are minimized. Especially if several model parameters are simultaneously fitted to the same set of experimental data great caution needs to be paid: The simultaneous adjustment of many model parameters generally leads to good agreement between theory and experiment, even if the theory is not appropriate. Ideally, only one model parameter should be fitted at a time, using a set of at least 12 experimental data points. In the case of fittings to experimentally measured drug release kinetics, it is furthermore important that the entire drug release profile is described, and not only one part of it (e.g., the early, intermediate or final phase). A much more reliable comparison (and indication for the validity of a mathematical theory for a specific type of drug delivery system) is that of theoretical *predictions* and *independent* experimental results. In this case, first all system-specific parameters are determined via fittings to different sets of experimental results. Once all required model parameters are known, the effects of different formulation and/or processing parameters on the systems' properties (e.g., drug release kinetics) are predicted *in silico*. Then, the respective devices are prepared in reality and the predicted systems' properties experimentally measured. If possible, not only one specific type of experimental results should be determined, but different device properties should be measured, such as the drug release kinetics, dry mass loss behavior, changes in wet weight as well as drug and excipient concentration profiles.

(iii) There is no general mathematical theory that can be applied to all types of drug delivery systems. Certain models are appli-

cable to only a very limited number of drug delivery systems, others have a much broader application spectrum.

(iv) Even if a model shows good agreement between theoretical predictions and various types of independent experimental results, one should always be cautious and ready to abandon the theory if appropriate experimental evidence is given. A model describing drug delivery is always a simplification of the real system and its suitability is always restricted to certain cases.

The aim of this article is to give an overview on the current state of the art of empirical/semi-empirical and mechanistic realistic mathematical theories quantifying drug delivery and to provide an outlook into the future of this field of research. Due to the substantially high number of variables, no effort was made 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. Drug release mechanisms

Depending on the type of drug(s), incorporated drug dose(s), types and amounts of excipients, preparation technique, environmental conditions during drug release as well as geometry and dimensions of the drug delivery system, one or more of the following phenomena might be involved in the control of drug release from a dosage form, to mention just a few (Gallagher and Corrigan, 2000; Grassi et al., 2003; Zhou et al., 2005; Berchane et al., 2007; Bertrand et al., 2007; Chirico et al., 2007; Abdekhodaie and Wu, 2008):

- Wetting of the system's surface with water.
- Water penetration into the device (e.g., via pores and/or through continuous polymeric networks).
- Phase transitions of (polymeric) excipients (e.g., glassy-to-rubbery-phase transitions).
- Drug and excipient dissolution.
- Hindrance of rapid and complete drug and excipient dissolution due to limited solubility and/or dissolution rates under the given conditions.
- Drug and/or excipient degradation.
- Dissolution and/or precipitation of degradation products.
- Creation of water-filled pores.
- Pore closing due to polymer swelling.
- Creation of significant hydrostatic pressure within the delivery system, e.g. in the case of coated dosage forms.
- Convection driven drug release due to significant hydrostatic pressure created within the device.
- Creation of cracks within release rate limiting membranes.
- Creation of acidic or basic microenvironments within the dosage forms due to degradation products.
- Changes in the rate of drug and/or excipient degradation rate due to changes in the microenvironmental pH.
- Physical drug-excipient interactions (e.g., ion–ion attraction/repulsion and Van der Waals forces), which might significantly vary with time and position due to changes in the microenvironmental conditions, such as the pH, presence of counter ions and ionic strength.
- Changes in drug and/or excipient solubility due to altered microenvironmental conditions (e.g., pH, ionic strength, etc.).
- Diffusion of drugs and/or excipients out of the dosage form with potentially time- and/or position-dependent diffusion coefficients.
- Diffusion of drugs and/or excipients through the liquid unstirred layer surrounding the device.
- Penetration of acids, bases or salts from the surrounding bulk fluid into the drug delivery system.
- Hindrance in further drug and/or excipient release due to significant drug/excipient concentrations in the bulk fluid (non-sink conditions).
- Chemical reactions between drugs and excipients and/or water, e.g. hydrolytic cleavage of ester bonds that covalently bind drugs to polymeric matrix formers.
- Changes in the device geometry and/or dimensions due to shear forces.

It is virtually impossible to list *all* potentially involved phenomena (Brazel and Peppas, 2000; Charlier et al., 2000; Siegel, 2000; Mollo and Corrigan, 2003; Grassi et al., 2004; Siepmann et al., 2004, 2006a; Faisant et al., 2006). Furthermore, this list only concerns drug transport *within* the dosage form, not the subsequent drug fate in the living body. Different mathematical theories have been proposed to quantitatively describe drug transport in the human organism (Saltzman and Radomsky, 1991; Krewson and Saltzman, 1996; Harashima et al., 1999; Nicholson, 2001; Veng-Pedersen, 2001; Clairambault, 2007; Geldof et al., 2008). However, many of these theories are based on important simplifications, e.g. the extremely complex human body is represented by one or two well stirred liquid compartments. Often, various phenomena, such as enzymatic degradation, protein binding, active and passive drug uptake into cells, intra-cellular drug transport, interactions with compounds in the extra- and intracellular space, convection, first pass metabolism, drainage into the lymphatic system, transport across the Blood Brain Barrier and other major obstacles (to give only a few examples) are not explicitly taken into account (Siepmann et al., 2006b). Please note that this article does not address the *in vivo* aspect of drug delivery, but focuses on the physico-chemical processes within the dosage forms. In the future it will be of major importance to combine comprehensive, mechanistic mathematical theories describing drug transport within the dosage form with comprehensive, mechanistic models quantifying the subsequent drug fate in the human body.

3. Mechanistic realistic theories

A mechanistic realistic mathematical model is based on equations that describe real phenomena, e.g. mass transport by diffusion, dissolution of drug and/or excipient particles, and/or the transition of a polymer from the glassy to the rubbery state (Fick, 1855; Noyes and Whitney, 1897; Frisch, 1980; Park, 1986; Lao et al., in press). These equations form the basis of the mathematical theory. Often, partial differential equations are involved (Wang et al., 1968; Crank, 1975). To be able to solve them, the given initial and boundary conditions must be known, for instance the drug distribution within the dosage form before exposure to the release medium, the potential maintenance of perfect sink conditions throughout the experiment or the potential movement of specific boundaries (such as the front that separates the dosage form from the bulk fluid). Depending on the complexity of the resulting set of mathematical equations, either *analytical* or *numerical* solutions can be derived. If the equations are relatively simple, exact mathematical expressions can be found (analytical analysis) allowing for the calculation of the resulting drug release rate as a function of the system-specific parameters (e.g., initial dimensions). If the amount of drug released or release rate can be separated from all other variables and parameters on one side of the equation, the solution is called *explicit* and the effects of the considered formulation and

processing parameters can be (more or less) directly be seen. In contrast, if it is not possible to separate the amount/rate of drug release from the other variables and parameters, only a so-called *implicit* solution can be derived, and the effects of the formulation and processing parameters is often less direct. Furthermore, if the set of mathematical equations is complex (e.g., in the case of time- and position-dependent diffusion coefficients), no analytical solution can be derived, but approximations must be made (numerical analysis). The idea is to make certain simplifications, while limiting the introduced error. For example, first derivatives might be approximated by finite differences with very small time or length steps. It must be pointed out that due to the advances in information technology numerical solutions are nowadays very accurate and often easy to use. In the following, both, analytical as well as numerical solutions will be discussed.

3.1. Theories based on Fick's law of diffusion

If drug release is purely diffusion controlled with constant diffusion coefficients, the mathematical treatment can be rather straightforward. As illustrated in Fig. 1, different types of systems can be distinguished, including: (i) reservoir devices consisting of a drug depot, which is surrounded by a release rate controlling barrier membrane (often polymer-based), and (ii) monolithic systems, also called "one-block" systems, because there is no local separation between a drug reservoir and a release rate controlling barrier. For both types of systems two subclasses can be distinguished: the initial drug concentration is either below or above drug solubility in the device. In the case of a reservoir device with an initial drug concentration below drug solubility (e.g., a polymer-coated tablet or pellet with a low drug loading), released drug molecules are not replaced and the drug concentration at the inner membrane's surface continuously decreases with time (=non-constant activity source). If the membrane does not swell or dissolve, if perfect sink conditions are provided throughout the release period and if the drug permeability through the barrier remains constant, first order release kinetics result, irrespective of the geometry of the device (Baker, 1987):

$$\frac{dM_t}{dt} = \frac{ADKc_t}{l} = \frac{ADK}{l}\frac{M_0 - M_t}{V} \quad (1)$$

where M_t represents the absolute cumulative amount of drug released at time t; c_t denotes the concentration of the drug in the release medium at time t; M_0 is the initial amount of drug within the dosage form; V the volume of the drug reservoir, A the total surface area of the device, and l the thickness of the membrane; K represents the partition coefficient of the drug between the membrane and the reservoir, and D the diffusion coefficient of the drug within the membrane.

