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Review

Modeling of diffusion controlled drug delivery

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ABSTRACT

Mathematical modeling of drug release can be very helpful to speed up product development and to better understand the mechanisms controlling drug release from advanced delivery systems. Ideally, *in silico* simulations can quantitatively predict the impact of formulation and processing parameters on the resulting drug release kinetics. The aim of this article is to give an overview on the current state of the art of modeling drug release from delivery systems, which are predominantly controlled by diffusional mass transport. The inner structure of the device, the ratio "initial drug concentration:drug solubility" as well as the device geometry determine which type of mathematical equation must be applied. A straightforward "road map" is given, explaining how to identify the appropriate equation for a particular type of drug delivery system. The respective equations for a broad range of devices are indicated, including reservoir and matrix systems, exhibiting or not an initial excess of drug and the geometry of slabs, spheres and cylinders. The assumptions the models are based on as well as their limitations are pointed out. Practical examples illustrate the usefulness of mathematical modeling of diffusion controlled drug delivery. Due to the advances in information technology the importance of *in silico* optimization of advanced drug delivery systems can be expected to significantly increase in the future.

Contents

1. Introduction

The mechanistic realistic mathematical description of mass transport in controlled drug delivery systems can be highly beneficial [1–5]: firstly, it can allow getting deeper insight into the mechanisms, which control drug release from a particular type of dosage forms [6–14]. Thus, the safety of the respective treatment can be improved. Secondly, it can allow for the quantitative prediction of the effects of formulation and processing parameters on the resulting drug release kinetics [15–17]. Consequently, *in silico* simulations can help to identify the required composition of the drug delivery system and manufacturing procedure in order to provide a specific, desired drug release profile. Hence, drug product development can be accelerated and time- and cost-intensive series of trial-and-error experiments can be replaced.

Different types of mass transport processes can be involved in the control of drug release out of a dosage form [18–25]. This might include the diffusion of water into the system, drug diffusion out of the device, drug dissolution, polymer swelling, matrix former erosion, osmotic effects and various other phenomena [26–34]. If several of these

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processes occur in a sequence and one of the processes is much slower than all the others, this one is the rate-limiting step for the entire sequence. Thus, the mathematical description of the drug release rate can be very much simplified: only the slowest mass transport step needs to be considered.

Diffusional mass transport is almost always involved in the control of drug release out of a dosage form [35–42]. In various cases, drug diffusion is *the predominant* step [2,43–48], in others it "only" plays a major role, e.g. in combination with polymer swelling [49–54] or polymer degradation/matrix erosion [55–61]. In certain cases it even plays only a minor role [4]. In this article an overview is given on the current state of the art of mathematical modeling of predominantly diffusion controlled drug delivery systems. They are referred to as "diffusion controlled" devices. For reasons of simplicity, also systems in which *limited drug solubility* is of major importance (in addition to diffusional mass transport), are called "diffusion controlled" (note that this is not fully exact, but this terminology is commonly used in the literature).

In order to quantify diffusional mass transport, Fick's laws of diffusion can be used [62,63]:

Fick's first law of diffusion:

$$F = -D\frac{\partial c}{\partial x} \tag{1}$$

where F is the rate of transfer per unit area of section (flux); c is the concentration of the diffusing species and D denotes the diffusion coefficient (also called diffusivity).

Fick's second law of diffusion (which can be derived from Fick's first law and mass balance considerations):

$$\frac{\partial c}{\partial x} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right) \tag{2}$$

where c is the concentration of the diffusing species; t denotes time, D is the diffusion coefficient and x, y and z are the three spatial (Cartesian) coordinates.

For each type of drug delivery system and type of release conditions the given, so-called "initial and boundary" conditions need to be considered. The "initial conditions" concern the initial distribution of the diffusing species in the system. The mathematical treatment is much simpler if this distribution is homogeneous. The "boundary conditions" concern the conditions for diffusion at the boundaries of the drug delivery system. If the device dimensions are constant with time (no significant swelling or dissolution/erosion), the boundaries are called "stationary". In contrast, in case of time-dependent device dimensions, the boundary conditions are called "moving". If the device swells significantly, the boundaries are moving outwards; if the system dissolves/erodes significantly, they move inwards. In case of "perfect sink conditions" the drug concentration in the surrounding bulk fluid can be considered negligible. Furthermore, if the release medium is well stirred, the liquid unstirred boundary layer surrounding the device is generally thin. If the mass transfer resistance within the drug delivery system for drug diffusion is much higher than the mass transfer resistance in this liquid boundary layer, the latter can generally be neglected.

Another very important aspect when solving Fick's second law of diffusion is the fact whether or not the diffusion coefficient of the diffusing species is constant or not. The mathematical treatment is much simpler if D is constant. Reasons for *time*- and *position*-dependent diffusion coefficients might include matrix erosion, polymer swelling and/or degradation [64–69]. In these cases, generally no "analytical solutions" of Fick's law can be derived (no "exact" solutions quantifying the amount of drug released as a function of time), but "numerical solutions" ("approximate" solutions) can be used [62,70–75]. It has to be pointed out that the term "approximate" in this context is misleading, since the accuracy of numerical solutions (calculated with standard personal computers in reasonable times) is often extremely high. However, the use of such numerical solutions requires either "special" software or programming knowledge. In this review we restrict the mathematical modeling to the "simplest cases". All reviewed theories are based on the following assumptions:

- Diffusional mass transport (generally of the drug) is release-rate limiting.
- The diffusion coefficient of the diffusing species is constant.
- Perfect sink conditions are provided in the release medium during the entire time period.
- The device is not significantly swelling (or swells very rapidly upon contact with body fluids and then reaches an equilibrium state).
- The device is not significantly eroding during drug release.
- Mass transfer resistance due to liquid unstirred boundary layers on the surface of the system is negligible.

For the *appropriate selection of the mathematical equation*, that is valid for a particular type of diffusion controlled dosage form, the following information is crucial:

1. Is it a "reservoir system", also called "core-shell system", in which the drug and the release rate controlling barrier material (often polymers are used for this purpose) are "completely" physically separated? In this case, the drug is located at the center of the dosage form, whereas the polymer forms a membrane surrounding this drug depot (Fig. 1, upper part). Or is it a "matrix system", also called "one-block system" or "monolithic system", in which the drug and the release rate controlling material (often polymers or lipids are used for this purpose) are more or less homogeneously distributed throughout the device (Fig. 1, bottom part)?
2. Is the initial drug concentration below or above drug solubility? It has to be pointed out that the solubility of the drug in the *wetted* device is decisive, a value which is generally unfortunately unknown. As a very rough estimation the drug solubility in the release medium at 37 °C might be used, but great caution has to be paid, because the presence of other dissolved compounds might significantly affect drug solubility. Furthermore, the amount of water available for drug dissolution within the dosage form might be limited.
3. What is the geometry of the drug delivery system? This article is limited to slabs, spheres and cylinders (Fig. 1). Here, the term "slab" is defined as "thin film with negligible edge effects". This means that diffusional mass transport through the edges of the film is negligible compared to diffusional mass transport through the film's main surface. For other geometries the mathematical treatment is generally much more complex and the reader is referred to the literature [62,76–78].

