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Review

Modelling drug release from inert matrix systems: From moving-boundary to continuous-field descriptions

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ABSTRACT

The purpose of this review is to provide a comprehensive overview of mathematical procedures that can be used to describe the release of drugs from inert matrix systems. The review focuses on general principles rather than particular applications. The inherent multiscale nature of the drug-release process is pointed out and multiscale modelling is exemplified for inert porous matrices. Although effects of stagnant layers and finite volumes of release media are briefly discussed, the systematic analysis is restricted to systems under sink conditions. When the initial drug loading exceeds the drug solubility in the matrix, Higuchi-type moving-boundary descriptions continue to be highly valuable for obtaining approximate analytical solutions, especially when coupled with integral balance methods. Continuous-field descriptions have decisive advantages when numerical solutions are sought. This is because the mathematical formulation reduces to a diffusion equation with a nonlinear source term, valid over the entire matrix domain. Solutions can thus be effortlessly determined for arbitrary geometries using standard numerical packages.

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1. Introduction

The timely and reproducible release of active pharmaceutical ingredients from delivery vehicles of various kinds is, for obvious reasons, of paramount importance for an efficient and safe pharmacological treatment of disease. Mathematical modelling plays an important role in this context, providing tools to analyse experimental release data and to elucidate the manner in which formulation and design factors affect the release profile. It is therefore natural that much effort has been devoted to developing models for the drug-release process (see, e.g., Fan and Singh, 1989; Siepmann and Peppas, 2001; Siepmann and Göpferich, 2001; Lin and Metters, 2006; Siepmann and Siepmann, 2008).

Such models can be grouped according to various criteria. It is common to distinguish between empirical/semi-empirical models, on the one hand, and mechanistic models, on the other, as has been discussed by Siepmann and Siepmann (2008). Whereas empirical/semi-empirical models aim for a description of release profiles without necessarily taking the underlying processes into account, the aspiration of mechanistic models is to explain the release on the basis of the physical and chemical processes that control the release rate (such as diffusion and dissolution). One of the most commonly used semi-empirical models of drug release is the Korsmeyer–Peppas power-law (Korsmeyer et al., 1983; Peppas, 1985). The archetypical mechanistic model of drug release is the Higuchi (1961) square root of time law. As an immediate consequence of the extent to which underlying mechanisms are taken into account, empirical/semi-empirical models can be successfully used to summarise and evaluate experimental release data, but mechanistic models are needed to relate these observations to characteristics of the delivery vehicles and to predict release profiles during design of new formulations.

Depending on the methods used to obtain the solution (i.e., the release rate/profile), models can also be broadly classified as being either analytical or numerical. For analytical models, solutions can be determined by symbolic calculation and expressed in the form of equations, such as the one derived by Higuchi (1961). In some situations, exact analytical solutions can be found, but often approximations have to be made. In any case, analytical solutions are highly valuable because they symbolically relate a response variable (such as the amount of released drug) to one or more independent variables (time in this case) and one or more parameters (such as the diffusion coefficient, the drug solubility and the initial drug loading). Thus, an analytical drug-release model not only immediately provides the kinetics of the release (e.g., amount of released drug proportional to the square root of time) but also explicitly shows how the release rate depends on various parameters (e.g., proportional to the square root of the diffusion coefficient).

Many problems of practical interest are too complicated to be solved by analytical methods. This is often due to nonlinearities and/or complex geometries. In these cases, one has to resort to numerical analysis or simulation, where, given a certain set of parameter values, the corresponding solution is determined by numerical calculation. A numerical solution is inherently approximate, but may nevertheless be determined with high accuracy. For numerical methods, each set of parameter values requires a new solution to be determined, which makes them more difficult to apply. Having said that, it should be emphasised that numerical methods are highly valuable, since they considerably expand the range of problems that are amenable to being solved. The two most commonly used numerical methods are the finite-difference (FD) and the finite-element (FE) method; see, e.g., the textbooks by LeVeque (2007) and Hughes (2000). In principle, the FD method is more intuitive and easy to apply, but the FE method is better suited for complex geometries. Today, numerical analysis is often carried out by commercially available software packages, in which case either method can be applied without much effort.