In contrast, if the initial drug concentration exceeds the drug solubility in a reservoir device, released molecules are replaced by the (partial) dissolution of drug crystals/amorphous aggregates, resulting in constant drug concentrations (saturated solutions) at the inner membrane's surface (constant activity source, Fig. 1). If the properties of the release rate controlling barrier (including its thickness and permeability for the drug) remain constant and if perfect sink conditions are provided throughout the release period, zero order release kinetics result as long as drug excess is provided, irrespective of the geometry of the system (Baker, 1987):

$$\frac{dM_t}{dt} = \frac{AJ_{lim}}{l} = \frac{ADKc_s}{l} \quad (2)$$

where M_t is the amount of drug release at time t; dM_t/dt denotes the steady state release rate at time t; A is the total surface area of the device, J_{lim} the membrane-limiting flux, l the thickness of the mem-

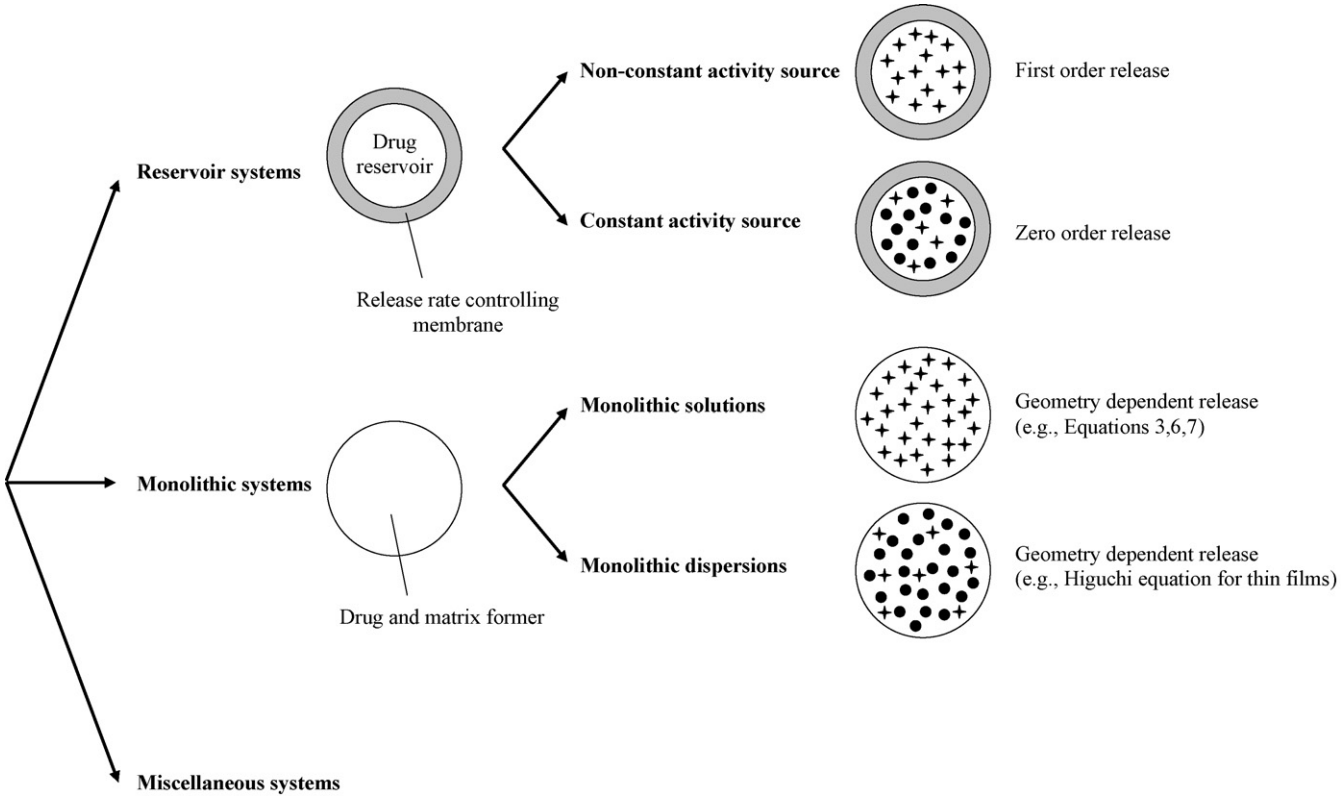

Fig. 1. Classification system for primarily diffusion controlled drug delivery systems. Stars represent individual drug molecules, black circles drug crystals and/or amorphous aggregates. Only spherical dosage forms are illustrated, but the classification system is applicable to any type of geometry.

brane, D the diffusion coefficient of the drug within the membrane, K the partition coefficient of the drug between the membrane and the reservoir, and c_s the solubility of the drug in the reservoir.

However, in practice often deviations from these "ideal" systems are observed, for instance the film coatings show crack formation due to significant hydrostatic pressure built up within the device or due to membrane swelling and/or (partial) dissolution (Borgquist et al., 2002; Frenning et al., 2003; Marucci et al., 2008). This renders the mathematical treatment much more complicated and yet there is a significant lack of mechanistic realistic mathematical theories taking these phenomena appropriately into account.

In the case of *monolithic* devices (Fig. 1), the system geometry significantly affects the resulting drug release kinetics. If the initial drug concentration is below drug solubility, the drug molecules are individualized/dissolved within the carrier material (monolithic solution). Otherwise, dissolved drug molecules co-exist with amorphous aggregates and/or drug crystals (monolithic dispersions). In the case of *monolithic solutions* and in the absence of significant changes in the carrier matrix during drug release (e.g., constant porosity, no swelling, time-independent permeability for the drug) and if perfect sink conditions are maintained throughout the release period and if drug release is primarily controlled by diffusion through the carrier matrix, the resulting release can be calculated as follows, depending on the system's geometry:

(i) In the case of *thin films* with negligible edge effects (Crank, 1975):

$$\frac{M_t}{M_0} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\ \exp\left(\frac{-D(2n+1)^2\pi^2 t}{L^2}\right) \tag{3}$$

where M_t and M_∞ denote the absolute cumulative amounts of drug released at time t and infinity, respectively; n is a dummy variable, D the diffusion coefficient of the drug within the matrix former, L is the thickness of the film. To avoid the use of infinite series of exponential functions, the following early and late time approximations have been proposed for this equation (Baker, 1987):

$$\frac{M_t}{M_0} = 4\sqrt{\frac{Dt}{\pi L^2}} \quad \text{for } 0 \le \frac{M_t}{M_0} \le 0.6 \tag{4}$$

$$\frac{M_t}{M_0} = 1 - \frac{8}{\pi^2}\ \exp\left(\frac{-\pi^2 Dt}{L^2}\right) \quad \text{for } 0.4 \le \frac{M_t}{M_0} \le 1.0 \tag{5}$$

(ii) In the case of *spherical dosage forms* (Crank, 1975):

$$\frac{M_t}{M_0} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\ \exp\left(-\frac{Dn^2\pi^2 t}{R^2}\right) \tag{6}$$

where M_t and M_∞ denote the absolute cumulative amounts of drug released at time t and infinity, respectively; n is a dummy variable, D the diffusion coefficient of the drug within the matrix former, and R the radius of the sphere. This equation has for example successfully been used to quantify drug release from non-degradable controlled release microparticles (Hombreiro-Pérez et al., 2003). Based on the mathematical analysis, deeper insight into the changes in the systems' composition during drug release could be gained. Fig. 2 shows for instance the concentration profiles of propranolol HCl within ammonio methacrylate copolymer-based microparticles after 5 min, 1 h and 8 h exposure to phosphate buffer pH 7.4.

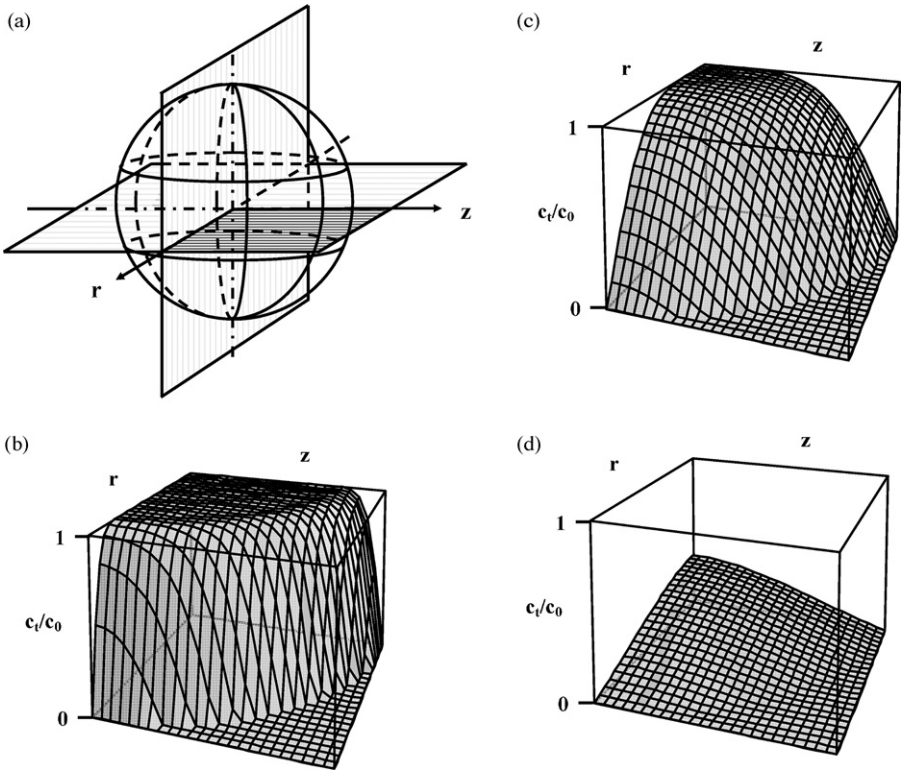

Fig. 2. Calculated changes in the drug concentration gradients within spherical, propranolol HCl-loaded microparticles upon exposure to phosphate buffer pH 7.4: (a) illustration of the point of view; (b) concentration profile after 5 min; (c) 1 h; and (d) 8 h (reproduced with permission from Hombreiro-Pérez et al., 2003).