With this information the respective "category" of drug delivery system can be easily identified using Fig. 1. In this review the appropriate mathematical equations for each type of systems will be presented. For reasons of simplicity the term "drug molecule" is used for "real drug molecules" as well as for "drug ions" and "drug atoms".

If one of the parameters needed for the calculations is unknown (e.g., the diffusion coefficient of the drug within a given polymeric network), the respective equation can be "fitted" to sets of experimental data. This means that the unknown parameter is optimized in order to minimize the differences between experimental and theoretical data points. Ideally, only one parameter should be fitted at a time and a set of at least 12 experimental data points (which should describe the entire drug release profile) should be given. If too many parameters are fitted simultaneously, the determined values are questionable and good agreement observed between theory and experiment is not a proof for the validity of the model. In order to evaluate the latter, the model should be used to quantitatively *predict* the impact of a certain

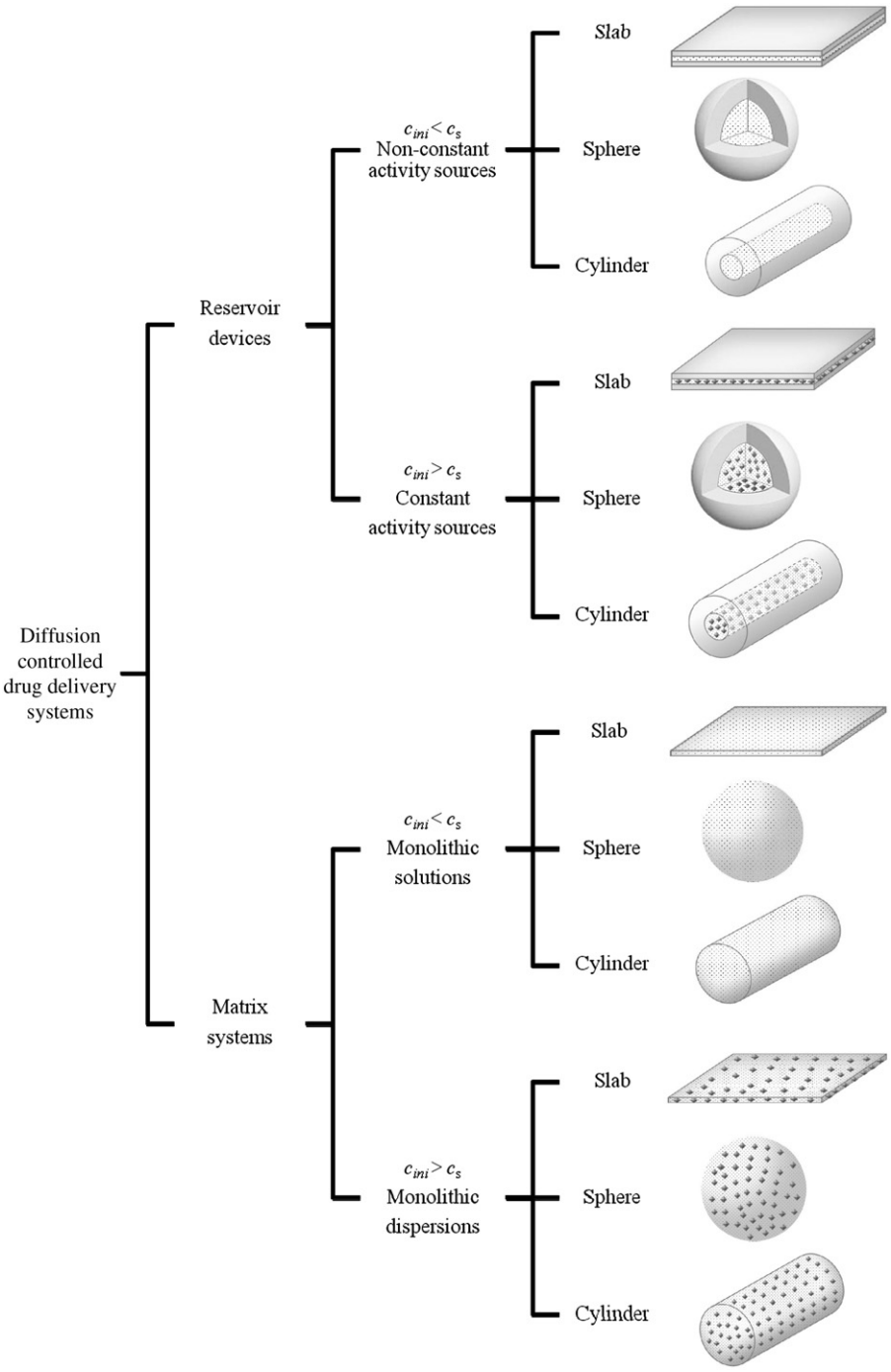

Fig. 1. Classification scheme of predominantly diffusion-controlled drug delivery systems, according to the: (i) inner structure of the device, (ii) initial drug content (in relation to drug solubility), and (iii) geometry. The dots indicate dissolved drug molecules, the circles non-dissolved drug particles, c_{ini} denotes the initial drug concentration, c_s drug solubility.

parameter (e.g., of the height of a tablet) on the resulting drug release kinetics. Such theoretical predictions should then be compared with *independent* experimental results (obtained only after the predictions were made).

2. Reservoir systems with non-constant activity source

In these cases, the drug is physically "completely" separated from the release rate controlling material, which forms a barrier membrane surrounding the drug depot ("core-shell-structure"). Furthermore, the initial drug concentration is below drug solubility. This means that the drug is *molecularly* dispersed within the core of the (wetted) formulation. Note that this covers two cases: (i) the drug is molecularly dispersed in the excipients forming the core of the formulation, or (ii) upon water penetration into the system the drug particles rapidly dissolve. Since drug dissolution is fast compared to drug diffusion (see assumptions discussed above), this step can be neglected for the mathematical analysis.

Fig. 2 shows schemes of these types of systems, exhibiting the geometry of slabs, spheres and cylinders. The dots indicate *dissolved* (individualized) drug molecules. Once these devices get into contact with aqueous body fluids, water penetrates into the system, dissolves the drug (if the latter is not already molecularly dispersed) and the dissolved drug molecules diffuse out of the device through the surrounding membrane. Since drug diffusion through the latter is much slower then water penetration into the system and much slower