As pointed out by Siepmann and Siepmann (2008), no drug-release model can be expected to be universally valid, and models could therefore be classified on the basis of the systems to which they apply. This is particularly true for mechanistic models, because the rate-controlling mechanisms vary between systems. Matrix (or monolithic) systems of the type considered in this review are typically diffusion-controlled (Fan and Singh, 1989), but dissolution kinetics can sometimes affect the release profile in its early stages (Peppas, 1983; Frenning et al., 2005).

The purpose of this review is to provide a comprehensive overview of mathematical procedures that can be used to describe the release of drugs from inert matrix systems, focusing on general principles rather than particular applications. To put this work into context, a brief overview of drug delivery systems and release mechanisms is provided in Section 2. Drug release processes tend to have a multiscale character, and multiscale modelling may therefore provide additional insights, as elaborated upon in Section 3. Factors that affect the release from matrix systems, such as initial drug loading/solubility, boundary conditions and matrix geometry, are discussed in Section 4. The initial drug loading – relative to the drug solubility in the matrix – is known to have a decisive influence on the release. When no solubility or dissolution limitations exist, the drug release can be inferred from solutions to the diffusion equation, as described in Section 5. As discussed in Section 6, the analysis becomes more challenging when the initial drug loading exceeds the solubility, in which case the main solution procedures rely on moving-boundary and continuous-field descriptions. The modifications necessary for porous matrices are dealt with in Section 7, including effective diffusion coefficients, percolation effects and pore-network modelling. Conclusions are drawn in Section 8.

2. Drug delivery systems and release mechanisms

Drug delivery systems are often classified on the basis of their design or their rate-controlling release mechanism (such as diffusion, erosion/chemical reactions, swelling and osmosis) (Langer, 1980; Langer and Peppas, 1983; Fan and Singh, 1989). This review focuses on diffusion-controlled release systems, that are split into two types; reservoir system and matrix or monolithic systems (Langer, 1980; Wen and Park, 2010). The reservoir system utilises a membrane that serves as the main diffusion barrier, enclosing a core containing the drug. The drug loading is typically high enough to ensure that a saturated solution is maintained within the core for an extended period. Such a design ideally leads to a constant release rate (zero-order release) as long as solid drug is present in the core and no inhibitory buildup of drug takes place in the dissolution medium. Under these circumstances, the release rate is proportional to the device area but otherwise independent of its geometry (Siepmann and Siepmann, 2008). Although reservoir systems have the benefit of a zero-order release profile, they run the risk of dose dumping caused by membrane rupture. This is particularly unsuitable for highly potent drugs (Forsgren et al., 2010). Reservoir systems are similar in design to osmotic pumping systems, where the dissolved drug and constituent materials induce an osmotic pressure within the core. This pressure results in outward convection of dissolved drug, through holes in the coating (Theeuwes, 1975). Although diffusion is generally considered to be the dominating release mechanism in reservoir systems, osmotic pumping can also influence the release rate (Borgquist et al., 2002).

In the matrix or monolithic system, drug is distributed through a polymer that serves as the diffusion barrier (Wen and Park, 2010). The polymer matrix can either be nonporous/homogeneous or porous/granular. In the former, the matrix can be considered to consist of one phase through which the drug diffuses. In the lat-

ter, diffusion is restricted to pores in an otherwise impermeable material. The drug can be dissolved in the matrix or be dispersed in solid form. Whereas diffusion is the major rate-controlling mechanism for inert matrices of the type considered in this review, matrix swelling (Colombo, 1993; Colombo et al., 1995) and erosion (Göpferich, 1996a,b) can have significant impacts on the release rate for other matrix materials. Siepmann and Peppas (2001) have reviewed models of swelling matrices, focusing on hydroxypropyl methylcellulose (HPMC). A review of models applicable to eroding matrices has been presented by Siepmann and Göpferich (2001). Although matrix systems run less risk of dose dumping than reservoir systems, burst release is not uncommon, as discussed by Huang and Brazel (2001).

3. Drug release as a multiscale process

During recent years, multiscale modelling and simulation has attracted considerable interest in various fields of science (see, e.g., Goddard et al., 2001; E and Engquist, 2003; Deen et al., 2004). The underlying idea is to link processes occurring on different spatial (or temporal) scales – typically in a sequential manner – to obtain a mechanistic description of complex phenomena. It is instructive to look at drug release from this perspective, and we will use inert porous matrices as an example. For simplicity we will assume that all drug is dissolved in the liquid present within the pores.