(iii) In the case of *cylinders* (considering axial as well as radial mass transport) (Vergnaud, 1993):

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{q_n^2}\exp\left(-\frac{q_n^2}{R^2}Dt\right) \times \sum_{p=0}^{\infty}\frac{1}{(2p+1)^2}\exp\left(-\frac{(2p+1)^2\pi^2}{H^2}Dt\right) \quad (7)$$

where M_t and M_∞ denote the absolute cumulative amounts of drug released at time t and infinity, respectively; n and p denote dummy variables; the q_n are the roots of the Bessel function of the first kind of zero order [$J_0(q_n)=0$], and R and H denote the radius and height of the cylinder. This equation can for instance be used to quantify drug release from lipid implants (Guse et al., 2006; Herrmann et al., 2007a). As an example, the release of the protein drug rh-interferon α-2a (IFN-α) from tristearin-based cylinders can successfully be described (Herrmann et al., 2007a). Interestingly, the addition of poly(ethylene glycol) (PEG) (which is commonly used as a pore former in inert matrices) results in protein precipitation/very limited IFN-α solubility within the water-filled pores of the implants and, thus, significant deviations from Eq. (7) (Herrmann et al., 2007a,b). When considering also potentially limited local drug solubility, time- and position-dependent PEG concentrations and implant porosity, resulting in time- and position-dependent drug diffusion coefficients, this more comprehensive mathematical theory is able to quantitatively describe the resulting protein release kinetics (Siepmann et al., 2008). However, due to the complexity of the respective set of partial differential equations, no analytical solution can be derived for this theory, but numerical analysis can be used for the implementation of the model. Importantly, this type of mathematical theory is not only able to give deeper insight into the underlying drug release mechanisms (e.g., relative importance of drug diffusion, limited solubility and changes in local porosity), but allows also for quantitative predictions of the resulting drug release kinetics as a function of the device design. Fig. 3 shows as an example the theoretically predicted and experimentally verified release of IFN-α into phosphate buffer pH 7.4 from tristearin-based implants containing 10% IFN-α/hydroxypropyl-β-cyclodextrin (HP-β-CD) and 20% PEG.

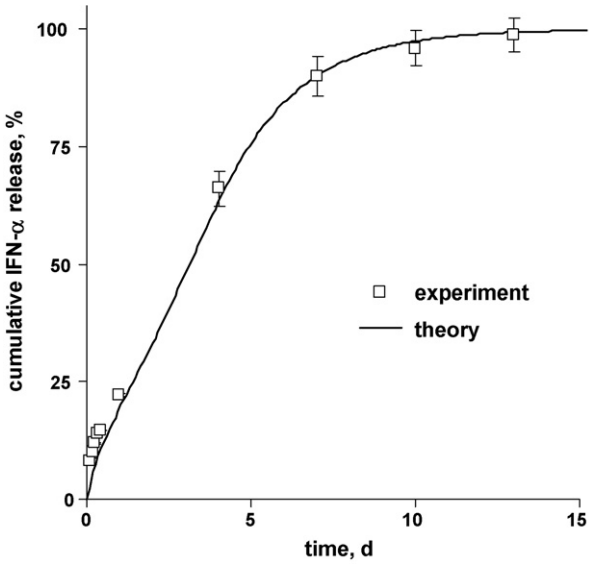

Fig. 3. Theory and experiment: IFN-α release into phosphate buffer pH 7.4 from tristearin-based implants: theoretical prediction (curve) and *independent* experimental verification (symbols) in the case of implants initially containing 10% IFN-α/HP-β-CD and 20% PEG (experimental results: average ± S.D.; $n=3$) (reproduced with permission from Siepmann et al., 2008).

For *monolithic dispersions* the mathematical description becomes even more complex. For the simplest geometry of thin films with negligible edge effects, Takeru Higuchi published the famous square root of time relationship between the amount of drug released from a thin ointment film with a large excess of drug (initial drug concentration ≫ drug solubility in the carrier material) in 1961 (Higuchi, 1961a,b):

$$\frac{M_t}{A} = \sqrt{D(2c_0 - c_s)c_s t} \quad (8)$$

where M_t is the cumulative absolute amount of drug released at time t, A is the surface area of the film exposed to the release medium, D is the drug diffusivity in the carrier material, and c_0 and c_s represent the initial drug concentration and the solubility of the drug in the carrier material, respectively. An important advantage of this equation is its simplicity. However, when applying it to controlled drug delivery systems, the assumptions Higuchi based this equation on must be fulfilled, including:

(i) The initial drug concentration in the system must be much higher than drug solubility. This aspect is crucial, because it provides the basis for the justification of the applied pseudo-steady state approach. The concentration profile of a drug that is homogeneously suspended within an ointment is illustrated in Fig. 4. The solid line represents the concentration profile after exposure of the ointment to perfect sink for a certain time t. Importantly, a sharp discontinuity is observed at distance h from the surface/release medium. For this distance h 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 ($c_0 \gg c_s$) (pseudo-steady-state). After an additional time interval, Δt, the new concentration profile of the drug is indicated by the dotted line. Again, a sharp discontinuity and otherwise linear concentration profiles result.

(ii) The device geometry is that of a thin film with negligible edge effects.

(iii) The size of the drug particles is much smaller than the thickness of the film.

(iv) The carrier material does not swell or dissolve.

(v) The diffusivity of the drug is constant (not dependent on time or position).

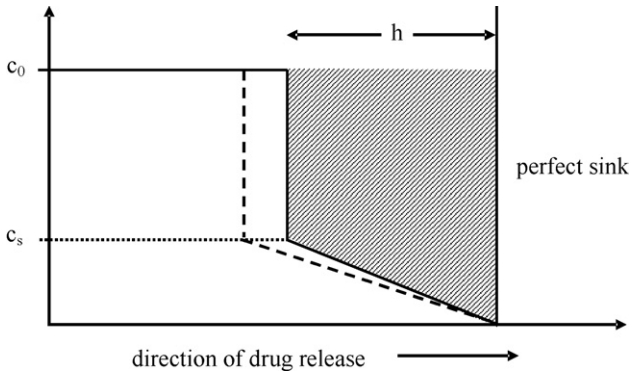

Fig. 4. Pseudo-steady state approach applied for the derivation of the classical Higuchi equation. Theoretical concentration profile existing in an ointment containing suspended drug and in contact with a perfect sink.

(vi) Perfect sink conditions are maintained throughout the experiment.

Unfortunately, Eq. (8) is often misused and applied to controlled drug delivery systems which do not fulfill all these assumptions. In these cases, any conclusion should be viewed with great caution. Even if the cumulative amount of drug that is released from a particular drug delivery system is proportional to the square root of time, this does not necessarily mean that the underlying drug release mechanism is the same as in the ointment Higuchi studied. For instance, the superposition of various other physicochemical phenomena (such as polymer swelling, time- and position-dependent changes in the diffusion coefficients of water and drug) might result in an apparent square root of time kinetics. Furthermore, as discussed above, the cumulative amount of drug released is proportional to the square root of time in the early time approximation for monolithic solutions with film geometry (Eq. (4)).

For monolithic dispersions with other geometries than that of a thin film with negligible edge effects, the reader is referred to the literature (Higuchi, 1963; Desai et al., 1965, 1966; Lapidus and Lordi, 1966, 1968; Fan and Singh, 1989). If both, diffusion through the inner device matrix as well as diffusion through a surrounding barrier membrane are of importance for drug release (Fig. 1, "miscellaneous" systems), the mathematical modeling is also more complex and geometry dependent. Again, the reader is referred to the literature for more details (Fan and Singh, 1989).

3.2. Theories considering polymer swelling

If polymer swelling is of importance for the control of drug release, e.g. as in the case of hydroxypropyl methylcellulose (HPMC)-based matrix tablets, the transition of the macromolecules from the glassy (less mobile) to the rubbery (more mobile) state has to be considered in the model (Doelker, 1986; Colombo, 1993; Siepmann and Peppas, 2001). The two most important consequences of significant polymer swelling in a controlled release matrix system are:

(i) The length of the diffusion pathways increases, resulting in decreasing drug concentration gradients (being the driving forces for diffusion) and, thus, potentially decreasing drug release rates.
(ii) The mobility of the macromolecules significantly increases, resulting in increased drug mobility and, thus, potentially increasing drug release rates. In dry tablets, diffusion is often negligible (diffusivities close to zero). In contrast, in a fully swollen polymer matrix the diffusion coefficient of the drug can be of the same order of magnitude as in an aqueous solution.

Depending on the type of polymer and type of drug delivery system, one of these effects potentially dominates, resulting in *de*creasing or *in*creasing drug release rates.