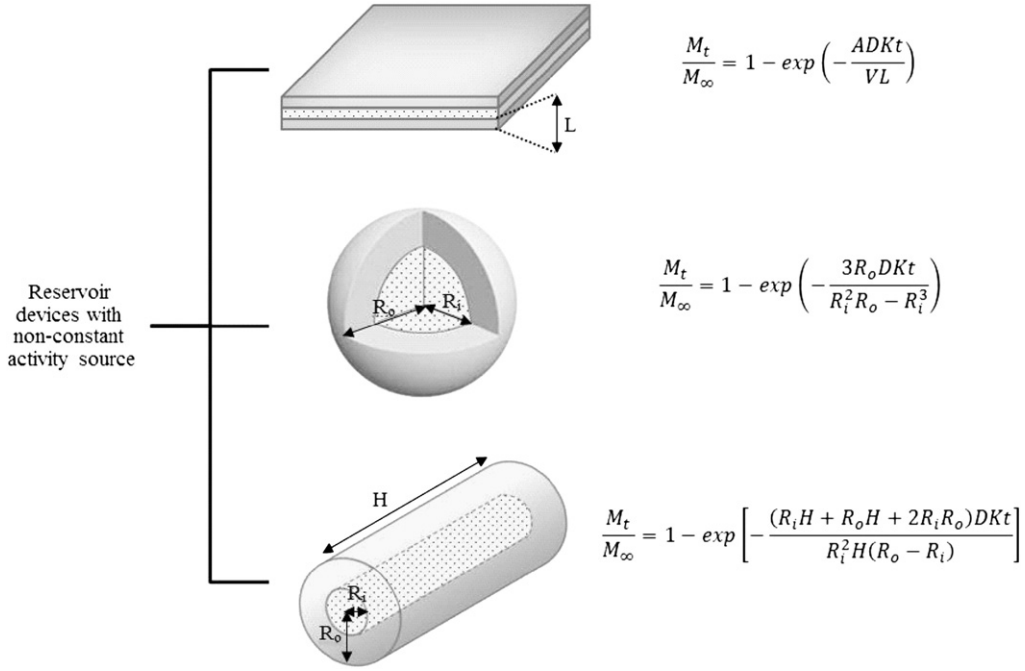

Fig. 2. Overview on the mathematical equations, which can be used to quantify drug release from reservoir systems with non-constant activity sources (initial drug concentration < drug solubility). The variables are explained in the text.

than drug dissolution, only this *drug diffusion step* needs to be considered in the mathematical analysis. Thus, Fick's law of diffusion can be applied, considering the given geometry. Importantly, perfect sink conditions are provided in the surrounding bulk fluid (in the models considered in this article). Furthermore, there is no drug excess in the core: Thus, released drug molecules are not replaced and the drug concentration at the inner membrane's surface decreases with time. This is the reason why this type of devices is called "reservoir systems with *non-constant* activity source". Under these conditions, the following equations can be derived for:

Slabs

$$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{ADKt}{VL}\right) \quad (3)$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and infinity, respectively; A is the total surface area of the device; D is the diffusion coefficient of the drug within the membrane; V, is the volume of the reservoir; K is the partition coefficient of the drug between the membrane and the reservoir, and L is the thickness of the membrane.

Spheres

$$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{3R_oDKt}{R_i^2R_o - R_i^3}\right) \quad (4)$$

where R_i and R_o are the inner and outer radii of the device. This equation is obtained when replacing: (i) the surface area "A" by "$4*\pi*R_0*R_i$", (ii) the volume of the core "V" by "$4/3*\pi*R_i^3$", and (iii) the length "L" by "$R_0 - R_i$" in Eq. (3).

Cylinders

$$\frac{M_t}{M_\infty} = 1 - \exp\left[-\frac{(R_iH + R_oH + 2R_iR_o)DKt}{R_i^2H(R_o - R_i)}\right] \quad (5)$$

where R_i and R_o are the inner and outer radii and H the length of the cylinder. This equation is obtained when replacing: (i) the surface

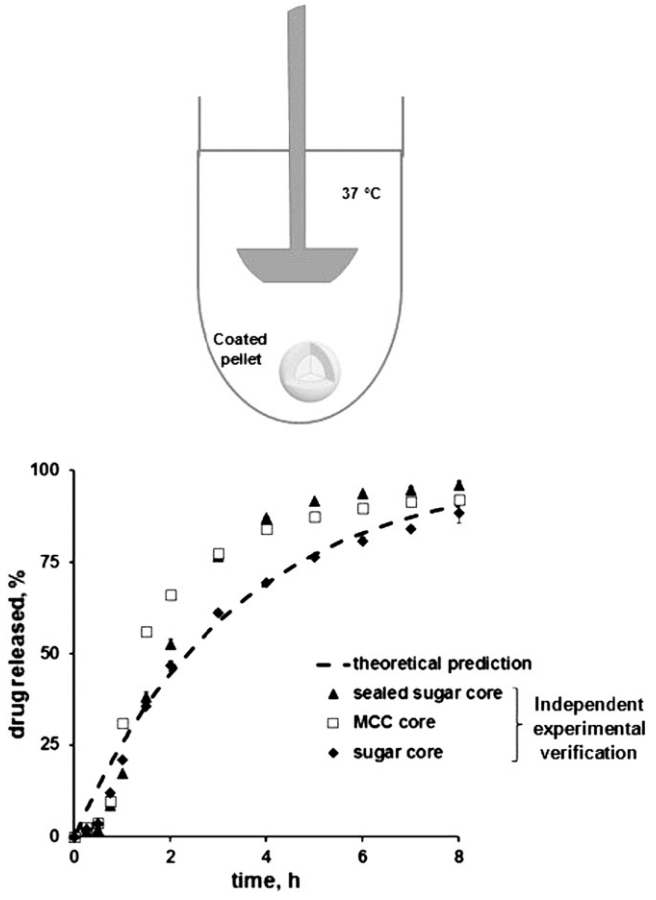

Fig. 3. Theoretically predicted (dotted curve) and experimentally verified (symbols) diltiazem HCl release kinetics from coated pellets in 0.1 N HCl. Drug-layered sugar, MCC and sealed sugar cores were coated with 25% ethylcellulose:PVA-PEG graft copolymer 90:10. Eq. (4) (valid for spherical reservoir systems with non-constant activity source) was used for the calculations. Adapted from [81].

area "A" by "$2*\pi*(R_0+R_i)/2*H+2*\pi*R_0*R_i$", (ii) the volume of the core "V" by "$\pi*R_i^2*H$", and (iii) the length "L" by "R_0-R_i" in Eq. (3).

When plotting the amount of drug *remaining in the dosage form* as a function of time, an exponentially decreasing curve is obtained. Since the drug release rate is proportional to *one* concentration (the steadily decreasing drug concentration at the inner membrane's surface), *first* order release kinetics are obtained for all geometries, and the release rate exponentially decreases with time.

Note that the partition coefficient "K" in Eqs. (3)–(5) is assumed to be equal on both sides of the release rate controlling membrane. This is true if the drug has similar affinities to the release medium and to the liquid phase in the core. Also, it is generally assumed that the partition coefficient is independent of the drug concentration.