As illustrated in Fig. 1, drug release can in this case be described as the sum effect of processes occurring on four different length scales. Firstly, it is well known that diffusion is driven by the thermal motion of individual molecules on the molecular scale (micro scale). Secondly, the molecular processes will result in certain drug concentrations within the pore system of the matrix (meso scale). Thirdly, on scales significantly larger than the average pore size (macro scale), it is usually possible to describe diffusion using effective diffusion coefficients. Fourthly, the macro scale diffusion will result in an overall release profile for the system as a whole (global scale).

In this context, mathematical modelling can be described as a tool that enables scale transitions to be performed. Assuming that all significant pores are large enough to exclude any restrictions posed by individual molecular behaviour (Sahimi, 1992), the micro to meso transition can be immediately accomplished by introducing the drug concentration C in the liquid present within the pores. Under this assumption, the flux J (i.e., the mass per unit time and area) in a certain spatial direction x can be determined using Ficks's first law (see, e.g., Cussler, 1997, Ch. 2),

$$J = -D\frac{\partial C}{\partial x}, \tag{1}$$

where D is the diffusion coefficient of the drug in the liquid present within the pores. The meso to macro transition is more challenging, however, pore-network modelling can accurately predict effective properties based on the pore structure (pore size distribution, connectivity and porosity) (Burganos and Sotirchos, 1987; Sahimi, 1992; Hollewand and Gladden, 1992; Sahimi, 1995). The outcome of such an analysis typically is an effective diffusion coefficient D_{eff} (or D', see Section 7), which can be used instead of D to describe diffusion in the matrix as a whole. The macro to global transition – from 'effective' matrix properties to the release profile – is commonly studied in drug-release modelling, and is also the main focus of this review.

4. Factors affecting drug release for matrix systems

A large number of factors influence the rate of drug release from inert matrix systems. This review will discuss some of them in order to provide a classification of mathematical models.

4.1. Initial drug loading, solubility and dissolution rate

The initial drug loading, A_0, is usually defined as the ratio between the amount of drug present in the matrix and the matrix volume (assuming a homogeneous distribution of drug on the macro scale). The magnitude of A_0, relative to the drug solubility in the matrix, C_s, plays a decisive role in determining the release kinetics. If $A_0 < C_s$, and dissolution is not rate limiting, all drug can be considered to be dissolved at the initial state. Hence the release kinetics can be inferred from solutions of the homogeneous diffusion equation (Fick's second law; see Section 5).

The situation becomes considerably more difficult when $A_0 > C_s$. Since all drug cannot be present in dissolved form in the initial state, it makes sense to subdivide the total amount A_0 into dissolved (C_0) and solid (S_0) parts, so that $A_0 = C_0 + S_0$. Typically, $C_0 = C_s$, such that