Fig. 5 schematically illustrates the physical phenomena which can be involved in the control of drug release from a swellable delivery system. This might represent a cross-section through half of a matrix tablet which is exposed to an aqueous bulk fluid in radial direction. On the right hand side, the inner tablet core is still dry and in the glassy state (non-swollen), on the left hand side the bulk fluid is located. Upon contact with the release medium, water diffuses into the system. With increasing water content, the mobility of the polymer chains (and, thus, also drug molecules) increases. As soon as a certain, polymer-specific water concentration is reached, the macromolecular mobility steeply increases. This phenomenon is called "polymer chain relaxation" or "glassy-to-rubbery-phase-transition". The front at which this process takes place is called "swelling front", which separates the swollen from non-swollen matrix. Importantly, this is not a *stationary* boundary, but a *moving* one. If the initial drug concentration in the delivery system exceeds drug solubility, dissolved and non-dissolved drug co-exist within the matrix. Due to concentration gradients and the significantly increased mobility, dissolved drug molecules diffuse out of the swollen matrix into the release medium. As long as a non-dissolved excess of drug exists, the concentration of dissolved drug in this part of the system is constant (drug molecules that are released are replaced by the dissolution of non-dissolved drug, providing a saturated solution). But as soon as all excess drug is dissolved, the concentration within the swollen matrix decreases. The front that separates the swollen matrix containing only dissolved drug from the swollen matrix that contains both, dissolved and non-dissolved drug, is called "diffusion front" (Fig. 5) (Colombo

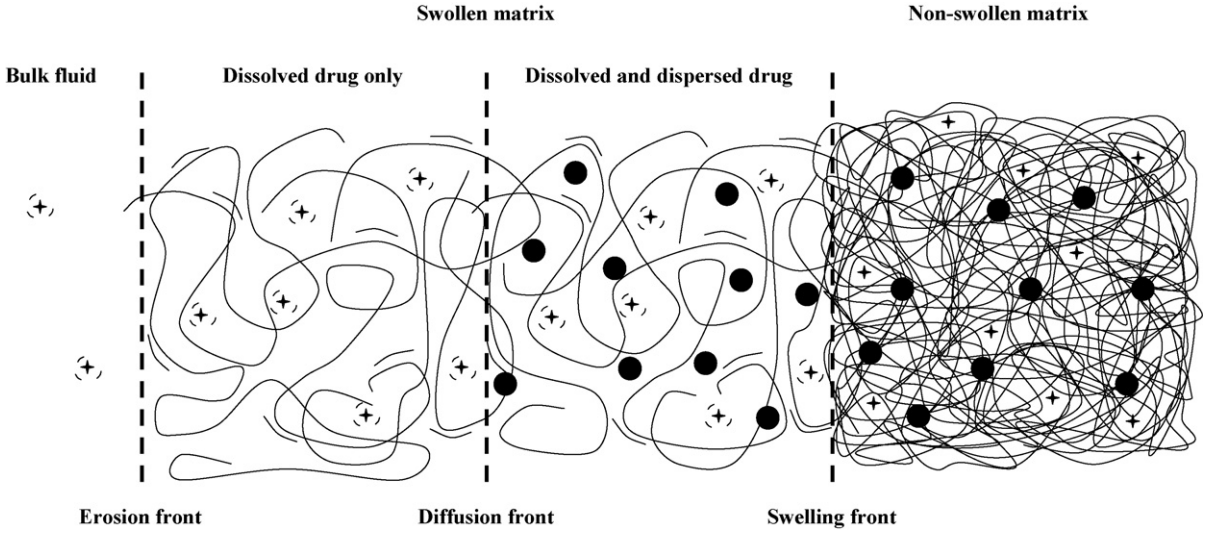

Fig. 5. Schematic presentation of a swelling controlled drug delivery system containing dissolved and dispersed drug (stars and black circles, respectively), exhibiting the following moving boundaries: (i) an "erosion front", separating the bulk fluid from the delivery system; (ii) a "diffusion front", separating the swollen matrix containing dissolved drug only and the swollen matrix containing dissolved and dispersed drug; and (iii) a "swelling front", separating the swollen and non-swollen matrix.

et al., 1999, 2000). Importantly, also this front is moving. Furthermore, a third front can be distinguished, which separates the drug delivery system from the release medium and which is also moving. In the case of water-soluble matrix formers, this front is called "erosion front".

If the polymer relaxation process is rate-limiting (e.g., all other phenomena, such as diffusion and dissolution are much faster) and if the device has the geometry of a thin film (with negligible edge effects) and an initial homogeneous drug and polymer distribution, zero order drug release kinetics result, because the rate at which the swelling front moves is independent of its position (and, thus, constant). However, in the case of the geometry of a sphere or a cylinder, the movement of a swelling front at a constant rate does not result in zero order release kinetics, but in a proportionality of the cumulative amount of drug released to the time to the power of 0.85 and 0.89, respectively (due to the change in the surface area that is affected by the swelling with time) (Peppas and Sahlin, 1989).

A very interesting, mechanistic realistic mathematical theory allowing for the quantification of drug release from swellable polymer films has been proposed by Korsmeyer et al. (1986a,b). It allows for a *simultaneous* consideration of the diffusion of water into the device and drug out of the system as well as of polymer swelling. To account for the increase in water and drug mobility with increasing water content of the polymer matrix, a Fujita-type exponential relationship was chosen (Fujita, 1961) and shown to be appropriate for the prediction of different types of transport behaviors. Dimensional changes in the films are accounted for by allowing each spatial increment to expand according to the amount of water that diffused in. At early time points, the swelling is restricted to one dimension by the glassy core of the sample. At later time points, when enough water has penetrated into the core of the system to plasticize it, the sample relaxes to an isotropically swollen state. Afterwards, swelling is three-dimensional. Under these conditions, water (subscript 1) diffusion can be described as follows:

$$\frac{\partial c_1}{\partial \tau} = \frac{\partial}{\partial \xi}\left(D_1 \frac{\partial c_1}{\partial \xi}\right) \tag{9}$$

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

$$c_1 = \frac{c_w}{c_{w,e}} \tag{10}$$

Here, c_w is the water concentration in the film at a particular position, and $c_{w,e}$ is the *equilibrium* water concentration in the system. Time t is scaled according to the water diffusivity in the fully swollen system, $D_{1,s}$, and the dry thickness of the film, L_0:

$$\tau = \frac{tD_{1,s}}{L_0^2} \tag{11}$$

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

$$\xi = \frac{x}{L_0} \tag{12}$$

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

$$\frac{\partial c_2}{\partial \tau} = \frac{\partial}{\partial \xi}\left(D_2 \frac{\partial c_2}{\partial \xi}\right) \tag{13}$$

$$c_2 = \frac{c_s}{c_{s,i}} \tag{14}$$

Here, D_2 is the diffusion coefficient of the drug, and c_2 is the *normalized* drug concentration; c_s denotes the drug concentration in the film, and $c_{s,i}$ the initial drug concentration in the system. The following boundary conditions are considered:

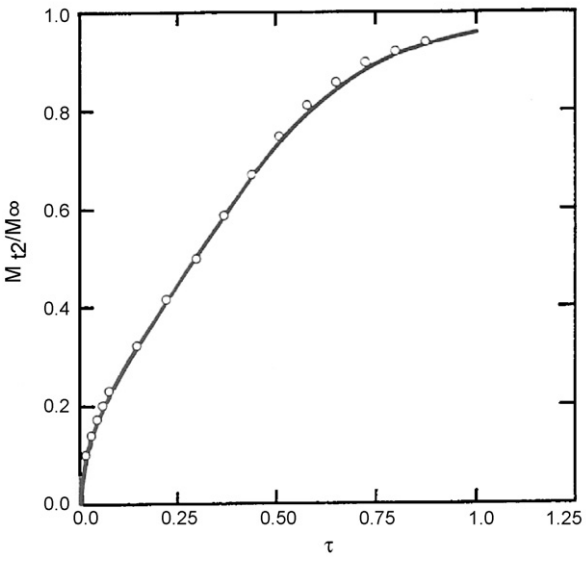

Fig. 6. Fit of the Korsmeyer–Peppas model to experimentally determined theophylline release kinetics from hydroxyethyl methacrylate-*co*-*N*-vinyl-2-pyrrolidone copolymers-based films (curve = theory, symbols = experiment) (reproduced with permission from Korsmeyer et al., 1986b).

$$c_1(0, \tau) = c_1(\xi, \tau) = 1 \tag{15}$$

$$c_2(0, \tau) = c_2(\xi, \tau) = 0 \tag{16}$$

where 0 and ξ are the two surfaces of the thin film. Please note that ξ describes the continuously *moving* outside surface of the film. The following initial conditions are considered:

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

$$c_2(\xi, 0) = 1 \tag{18}$$

Due to the complexity of this set of partial differential equations, the latter was solved numerically. As it can be seen in Fig. 6, good agreement between theory and experiment was obtained when fitting this model to sets of experimentally measure theophylline release kinetics from (hydroxyethyl methacrylate-*co*-*N*-vinyl-2-pyrrolidone) copolymers-based films.

3.3. Theories considering polymer swelling and polymer and drug dissolution

In practice, often even more processes are simultaneously involved in the control of drug release from oral controlled release matrix tablets: Generally, the matrix former is water-soluble. Thus, also polymer dissolution must be taken into account. Different comprehensive mathematical theories have been proposed aiming to describe this type of drug delivery systems (Ju et al., 1995a,b, 1997; Siepmann and Peppas, 2001). In the following only one example will briefly be described. The reader is referred to the literature for more details (Siepmann and Peppas, 2001).