A practical example for a spherical dosage form of this type is illustrated in Fig. 3: diltiazem HCl was layered onto three types of starter cores (10% drug loading): (i) osmotically active sugar cores, (ii) osmotically "inactive" microcrystalline cellulose (MCC) cores, and (iii) "sealed sugar cores" (sugar cores, which were coated with pure ethylcellulose in order to minimize water penetration into the core and, thus, to render the core osmotically "inactive"). These drug layered sugar cores were coated with a 90:10 blend of ethylcellulose:PVA-PEG graft copolymer (25% coating level). This polymer coating acted as the release rate controlling barrier membrane. Since the system clearly exhibits a "core-shell-structure" and spherical geometry and since diltiazem HCl is freely water soluble and the initial drug loading relatively low, this type of device can be considered as a "reservoir system with non-constant activity source". Thus, Eq. (4) can be used to quantify the resulting drug release kinetics (provided all the above discussed assumptions are valid). Note that the mathematical model only considers the drug diffusion step through the polymeric membrane. Thus, differences in the type of starter core are neglected (this very much simplifies the mathematical analysis). The dotted curve in Fig. 3 shows the *theoretically predicted* drug release profile from these pellets (the drug diffusion coefficient was known from experiments with thin, free films). In order to evaluate the validity of this theoretical prediction, the respective pellets were prepared in reality and drug release was measured using the USP paddle apparatus (100 rpm) in 0.1 N HCl (symbols in Fig. 3). As it can be seen, rather good agreement between theory and experiment was obtained, especially in the case of sugar starter cores. Thus, the mathematical model is likely to consider the most important mass transport steps involved in the control of drug release from this type of dosage forms. The impact of the presence of "osmotically active" versus "osmotically inactive" substances in the core of the formulation is limited in this case. It has to be pointed out that this is not necessarily true for other types of systems (in these cases Eq. (4) cannot be used to quantify drug release). Also, in certain systems, the release rate controlling barrier membrane might eventually not stay intact throughout the entire release period: If the mechanical strength of the shell is limited and the hydrostatic pressure built up in the core (due to water penetration into the system) is important, the membrane might rupture at a certain time point. In this case, drug release can be expected to occur also through water-filled cracks: by diffusion and convection (due to the pressure difference: "inside-outside" the pellets). Also in these cases Eq. (4) is not applicable and much more complex mathematical theories need to be applied [79, 80].

3. Reservoir systems with constant activity source

In these cases, the drug is also physically "completely" separated from the rate controlling barrier membrane ("core-shell-structure"), but the initial drug concentration is *above* drug solubility. This means that upon water penetration into the device not all of the drug is dissolved (due to limited drug solubility/limited amounts of water available for drug dissolution). Thus, a saturated drug solution is rapidly created in the core (drug dissolution is assumed to be fast compared to drug diffusion through the membrane) and released drug molecules are rapidly replaced by the (partial) dissolution of remaining drug excess. Consequently, the drug concentration at the inner membrane's surface remains constant (as long as drug excess is present). This is why this type of devices is also called "reservoir systems with *constant* activity source". Note the difference between the terms "drug dissolution rate" and "drug solubility". The dissolution *rate* addresses a kinetic process, whereas drug *solubility* addresses an

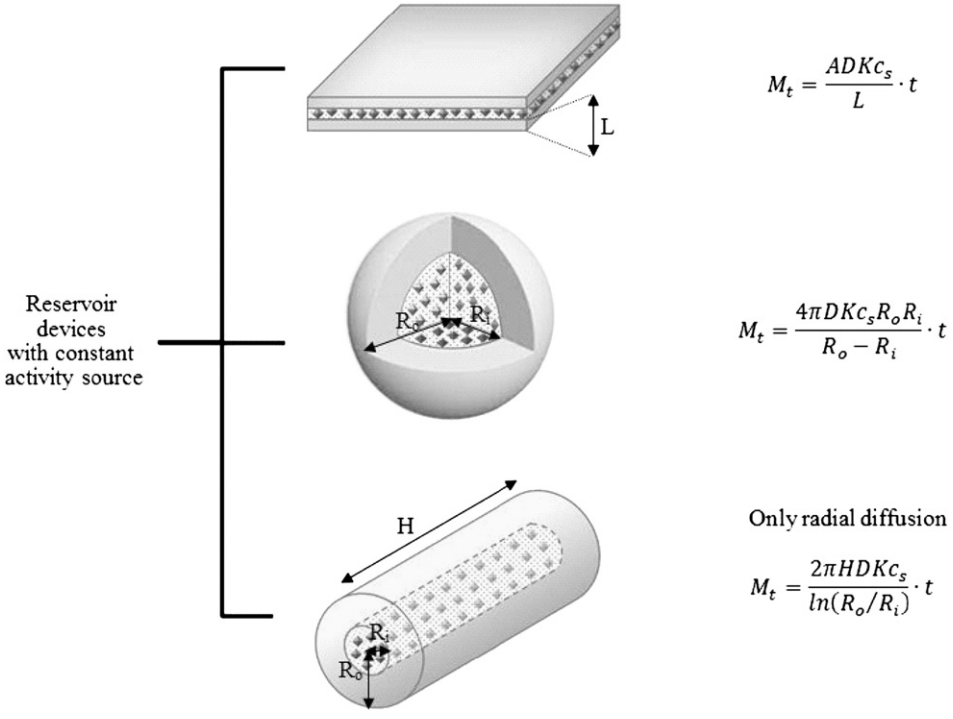

Fig. 4. Overview on the mathematical equations, which can be used to quantify drug release from reservoir systems with constant activity sources (initial drug concentration > drug solubility). The variables are explained in the text.

equilibrium state. The dissolution rate of a drug can for instance be calculated using the Noyes–Whitney equation [82]. In this review, only mathematical theories are considered, which assume that this process is rapid compared to drug diffusion through the surrounding membrane barrier. In contrast, the term "drug solubility" addresses the "maximum" concentration of drug, which can be dissolved and become available for diffusion (note that only dissolved drug is able to diffuse, not non-dissolved drug). In the considered types of drug delivery systems the drug *solubility* is limited, but not the drug dissolution *rate*.

Fig. 4 schematically illustrates these types of devices, exhibiting the geometry of slabs, spheres and cylinders. The dots indicate *dissolved* drug molecules, whereas the stars represent *non-dissolved* drug excess. Once these systems get into contact with aqueous body fluids, water penetrates into the devices, rapidly dissolves parts of the drug (providing saturated drug solutions at the inner membrane's surface) and the dissolved drug diffuses out of the system through the membrane barrier. Assuming the latter step to be the release rate limiting step (and the other assumptions discussed above), the following equations can be derived, which are valid as long as non-dissolved drug excess is provided in the center of the dosage form, for:

Slabs

$$M_t = \frac{ADKc_s}{L} \cdot t \tag{6}$$

where M_t denotes the cumulative amount of drug released at time t; A is the total surface area of the device (both surfaces of the film, if both are exposed to the release medium); D is the diffusion coefficient of the drug within the membrane; K is the partition coefficient of the drug between the membrane and the reservoir; c_s is the solubility of the drug in the core, and L is the thickness of the membrane.

Spheres

$$M_t = \frac{4\pi DKc_s R_o R_i}{R_o - R_i} \cdot t \tag{7}$$

where R_i and R_o are the inner and outer radii of the device.

Cylinders

$$M_t = \frac{2\pi HDKc_s}{\ln(R_o/R_i)} \cdot t \tag{8}$$

where R_i and R_o are the inner and outer radii and H the length of the cylinder (considering only radial diffusion).

Thus, in all cases the cumulative amount of drug released increases linearly with time. In other words, the release rate is constant. These kinetics are also called "*zero*-order release kinetics".