The so-called "sequential layer model" takes into account the diffusion of water and drug with time- and position-dependent diffusivities, moving boundary conditions, the swelling of the system, polymer and drug dissolution, and radial and axial mass transfer within cylindrical tablets (Siepmann and Peppas, 2000). The model was successfully fitted to drug release kinetics from matrices based on hydroxypropyl methylcellulose (HPMC) and HPMC derivatives,

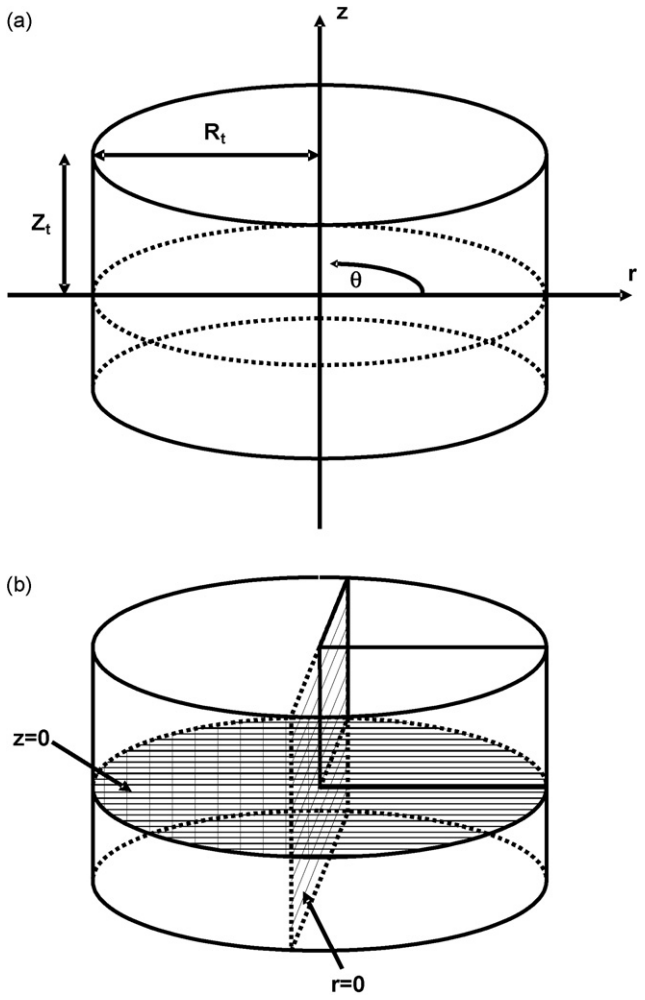

Fig. 7. Mathematical modeling of drug release from HPMC-based matrix tablets: (a) scheme of a cylindrical tablet for mathematical analysis, with (b) symmetry planes in axial and radial direction for the water and drug concentration profiles (R_t and Z_t represent the time dependent radius and half-height of the cylinder, respectively).

e.g. hydroxypropyl methylcellulose acetate succinate (HPMCAS) (Streubel et al., 2000). The theory is applicable to freely and poorly water-soluble drugs and a wide range of initial drug loadings. Its practical usefulness could be demonstrated via quantitative predictions of the effects of the design parameters of HPMC-based controlled release matrix tablets (including the size, shape and composition of the systems) on the resulting drug release kinetics. Water and drug diffusion are considered based on Fick's second law of diffusion for cylindrical geometry, taking into account axial and radial mass transport and concentration-dependent diffusivities (Crank, 1975):

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\} \quad (19)$$

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 (Fig. 7a), and t represents time. Analogous to the Korsmeyer–Peppas model described above, a Fujita-type (Fujita, 1961) exponential dependence of the water and drug diffusion coefficients on the water content of the system is taken into account:

$$D_k = D_{k\text{crit}} \exp\left\{-\beta_k\left(1 - \frac{c_1}{c_{1\text{crit}}}\right)\right\} \quad (20)$$

where β_1 and β_2 are dimensionless constants characterizing this concentration-dependence. Also $D_{1\text{crit}}$ and $D_{2\text{crit}}$ denote the diffusion coefficients of water and drug at the interface tablet/release medium, where polymer chain disentanglement occurs (Ju et al., 1995b; Narasimhan and Peppas, 1996a,b, 1997). Ideal mixing is assumed (no volume contraction upon mixing drug, polymer and water), and the total volume of the system at any time point is given by the sum of the volumes of the single components. The calculation of the new tablet dimensions is based on a mass balance considering drug, polymer and water. Polymer dissolution is taken into account using the reptation theory (Narasimhan and Peppas, 1996a,b, 1997): Above a certain critical water concentration ($c_{1\text{crit}}$), the polymer chains at the surface of the tablet start to disentangle and diffuse through the liquid, unstirred layer surrounding the device into the bulk fluid (release medium). A dissolution rate constant, k_{diss}, is considered characterizing the polymer mass loss velocity, which is normalized to the actual surface area of the system:

$$M_{\text{pt}} = M_{\text{p0}} - k_{\text{diss}} A_t t \quad (21)$$

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. The initial conditions reflect the fact that the matrix is dry and the drug uniformly distributed throughout the device at $t=0$. The boundary conditions are defined as follows: The water concentration at the surface of the matrix, $c_{1\text{crit}}$, is calculated from the critical polymer disentanglement concentration (Ju et al., 1995b; Narasimhan and Peppas, 1996a,b, 1997). The drug concentration at the surface of the tablet is assumed to be equal to zero (perfect sink condition). In order to reduce computation time, the origin of the coordinate system is placed at the center of the cylinder, resulting in two symmetry planes for the drug and water concentration profiles (Fig. 7b). Thus, only the concentration profiles within a quarter of the tablet need to be calculated. Due to the complexity of the resulting set of partial differential equations, also in this case a numerical solution is required. Fig. 8 shows an example for a practical application of this mathematical model: The theoretically predicted effects of the initial radius of HPMC-based matrix tablets (with an initial height of 2.6 mm, composition: 50% drug and 50% HPMC) on the resulting relative and absolute release of theophylline into phosphate buffer pH 7.4 is illustrated (Siepmann et al., 2002a). The curves show the theoretically predicted drug release profiles. Then, in a second step, the respective drug release rates were determined experimentally (symbols in Fig. 8). As it can be seen, good agreement between theory and experiment was obtained in all cases.

3.4. Theories considering polymer erosion/degradation

Unfortunately, the terms "erosion" and "degradation" are not uniformly used in the literature. In this article, the following definitions are applied (Goepferich, 1996a): Polymer *degradation* is the chain scission process by which polymer chains are cleaved into oligomers and monomers. In contrast, e*rosion* is defined as the process of material loss from the polymer bulk. Such materials may be monomers, oligomers, parts of the polymer backbone or even parts of the polymer bulk. Thus, the degradation of water-insoluble polymers is part of their erosion process. Depending on the relative rates of water penetration into such systems and of polymer chain cleavage, two extreme types of erosion can be distinguished: *surface (or heterogeneous) erosion* and *bulk*

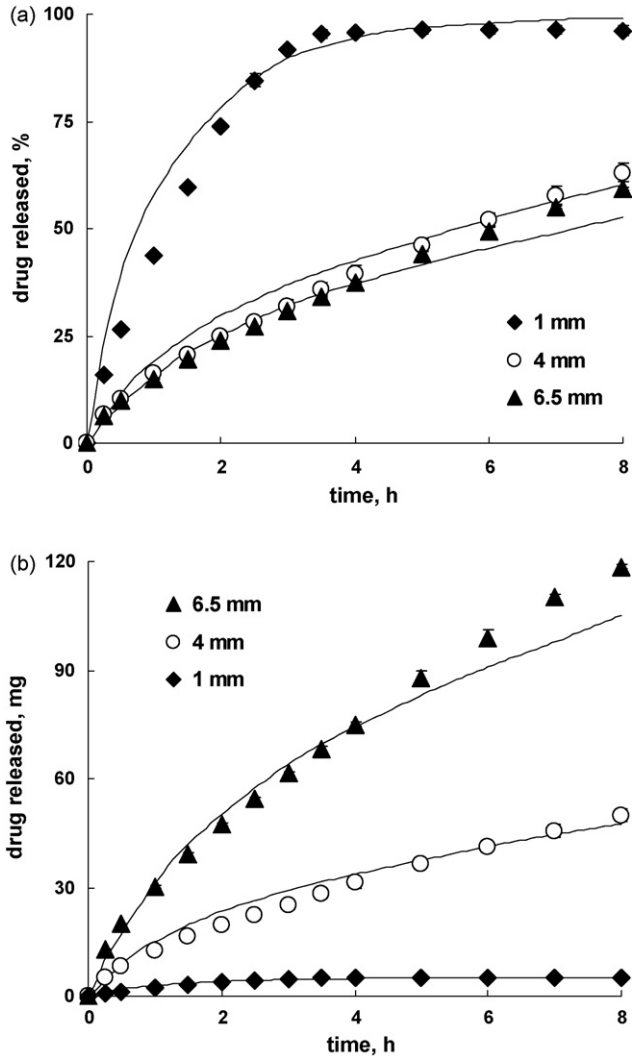

Fig. 8. Practical application of the "sequential layer model": Theoretically predicted effects of the initial tablet radius on the release patterns of theophylline from HPMC-based matrix tablets in phosphate buffer pH 7.4 and experimental verification: (a) relative amount of drug released and (b) absolute amount of drug released versus time (37 °C, initial tablet height = 2.6 mm, initial tablet radius indicated in the figures, 50% (w/w) initial drug loading) (curves: predicted values, symbols: independent experimental data) (reproduced with permission from Siepmann et al., 2002a).

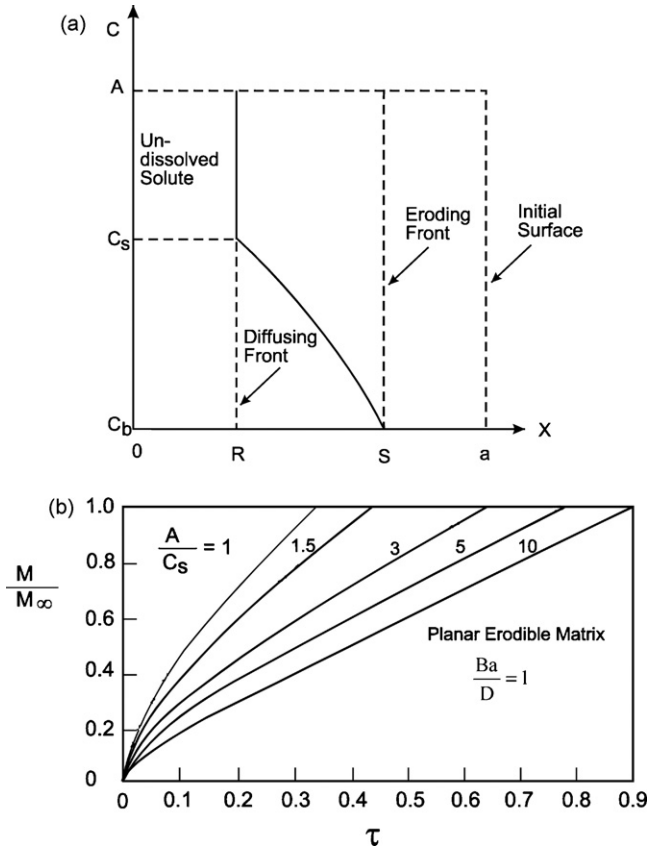

Fig. 9. Modeling drug release from surface eroding monolithic dispersions with film geometry: (a) scheme of the drug concentration profile within the system according to Lee (1980). Two moving fronts are considered: a diffusion front and an erosion front. (b) Calculated drug release profiles as a function of the "initial drug loading:drug solubility" ratio (A/C_s). The parameter Ba/D serves as a measure for the relative contribution of erosion and diffusion (adapted with permission from Lee, 1980).

(or homogeneous erosion) (Langer and Peppas, 1983). In the first case, the polymer chain cleavage is much faster than the water penetration into the system. Consequently, the degradation process is mostly restricted to the outermost polymer layers and the erosion predominantly affects the surface, and not the inner parts of the device. In contrast, if water penetration is much more rapid than polymer chain cleavage, the entire system is rapidly wetted and degradation occurs throughout the device (*bulk erosion*). Generally, drug delivery systems which are based on polymers with highly reactive bonds (e.g., polyanhydrides) in their backbone structure undergo surface erosion, whereas devices that are based on polymers with less reactive functional groups [e.g., poly(lactic-*co*-glycolic acid) (PLGA)] tend to be *bulk eroding*. However, please note that the dimensions of the drug delivery system affect the *relative* water penetration rate into the device and that for instance a PLGA-based sphere of the size of the moon would show surface erosion (Burkersroda and Goepferich, 1999).

An interesting mathematical theory for *surface eroding* drug delivery systems with film geometry was proposed by Lee in 1980 (Lee, 1980). It is an analytical solution that is valid for different "drug loading:drug solubility" ratios. As illustrated in Fig. 9a, the movements of two fronts are considered: a diffusion front, and an erosion front. Here, R denotes the time-dependent position of the diffusion front, and S the time-dependent position of the erosion front; A is the initial drug concentration within the delivery system, which is above drug solubility, C_s (monolithic dispersion); C_b represents the drug concentration in the well stirred release medium, and x the position (with $x = 0$ at the center, and $x = a$ at the surface of the film). It is assumed that the erosion front moves at a constant velocity, that edge effects are negligible and that perfect sink conditions are maintained throughout the experiment. Under these conditions, Lee derived the following equations allowing for a quantitative description of drug release:

$$\frac{M_t}{M_\infty} = \delta + \frac{Ba}{D}\tau - \delta\frac{C_s}{A}\left(\frac{1}{2} + \frac{a_3}{6}\right) \tag{22}$$

$$a_3 = \frac{A}{C_s} + \delta h - \sqrt{\left(\frac{A}{C_s} + \delta h\right)^2 - 1 - 2\delta h} \tag{23}$$

$$h = \frac{1}{2}\frac{Ba}{D}\left(1 - \frac{A}{C_s}\right) \tag{24}$$

Here, M_t and $M_{infinity}$ are the cumulative absolute amounts of drug released at time t and at infinite time, respectively; δ denotes the relative separation between the diffusion and erosion fronts

[$\delta = (S - R)/a$]; B is the *surface erosion* rate constant with the dimensions of a velocity; a represents the half-thickness of the film, D the drug diffusivity within the system, and τ is the dimensionless time ($\tau = Dt/a^2$). The parameter Ba/D is a measure for the relative contribution of erosion and diffusion to drug release. The calculated effects of the "initial drug loading:drug solubility" ratio (A/C_s) on the resulting drug release patterns are illustrated in Fig. 9b. In this example, the relative contributions of erosion and diffusion (represented by the term Ba/D) are kept constant (=1). As it can be seen, the relative drug release rate decreases with increasing A/C_s ratio. The model predicts that the release approaches zero order kinetics when the initial drug loading becomes much higher than drug solubility in the matrix.

As polymer chain cleavage is a random process, Monte Carlo simulations can effectively be used to simulate polymer degradation. Zygourakis (1989, 1990; Zygourakis and Markenscoff, 1996) was the first to propose this type of theories allowing for a quantitative description of drug release from surface eroding polymer matrices. The basic idea is to represent polymer matrix cross-sections by two-dimensional grids. Each pixel represents one of the system's components: drug, polymer, and potentially filler and pores. To simulate drug or polymer "dissolution" a so-called "life expectancy" is defined for each type of pixel. As soon as a pixel comes into contact with water, its "lifetime" starts to decrease. Once the "lifetime" expires, the pixel is assumed to "dissolve" instantaneously. Importantly, different "life expectancies" can be defined for the involved system compounds, taking into account differences in their dissolution rates. However, diffusional mass transport is not taken into account.

The first to combine Monte Carlo simulation to account for polymer degradation and diffusional mass transport (based on Fick's second law) was Achim Goepferich (Goepferich and Langer, 1995a,b; Goepferich et al., 1995; Goepferich, 1996a,b,c, 1997a,b). He developed theories that are applicable to surface eroding systems, but also models for bulk eroding devices. Furthermore, drug delivery systems containing both, surface and bulk eroding polymers can be considered, containing for instance poly(D,L-lactic acid) (PLA) and poly[1,3-bis(*p*-carboxyphenoxy)propane-sebacic acid] [p(CPP-SA)] (Goepferich, 1997a,b). In addition, the potential crystallization of polymer degradation products, and microenvironmental pH effects can be taken into account (Goepferich and Langer, 1995a). Later on, a similar approach (combining Monte Carlo simulations with diffusional mass transport) was used to quantify drug release from spherical poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles (Faisant et al., 2003; Siepmann et al., 2002b). For the mathematical analysis the latter are divided into concentric rings of equal volume (Fig. 10, the rings are described upon rotation of the pixels shown in Fig. 10b around the z-axis). Due to the symmetry planes at the $r = 0$ and $z = 0$ planes (in the case of homogenous initial drug and polymer distribution), it is sufficient to calculate the mass transport phenomena in only one quarter of the two-dimensional circle shown in Fig. 10b (Fig. 11a). At $t = 0$ each ring represents either drug or non-degraded polymer. Due to the identical volume of the polymer rings it is reasonable to assume that each of them contains a similar number of cleavable ester bonds. Thus, the probability with which a ring representing non-degraded polymer degrades upon its first contact with water is similar for all rings. As described above, life time expectancies are assigned to all polymer pixels (rings), reflecting the degradation rate of the macromolecules. Importantly, knowing the status of each pixel (ring) ("non-eroded polymer" or "pore") at each time point, the microparticle porosities in radial and axial direction (depending on time and position) can be calculated (Fig. 11b). Based on these porosity values, the position- and direction-dependent drug diffusivities within the spheres can be calculated as a function of the exposure time to the release medium. This information is essential for the accurate calculation of the diffusional mass transport processes using Fick's second law (Crank, 1975):