Eqs. (6)–(8) assume that steady state conditions are "instantaneously" established upon exposure to the release medium. In reality, two types of deviations from such an "ideal" behavior might be observed at early time points:

1) Lag-time effects:
Right after preparation of the dosage form, the release rate controlling membrane might be completely free of drug. Thus, it takes some time for the latter to diffuse into the membrane and to cross it. This leads to initially overestimated drug release rates when using Eqs. (6)–(8). To accurately calculate this initial drug release at early time points from reservoir systems with constant activity source and slab geometry, the following equation can be used:

$$M_t = -\frac{AKc_sL}{6} + \frac{AKc_sD}{L} \cdot t - \frac{2AKc_sL}{\pi^2} \sum_{n=1}^{\infty} \frac{\cos(n\pi)}{n^2} \exp\left(-\frac{Dn^2\pi^2 t}{L^2}\right) \tag{9}$$

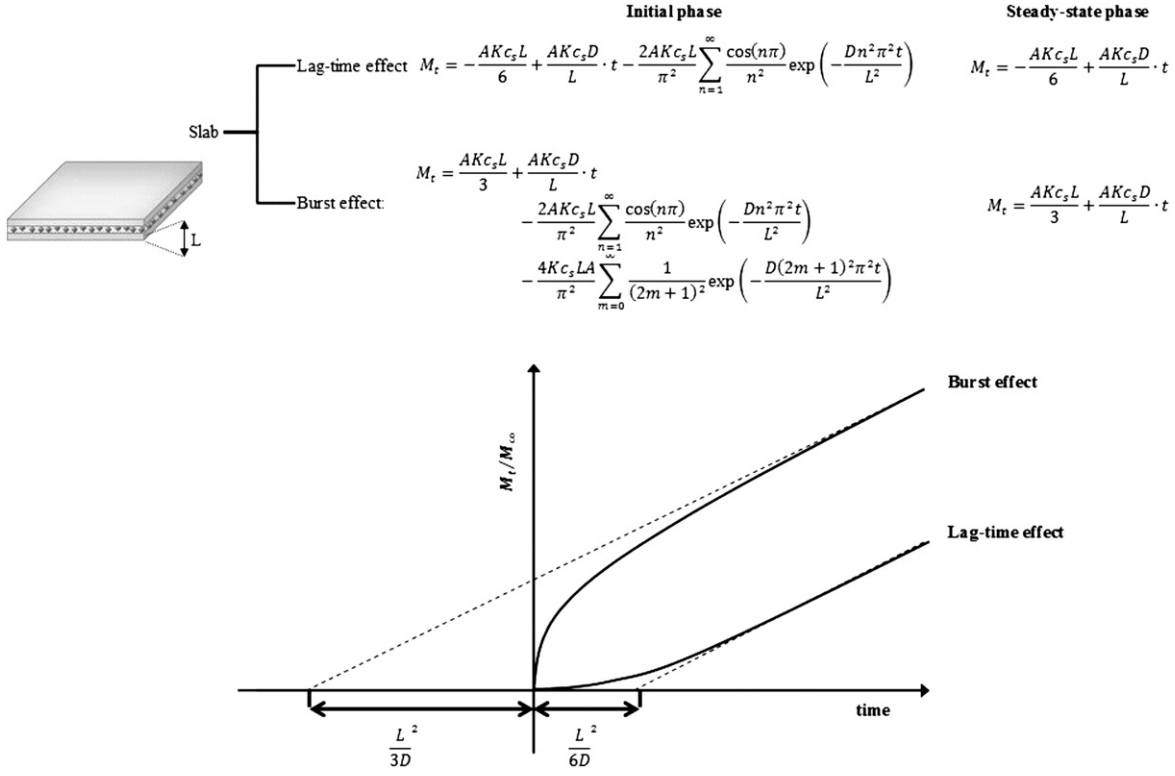

Fig. 5. Mathematical equations, which can be used to quantify "lag-time" and "burst" effects from reservoir devices with constant activity source and slab geometry. The scheme at the bottom illustrates the resulting drug release profiles. The equations on the right hand side can be used to describe drug release once the steady state is reached. The variables are explained in the text.

where M_t denotes the cumulative amount of drug released at time t; A is the total surface area of the device (both surfaces of the film, if both are exposed to the release medium); K is the partition coefficient of the drug between the membrane and the reservoir; c_s is the solubility of the drug in the core; L is the thickness of the membrane, and D is the diffusion coefficient of the drug within the membrane.

Eq. (9) takes into account that "drug concentration gradients are built" up within the membrane during the early phase of drug release. Once steady state is reached (determined by the saturated drug solution at the inner membrane's surface and negligible drug concentrations at the outer membrane's surface), the release rate is constant and the cumulative amount of drug release can be calculated as a function of time using the following equation:

$$M_t = -\frac{AKc_sL}{6} + \frac{AKc_sD}{L}\cdot t \tag{10}$$

where M_t denotes the cumulative amount of drug released at time t; A is the total surface area of the device (both surfaces of the film, if both are exposed to the release medium); K is the partition coefficient of the drug between the membrane and the reservoir; c_s is the solubility of the drug in the core; L is the thickness of the membrane, and D is the diffusion coefficient of the drug within the membrane.

The scheme in Fig. 5 illustrates the observed release kinetics in the case of significant lag-time effects (bottom curve). It can be shown that the extrapolation of the steady state *straight line* hits the time-axis at $t = "L^2/(6*D)"$ (setting M_t to zero in Eq. (10)). Thus, the importance of such lag-time effects essentially depends on the thickness of the release rate controlling barrier membrane and on the mobility of the drug within this barrier. The experimental measurement of these lag-times might be used to experimentally determine the diffusion coefficient of a drug in a specific barrier membrane (knowing the thickness of the membrane).

2) Burst effects:
In case the drug shows a significant affinity to the membrane and has sufficient time and mobility to diffuse into the release rate controlling membrane to a noteworthy extent (e.g. during long term storage). The membrane might be saturated with drug when exposed to the release medium. Thus, the resulting drug concentration gradients are initially steeper than at steady state and Eqs. (6)–(8) underestimate the release rate at early time points. To accurately calculate the amount of drug released as a function of time in this initial phase, the following equation can be used for slab geometry:

$$M_t = \frac{AKc_sL}{3} + \frac{AKc_sD}{L}\cdot t - \frac{2AKc_sL}{\pi^2}\sum_{n=1}^{\infty}\frac{\cos(n\pi)}{n^2}\exp\left(-\frac{Dn^2\pi^2t}{L^2}\right) - \frac{4AKc_sL}{\pi^2}\sum_{m=0}^{\infty}\frac{1}{(2m+1)^2}\exp\left(-\frac{D(2m+1)^2\pi^2t}{L^2}\right) \tag{11}$$

where M_t denotes the cumulative amount of drug released at time t; A is the total surface area of the device (both surfaces of the film, if both are exposed to the release medium); K is the partition coefficient of the drug between the membrane and the reservoir; c_s is the solubility of the drug in the core; L is the thickness of the membrane, and D is the diffusion coefficient of the drug within the membrane.