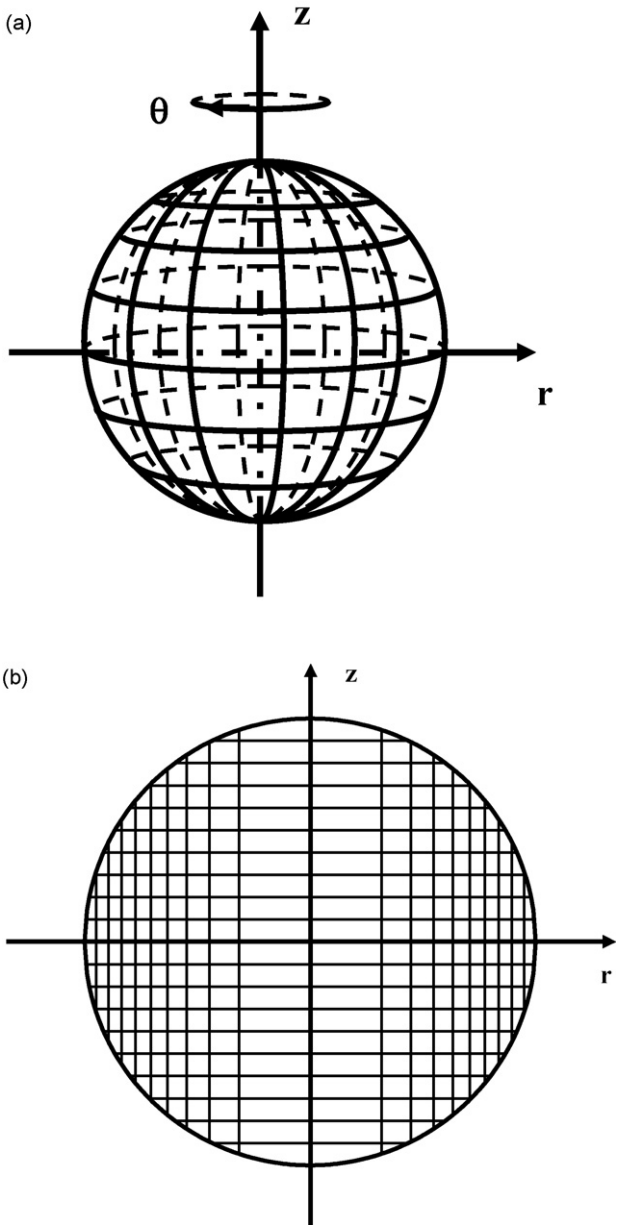

Fig. 10. Schematic presentation of a spherical PLGA-based microparticle for mathematical analysis: (a) three-dimensional geometry; (b) two-dimensional cross-section with two-dimensional pixel grid. Upon rotation of the latter around the z-axis, rings of identical volume are described (reproduced with permission from Siepmann et al., 2002b).

$$\frac{\partial c}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD\frac{\partial c}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r}\frac{\partial c}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD\frac{\partial c}{\partial z}\right)\right\} \quad (25)$$

Here, c and D are the concentration and diffusion coefficient of the drug; r denotes the radial coordinate, z the axial coordinate, and θ the angle perpendicular to the r–z-plane. In addition, the limited solubility of the drug within the system is taken into account: Only drug which is soluble under the given conditions is considered to be available for diffusion. Taking into account the given initial and boundary conditions (initial homogeneous drug distribution and perfect sink conditions), the respective set of partial differen-

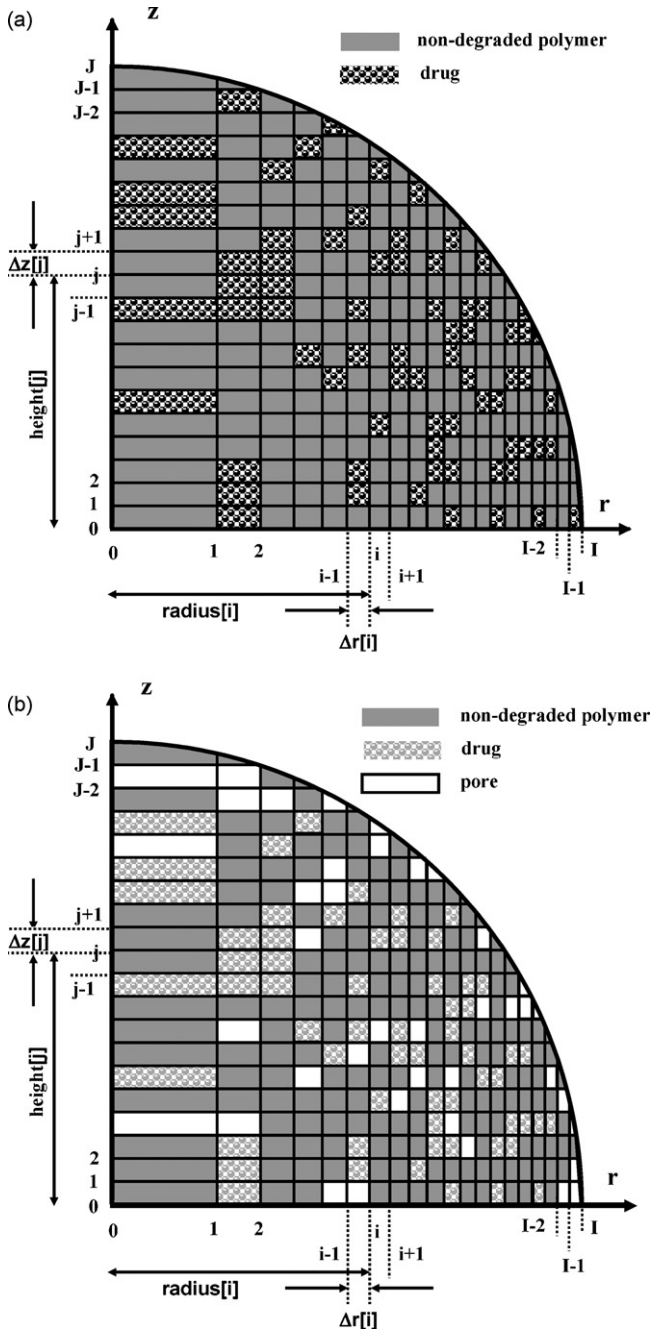

Fig. 11. Principle of a Monte Carlo-based approach to simulate polymer degradation and diffusional drug release from PLGA-based microparticles. Schematic structure of the system (one quarter of the two-dimensional grid shown in Fig. 10b): (a) at time $t = 0$ (before exposure to the release medium) and (b) during drug release. Gray, dotted and white pixels represent non-degraded polymer, drug and pores, respectively (reproduced with permission from Siepmann et al., 2002b).

tial equations is solved numerically, using finite differences (since the diffusion coefficients are time- and position-dependent there is no analytical solution). Importantly, good agreement between theory and experiment was obtained when fitting this model to experimentally measured drug release from 5-fluouracil-loaded, PLGA-based microparticles in phosphate buffer pH 7.4 (Fig. 12). Based on these calculations, system-specific parameters can be determined and the dominant physical and chemical phenomena in each of the release periods be identified. For instance, it can be shown that in this specific system the initial "burst release" is primarily controlled by pure drug diffusion. Furthermore, the model allows for quantitative predictions of the effects of formulation and processing parameters, including the initial microparticle size and drug loading.

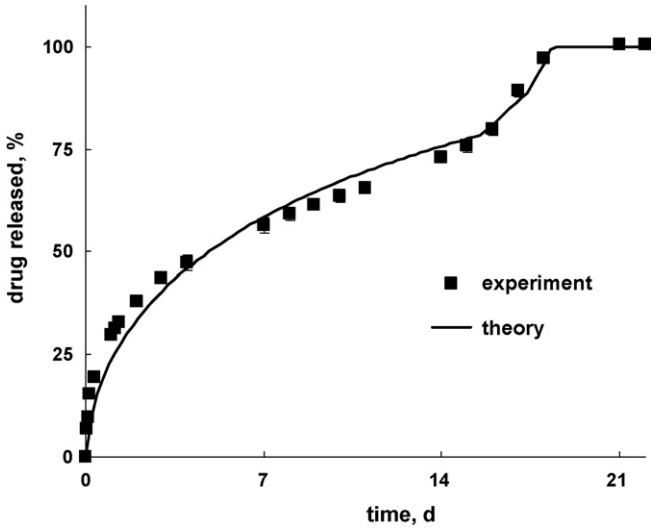

Fig. 12. Fit of a mechanistic realistic mathematical theory based on Monte Carlo simulations and considering diffusional mass transport as well as limited local drug solubility to experimentally determined drug release from 5-fluouracil-loaded, PLGA-based microparticles in phosphate buffer pH 7.4: experimental results (symbols) and fitted theory (curve) (reproduced with permission from Siepmann et al., 2002b).

4. Empirical and semi-empirical mathematical models

As discussed above, empirical/semi-empirical models should generally not be used if the underlying drug release mechanisms are to be elucidated and/or quantitative predictions of the effects of formulation and/or processing parameters on the resulting drug release profiles are to be made. However, such a descriptive mathematical analysis can be useful for a comparison of different drug release profiles (e.g., for experimental design studies). Semi-empirical models might be realistic in certain, extreme cases and give an indication for the underlying drug release mechanism under very specific conditions. Nevertheless, caution has to be paid and the potential violation of model assumptions must carefully be verified.

4.1. Peppas equation

A very frequently used and easy-to-apply model to describe drug release is the so-called Peppas equation, or power law (Peppas, 1985):

$$\frac{M_t}{M_\infty} = kt^n \tag{26}$$

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 system, and n is the release exponent, which might be indicative of the mechanism of drug release. Nicholas Peppas was the first to introduce this equation in the field of drug delivery (Peppas, 1985). Clearly, the classical Higuchi equation (Eq. (8)) as well as the above described short time approximation of the exact solution of Fick's second law for thin films with initial drug concentrations, which are below drug solubility (monolithic solutions, Eq. (4)) represent the special case of the Peppas equation where the

Table 1
Release exponent n of the Peppas equation and drug release mechanism from polymeric controlled delivery systems of different geometry.