Again, as soon as steady state is reached, a straight line is obtained (scheme in Fig. 5, top curve) and the cumulative amount of drug released can be calculated as follows:

$$M_t = \frac{AKc_sL}{3} + \frac{AKc_sD}{L}\cdot t \tag{12}$$

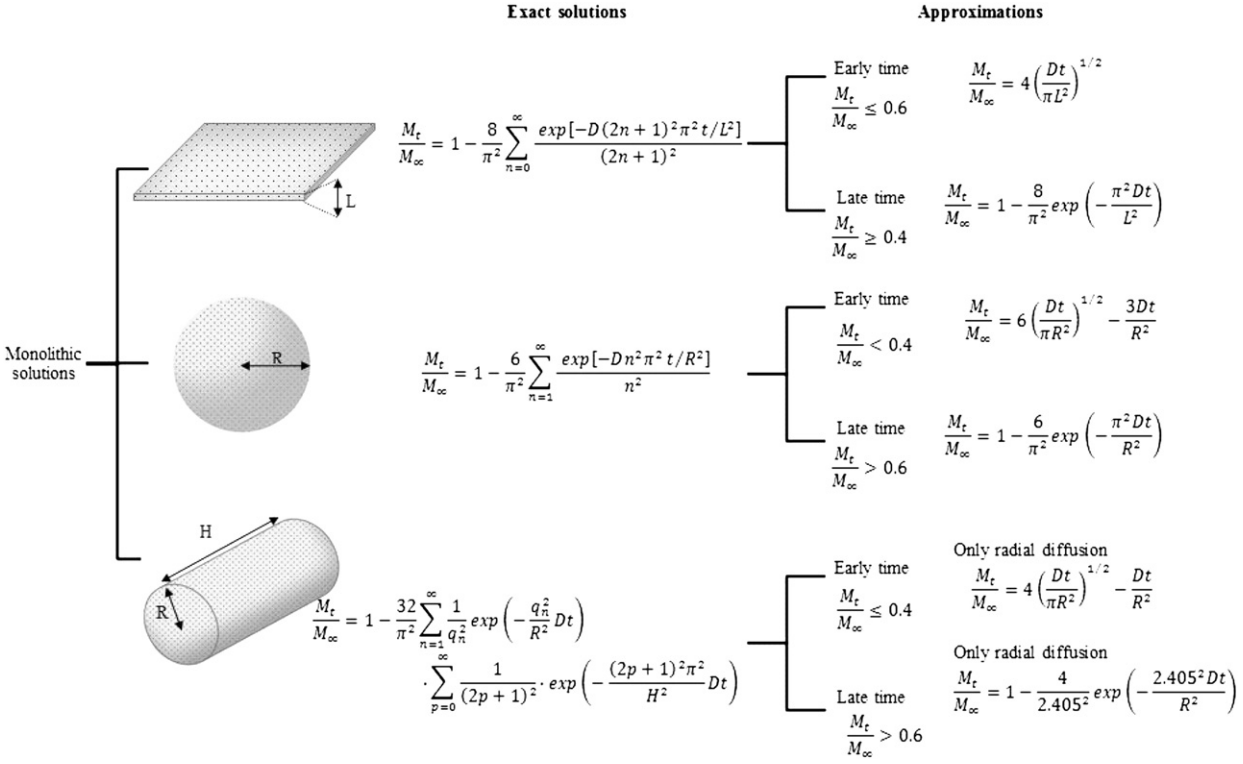

Fig. 6. Overview on the mathematical equations, which can be used to quantify drug release from monolithic solutions (initial drug concentration<drug solubility). The "exact" equations are valid during the entire release periods, the indicated early and late time approximations are only valid during parts of the release periods. The variables are explained in the text.

where M_t denotes the cumulative amount of drug released at time t; A is the total surface area of the device (both surfaces of the film, if both are exposed to the release medium); K is the partition coefficient of the drug between the membrane and the reservoir; c_s is the solubility of the drug in the core; L is the thickness of the membrane, and D is the diffusion coefficient of the drug within the membrane.

An extrapolation of this straight line hits the time axis at "$-L^2/(3*D)$" (setting M_t to zero in Eq. (12)), as schematically shown in Fig. 5 (dotted line). Thus, also the importance of the burst effect essentially depends on the membrane's thickness and on the mobility of the drug in this barrier. Again, the experimental measurement of the drug release rate allows determining the drug diffusion coefficient in the membrane: Extrapolation of the steady state *straight line* allows identifying the "$-L^2/(3*D)$" value. Knowing the membrane's thickness, D can be calculated.

4. Monolithic solutions

If the drug is not "completely" physically separated from the release rate controlling barrier ("core-shell-structure" as in the case of reservoir devices), but more or less homogeneously distributed within the latter, the device is called a "monolithic system". If the drug is molecularly dispersed in the matrix former, or if the drug is rapidly completely dissolved upon water penetration into the system, the device is called a "monolithic *solution*". Fig. 6 illustrates monolithic solutions exhibiting the geometries of slabs, spheres and cylinders. The dots represent individualized (dissolved) drug molecules. Considering the above mentioned assumptions and an initial homogeneous drug distribution within the system, Fick's second law of diffusion can be solved for each of these geometries, allowing for the calculation of the cumulative amount of drug released as a function of time t [62,73]:

Slabs

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{\exp\left[-D(2n+1)^2\pi^2 t/L^2\right]}{(2n+1)^2} \tag{13}$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system, and L represents the total thickness of the film.

Spheres

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{\exp\left[-Dn^2\pi^2 t/R^2\right]}{n^2} \tag{14}$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system, and R represents the radius of the sphere.

Cylinders

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{q_n^2}\exp\left(-\frac{q_n^2}{R^2}Dt\right)\cdot\sum_{p=0}^{\infty}\frac{1}{(2p+1)^2}\cdot\exp\left(-\frac{(2p+1)^2\pi^2}{H^2}Dt\right) \tag{15}$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system, and R and H represent the radius and height of the cylinder, respectively.

Infinite series of exponential functions are used in these equations. To avoid their use, alternatively the following short time and late time approximations might be applied:

Slabs

Short times

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi L^2}\right)^{1/2} \tag{16}$$

Late times

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\exp\left(-\frac{\pi^2 Dt}{L^2}\right) \tag{17}$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system, and L represents the total thickness of the film.