Thin film	Exponent, n		Drug release mechanism
	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	Polymer swelling

release exponent is equal to 0.5. Thus, a release exponent of 0.5 can serve as an indication for diffusion controlled drug release, but only if all assumptions these particular solutions are based on are fulfilled, in example film geometry with negligible edge effects, time- and position-independent diffusion coefficients in a non-swellable and insoluble matrix former. For other device geometries and pure drug diffusion control, different release exponent values have been derived (Table 1) (Ritger and Peppas, 1987a,b). In contrast, if polymer swelling is the solely release rate controlling mechanism and in the case of a delivery system with film geometry, zero order drug release kinetics are observed (as discussed above), corresponding to a release exponent of $n = 1$. But again, none of the model assumptions for this particular case must be violated. For other geometries than that of thin films with negligible edge effects, different n-values can serve as indicators for purely swelling controlled drug delivery (Table 1). Release exponents that are in-between these extreme values for the respective device geometry indicate so-called "anomalous" transport, thus, an overlapping of different types of phenomena, potentially including drug diffusion and polymer swelling.

4.2. Hopfenberg model

Hopfenberg (1976) proposed an interesting semi-empirical model allowing for a quantitative description of drug release from degradable drug delivery systems exhibiting a release rate which is proportional to the (time-dependent) surface area of the device. All mass transfer processes that are involved in the control of drug release are assumed to add up to a single zero order process (characterized by a rate constant, k_0), which is confined to the surface area of the system. This zero order process might correspond to one single physical or chemical phenomenon, but it might also result from the superposition of several processes, such as dissolution, swelling and/or polymer chain cleavage. The Hopfenberg model can for instance be applied to surface eroding polymer matrices for which a zero order surface detachment of the drug is the rate limiting release step. The general equation is as follows:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{c_0 a}\right)^n \quad (27)$$

Here, M_t and M_∞ are the cumulative absolute amounts of drug released at time t and at infinite time, respectively; c_0 denotes the uniform initial drug concentration within the system; and a is the radius of a cylinder or sphere or the half-thickness of a slab; n is a "shape factor" representing spherical ($n = 3$), cylindrical ($n = 2$) or slab geometry ($n = 1$). The model ignores edge and end effects.

4.3. Cooney model

A more detailed analysis for spheres and cylinders undergoing surface erosion was presented by Cooney (1972). Also his model is based on the assumption that there is one single zero order kinetics process, which is confined to the surface of the drug delivery system. As in the Hopfenberg model the release rate is assumed to be proportional to the surface area of the device, which is time-dependent. For a cylinder with the initial length L_0 and initial diameter D_0, the following equation was derived quantifying the drug release rate f as a function of time t:

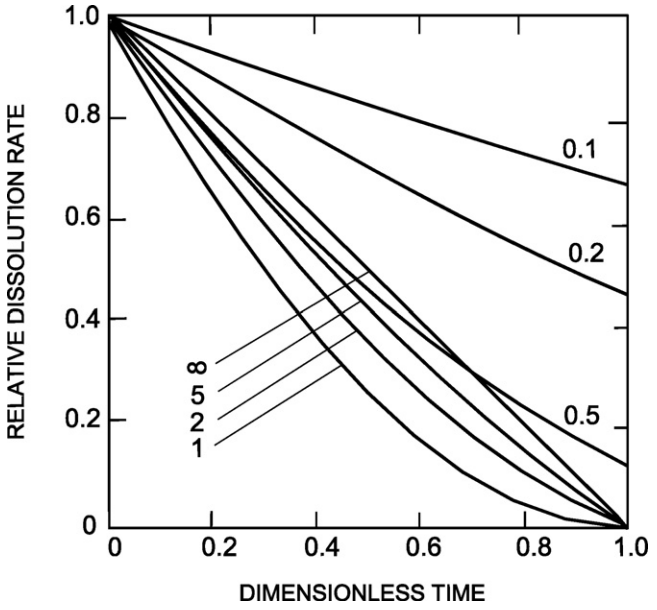

Fig. 13. Effects of the ratio "initial length:initial diameter" (L_0/D_0) of a cylinder on the resulting relative dissolution rate (or relative drug release rate) versus time according to the semi-empirical Cooney model. The numbers given at the curves indicate the respective L_0/D_0 ratios. The curve for L_0/D_0 approaching zero (film geometry) is a horizontal line at relative dissolution rate = 1.0 (reprinted with permission from Cooney, 1972).

$$f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2Kt)(L_0 - 2Kt)}{D_0^2 + 2D_0 L_0} \quad (28)$$

where K is a constant. Fig. 13 illustrates the effects of the ratio "initial length:initial diameter" (L_0/D_0) of a cylinder on the resulting relative drug release rate versus time (=relative dissolution rate in this example). When L_0/D_0 approaches zero (film geometry) the curves transform into a horizontal line with a constant relative drug release rate of 1. It is interesting to note that for *disc-like* cylinders (ratios of $L_0/D_0 < 1$, curves numbered 0.1, 0.2 and 0.5), the relative drug release rate remains finite up to complete drug release. In contrast, for *rod-like* cylinders ($L_0/D_0 > 1$, curves numbered 1, 2, 5 and infinity), the relative drug release rate approaches zero at late time points.

4.4. Artificial neural networks

Also artificial neural networks (ANNs) can be used to model drug delivery (Takahara et al., 1997; Chen et al., 1999; Takayama et al., 1999; Wu et al., 2000). The basic principle of this type of mathematical analysis is illustrated in Fig. 14. An ANN consists of one input layer, one output layer and one or more hidden intermediate layers. Each layer is composed of several units, corresponding to "neurons". The input layer encompasses n input values of causal factors, e.g. the drug loading, compression force or excipient content. The output layer can for instance consist of constants describing the drug release profile. As illustrated, the units of neighboring layers are interconnected, the links corresponding to "synapses". The strength of these links can vary, they are also called "weights". Upon definition of the model structure a set of experimental results (consisting of input and output values) is used to "train" the network, that is to define the optimal equations and weights allowing for the calculation of the output values based on the input values. Thus, ANNs

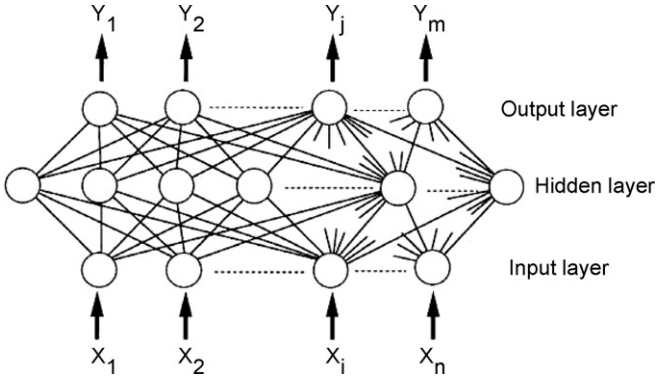

Fig. 14. Basic principle of mathematical modeling using artificial neural networks (ANNs): X_i represents the input value of causal factors, n is the number of causal factors, Y_i denotes the output value of responses and m the number of responses. Between the input and output layer, one or more hidden layers are located (reprinted with permission from Takahara et al., 1997).

can be considered as nonlinear regression analysis tools. Once the system is "trained", it can be used to make quantitative predictions for the output values based on new input values. This type of analysis was for instance used by Takahara et al. (1997) to simulate the effects of the amounts of microcrystalline cellulose and hydroxypropyl methylcellulose as well as of the compression pressure used to prepare trapidil-loaded matrix tablets on the resulting drug release kinetics. Ibric et al. (2002) applied ANNs to study acetylsalicylic acid release from Eudragit RS-based matrix tablets, whereas theophylline release from coated pellets was analyzed by Ghaffari et al. (2006) using this type of mathematical modeling approach. A further interesting application of neural networks in drug delivery was presented by Shao et al. (2006, 2007), predicting drug release from and tablet tensile strength of immediate release formulations.

5. Conclusions and future outlook

The mathematical modeling of drug delivery has a significant potential to facilitate product development in the future and to help understanding complex pharmaceutical dosage forms. Due to the advances in information technology the accuracy of these models steadily increases and they become more and more easy to apply. Similar to other scientific disciplines mathematical modeling of drug delivery can be expected to become an integral part of product development. However, it is unlikely that there will be one general theory that is applicable to any type of drug delivery system. It is much more likely that there will be a broad spectrum of different mathematical models, applicable to specific types of devices differing in geometry, drug and excipient type. Decision trees will allow for the identification of the appropriate model for a specific type of delivery system and type of task (e.g., prediction of the effects of formulation parameters or improved understanding of the underlying drug release mechanisms).

A particularly fruitful, but also very challenging aspect will be to combine these mathematical theories with models quantifying drug transport in the living organism, including drug distribution in the various organs and even within the different cell compartments. Ideally, theoretical calculations should allow for a quantitative prediction of the effects of formulation and processing parameters not only on the resulting drug release kinetics, but on the resulting drug concentration time profiles at the site of action in the human body and on the *pharmacodynamic* effects in the patients under the disease conditions. This type of mathematical modeling is much more complex, but in the very long run it could help to allow for customized drug delivery to the patient.

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