Spheres

Short times

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi R^2}\right)^{1/2} - \frac{3Dt}{R^2} \tag{18}$$

Late times

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left(-\frac{\pi^2 Dt}{R^2}\right) \tag{19}$$

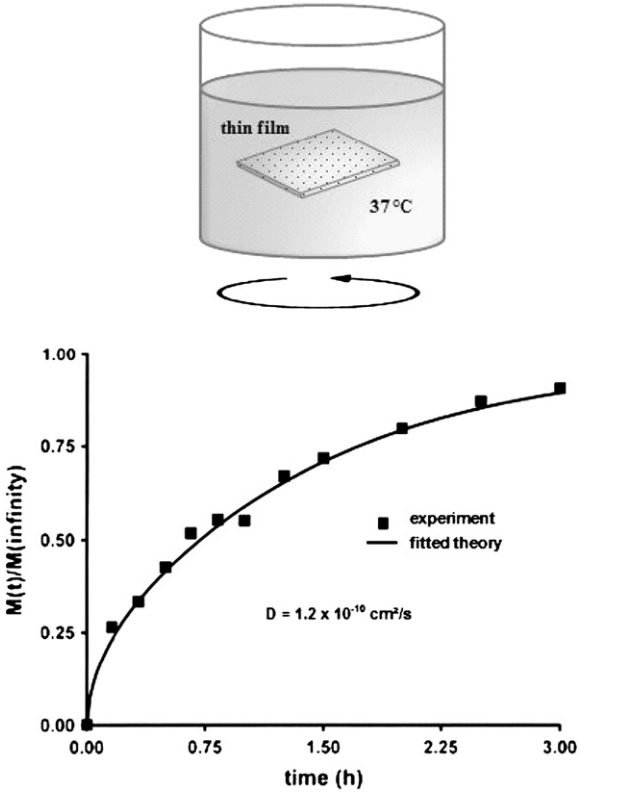

Fig. 7. Theophylline release from thin ethylcellulose films (plasticized with 17.5% TEC) in phosphate buffer pH 7.4: experimental results (symbols) and fitted theory (Eq. (13)—valid for monolithic solutions with slab geometry, curve). This type of experiments can be used to experimentally determine the diffusion coefficient of a drug within a polymeric system.

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system, and R represents the radius of the sphere.

Cylinders

Short times

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi R^2}\right)^{1/2} - \frac{Dt}{R^2} \quad (20)$$

Late times

$$\frac{M_t}{M_\infty} = 1 - \frac{4}{(2.405)^2}\exp\left(-\frac{(2.405)^2 Dt}{R^2}\right) \quad (21)$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system, and R represents the radius of the cylinder (only radial diffusion is considered).

A practical example is illustrated in Fig. 7. The release of theophylline from ethylcellulose based films (initial drug loading = 0.25%), plasticized with 17.5% triethylcitrate (TEC), was experimentally measured in phosphate buffer pH 7.4 (symbols). The release medium was well stirred and kept constant at 37 °C. The film's surface was large compared to its thickness (≈50 cm² vs. 50 μm). To avoid film folding or floating during the experiment, the slab was fixed in a holder (not shown in Fig. 7 for reasons of simplicity). Since it is a matrix system without initial excess of drug and since it is a thin film with negligible edge effects, Eq. (13) can be used to describe the resulting drug release kinetics under the above discussed assumptions. As the diffusion coefficient of the drug in the polymer was unknown in this case, Eq. (13) was *fitted* to the experimentally determined drug release kinetics (curve = theory and symbols = experiments in Fig. 7). As it can be seen, good agreement between theory and experiment was obtained, which can serve as an indication (but not as a real proof, because it is a *fitting*) that drug diffusion is indeed the release rate limiting mass transport step in this system. Importantly, based on these calculations, the apparent diffusion coefficient of theophylline in this polymeric system could be determined: $D = 1.2\ (\pm 0.1)\ 10^{-10}$ cm²/s.

Another example is shown in Fig. 8. In this case, the release of diprophylline from matrix tablets based on Kollidon SR [80% poly (vinyl acetate) (PVAc), 19% poly(vinyl pyrrolidone) (PVP), sodium lauryl sulfate and colloidal silicon dioxide] was measured in phosphate buffer pH 7.4 using the USP paddle apparatus (37 °C, 80 rpm). Since the drug is freely water soluble and since the drug loading was moderate (20%), it can be assumed that all of the drug is rapidly dissolved once water penetrates into the system. Note that Kollidon SR significantly swells upon contact with aqueous media [17]. Importantly, the water uptake is very rapid and complete upon exposure to the release medium. Thus, during most parts of the drug release period, about constant device dimensions (stationary boundary conditions) are given. The initial diameter of the tablets shown in Fig. 8 was 11.3 mm. In this case, the apparent diffusion coefficient of the drug within the polymeric matrix was known. Thus, Eq. (15) (valid for monolithic solutions with cylindrical geometry) could be used to theoretically *predict* the impact of varying the initial tablet height. In this example, the drug release rates for the tablet heights 1.3 and 3.9 mm were predicted (dotted curves in Fig. 8). As it can be seen, with increasing tablet height the relative drug release rate was expected to decrease, due to the increasing diffusion pathway lengths/decreasing relative surface area available for diffusion. In order to evaluate the validity of these theoretical predictions, the respective tablets were prepared in reality and diprophylline release was measured experimentally (symbols in Fig. 8). As it can be seen, good agreement was obtained between theoretical predictions and independent experiments, indicating the validity of this model for this type of drug delivery systems and illustrating the practical benefit of mathematical modeling of drug release: the impact of formulation parameters on drug release can be simulated *in silico*, potentially replacing time- and cost-intensive series of experimental studies.

5. Monolithic dispersions

If the drug is homogeneously distributed within a matrix former at an initial concentration that exceeds drug solubility (in the wetted system), this type of device is called "monolithic *dispersion*". Upon contact with aqueous body fluids, water penetrates into the system and only partially dissolves the drug. Thus, dissolved and non-dissolved drug co-exist within the matrix during drug release. Importantly, *only dissolved* drug is available for diffusion.

Fifty years ago a surprisingly simple equation was proposed to quantify drug release from monolithic dispersions with slab geometry (under the above discussed assumptions): the famous Higuchi equation [83]:

$$M_t = A\sqrt{Dc_s(2c_{ini} - c_s)\cdot t} \quad (22)$$

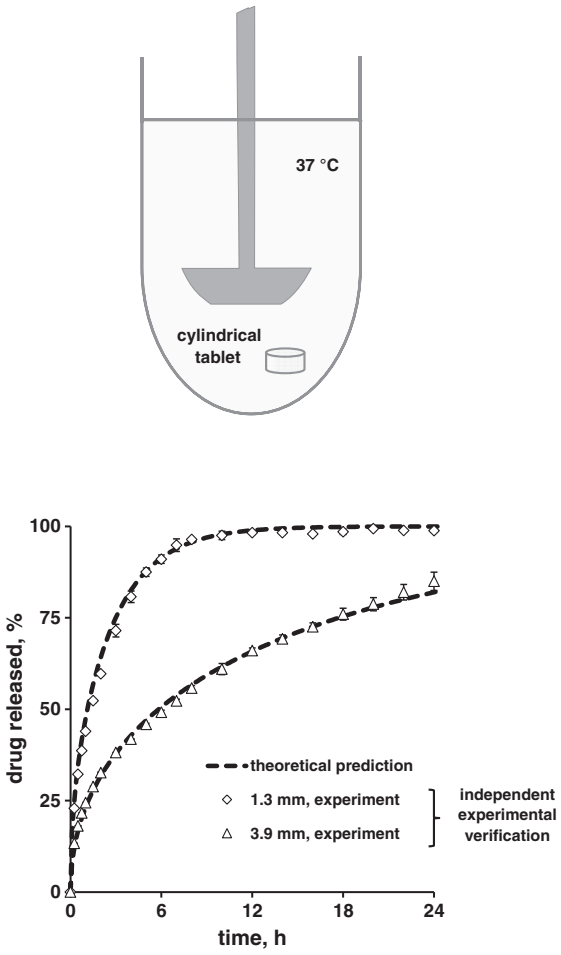

Fig. 8. Theoretically predicted (dotted curves) and experimentally verified (symbols) impact of the height of Kollidon SR-based tablets on diprophylline release in phosphate buffer pH 7.4. Eq. (15) (valid for monolithic solutions with cylindrical geometry) was used for the calculations. The drug loading was 20%, the tablet diameter was 11.3 mm, the tablet height was 1.3 or 3.9 mm, as indicated.

where M_t denotes the cumulative absolute amount of drug released at time t; A is the total surface area of the film exposed to the release medium (in his seminal contribution [83] Takeru Higuchi considered a thin ointment film with only one surface exposed to the skin, acting as "release medium"); D is the diffusion coefficient of the drug within the system; c_s denotes the drug solubility in the wetted matrix (not in the release medium), and c_{ini} represents the initial drug concentration in the system.

Takeru Higuchi – the "father of mathematical modeling of drug release" [84] – derived his classical equation using a steady state approach: The basic idea is that upon water penetration into the system drug release initially occurs only from the outermost layer(s) of the system (from one layer, if only one side of the film is exposed to the release medium; from two layers, if both sides of the film are exposed to the release medium). As long as non-dissolved drug is present in this layer (these layers), the partial dissolution of this excess of drug assures a saturated solution. Only once drug excess in this outermost layer (in these outermost layers) is completely exhausted, also drug from the adjacent layer(s) is released. Once the outermost layer(s) is (are) exhausted of drug excess, the next layer(s) starts to become depleted and so on. Thus, a front (two fronts) separating the part(s) of the slab, which contain(s) *only dissolved* drug, from the part(s) of the film, which contain(s) *dissolved and non-dissolved* drug, steadily move(s) inwards the system. In case of a significant drug excess (initial drug concentration >> drug solubility), this front (these fronts) move(s) very slowly and linear concentration gradients between the surface(s) of the slab (where perfect sink conditions are provided) and the front position(s) [where saturated drug solution(s) are provided] can be considered (steady state assumption). This very much simplifies the quantification of the amount of drug released as a function of time.

The conditions Takeru Higuchi considered for the derivation of his famous equations can be summarized as follows:

(1) Drug transport within the slab is rate limiting, whereas drug transport within the release medium and water penetration into the system are rapid.
(2) The dissolution of drug particles within the slab is rapid compared to the diffusion of dissolved drug molecules within the system.
(3) Perfect sink conditions are provided throughout the experiment.
(4) The initial drug concentration in the slab is much higher than the solubility of the drug in the (wetted) system.
(5) The drug is finely dispersed within the system (the size of the drug particles is much smaller than the thickness of the slab).
(6) The drug is initially homogeneously distributed throughout the slab.
(7) The diffusion coefficient of the drug within the slab is constant and does not depend on time or the position within the system.
(8) Edge effects are negligible: the surface of the slab exposed to the release medium is large compared to its thickness. The mathematical description of drug diffusion can be restricted to one dimension.
(9) The slab does not swell or dissolve during drug release.

Recently, the derivation as well as the applications, use and misuse of this seminal equation have been reviewed in more detail [85]. Later, the classical Higuchi equation has been extended to other geometries (e.g., [86–88]).

Unfortunately, it is not possible to derive similarly simple equations for monolithic dispersions of spherical and cylindrical geometry (Fig. 9). Roseman and Higuchi proposed the following *implicit* equations ("implicit" means that the "amount of drug released" is not "isolated" on one side of the equation) [87,89] for:

Spheres:

$$\frac{M_t}{M_\infty} - \frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right] = -\frac{3D}{R^2}\cdot\frac{c_s}{c_{ini}}\cdot t \tag{23}$$

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system; c_s denotes the drug solubility in the wetted matrix (not in the release medium); c_{ini} represents the initial drug concentration in the system, and R the radius of the sphere.

Cylinders

$$\frac{M_t}{M_\infty} + \left(1-\frac{M_t}{M_\infty}\right)\ln\left[1-\frac{M_t}{M_\infty}\right] = \frac{4D}{R^2}\cdot\frac{c_s}{c_{ini}}\cdot t \tag{24}$$

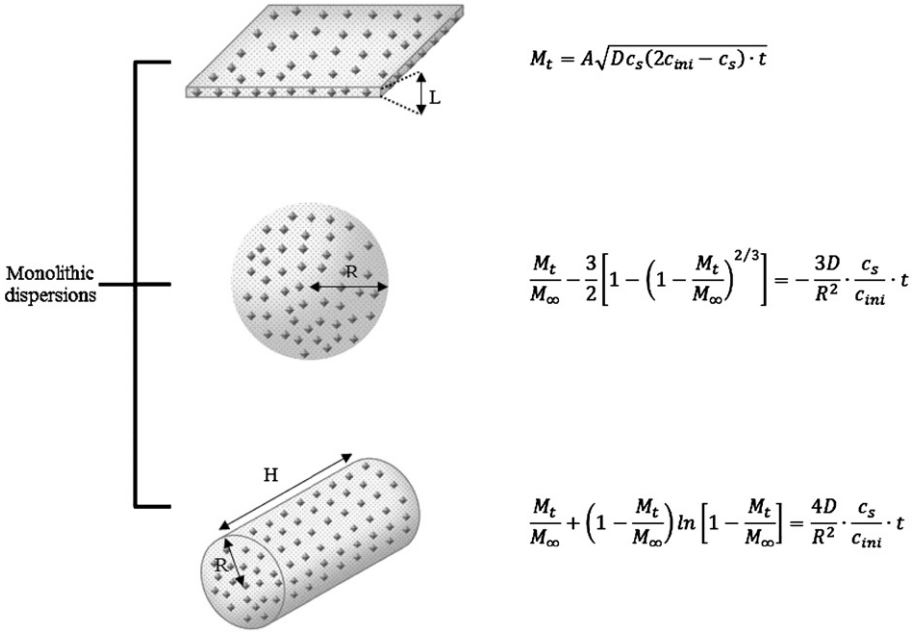

Fig. 9. Overview on the mathematical equations, which can be used to quantify drug release from monolithic dispersions (initial drug concentration > drug solubility). The variables are explained in the text.

where M_t and M_∞ denote the cumulative amounts of drug released at time t and at infinite time, respectively; D is the diffusion coefficient of the drug within the system; c_s denotes the drug solubility in the wetted matrix (not in the release medium); c_{ini} represents the initial drug concentration in the system, and R the radius of the cylinder.

Note that Eqs. (22)–(24) are only valid as long as drug excess is present in the delivery systems.

6. Conclusions

Relatively simple mathematical equations can be used to quantitatively describe drug release from predominantly diffusion controlled delivery systems. If applicable to a specific type of controlled drug delivery systems, they can very much help speeding up product development, since they allow for *in silico* simulations of the effects of formulation and processing parameters on the resulting drug release kinetics. In addition, they can provide deeper insight into the underlying drug release mechanisms. However, caution should be paid that none of the assumptions the equations are based on, are violated.

Due to the advances in information and computer technology it can be expected that *in silico* optimization of controlled drug delivery systems will become more and more powerful and frequently applied in the future.

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