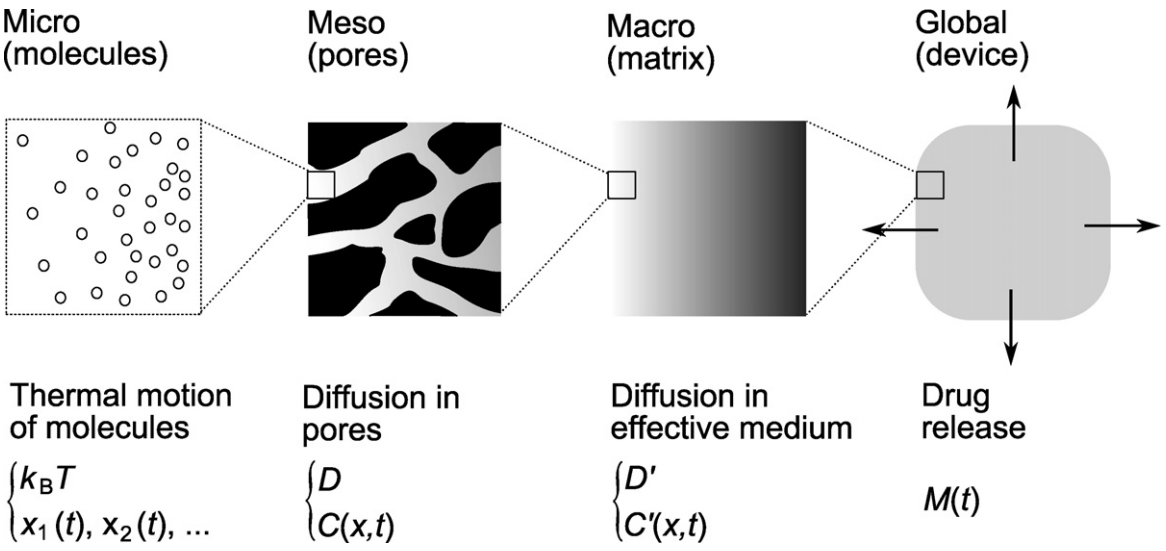

Fig. 1. Drug release as a multiscale process (exemplified by an inert porous matrix). The thermal energy k_BT results in certain trajectories $x_i(t)$ of individual drug molecules on the micro scale. Diffusion is considered to occur in pores on the meso scale and in an effective medium on the macro scale. This produces an overall drug release $M(t)$ on the global scale.

$S_0 = A_0 - C_s$. As is well-known, this case was considered by Higuchi (1961), who noted that the matrix can be subdivided into two zones, with a moving boundary in between (provided that dissolution is not rate-limiting). No drug transport is possible in the core where solid drug is present, since there is no concentration gradient in this region. No solid drug exists in the depleted zon, adjacent to the boundary, resulting in a concentration gradient and drug transport. As a consequence of this transport, the boundary between the two zones will move inwards with time, leading to a so-called moving-boundary description (Crank, 1984) of drug release (see Section 6.1).

Reducing the sharpness of this boundary, and considering both the dissolved and the solid drug concentrations as continuously varying fields, is desirable when a numerical solution is sought, and also provides a natural framework for systems with dissolution-rate limitations. Such continuous-field descriptions are discussed in Section 6.2.

A more general situation is that the matrix initially contains a nonuniform amount of drug. Lee (1984) used special preparation procedures to achieve a sigmoidal initial drug concentration despite that the initial drug loading nowhere exceeded the drug solubility in the matrix. The sigmoidal profile was experimentally and theoretically found to produce a release rate that varied considerably less over time than the one for a uniformly loaded matrix (Lee, 1984, 1986). Alternatively, a nonuniform initial drug concentration may result from unevenly dispersed solid drug. Although not elaborated upon in this review, a nonuniform initial amount of solid drug may be accommodated for both in the moving-boundary and in the continuous-field descriptions.

4.2. Boundary conditions

4.2.1. The sink condition

The most straightforward – and also often used – assumption is to regard the drug concentration at the boundary of the matrix (or delivery vehicle in the general case) to be zero (Siepmann and Siepmann, 2008). Such boundary conditions are often referred to as 'sink conditions'. The sink condition is a mathematical idealisation, but often adequately approximates real physical systems. In a strict mathematical sense, the sink condition cannot be valid unless release occurs into a perfectly mixed dissolution medium of infinite volume. In reality, a nonzero concentration always develops with time, unless special precautions are taken, such as a release vessel with a flow-through design.

4.2.2. Stagnant layers and external mass-transfer resistances

When a delivery vehicle is contained in a dissolution medium, its periphery is surrounded by a stagnant layer of liquid. The thickness of this layer is inversely proportional to the degree and rate at which the dissolution medium is stirred. Such stagnant layers have been extensively discussed in the literature, particularly in relation to dissolution rate. The modifications of the Noyes and Whitney (1897) equation proposed by Nernst (1904) and Brunner (1904), related the dissolution rate constant to the diffusion coefficient via a stagnant layer. The influence of hydrodynamic conditions on the stagnant-layer thickness has been discussed by Grijseels et al. (1981).

Although this review is largely focussed on matrix systems, we will use reservoir systems to discuss the main effects of stagnant layers on the release kinetics. Let us consider a reservoir system where the diffusion barrier is a membrane of thickness L_m with diffusion coefficient D_m (Fig. 2a). The analysis is somewhat complicated by the fact that a partition occurs at the interfaces. If a saturated solution exists in the reservoir, the drug concentration in the membrane at the membrane/reservoir interface will be $K_{m/r}C_s$, where $K_{m/r}$ is the membrane/reservoir partition coefficient. Under

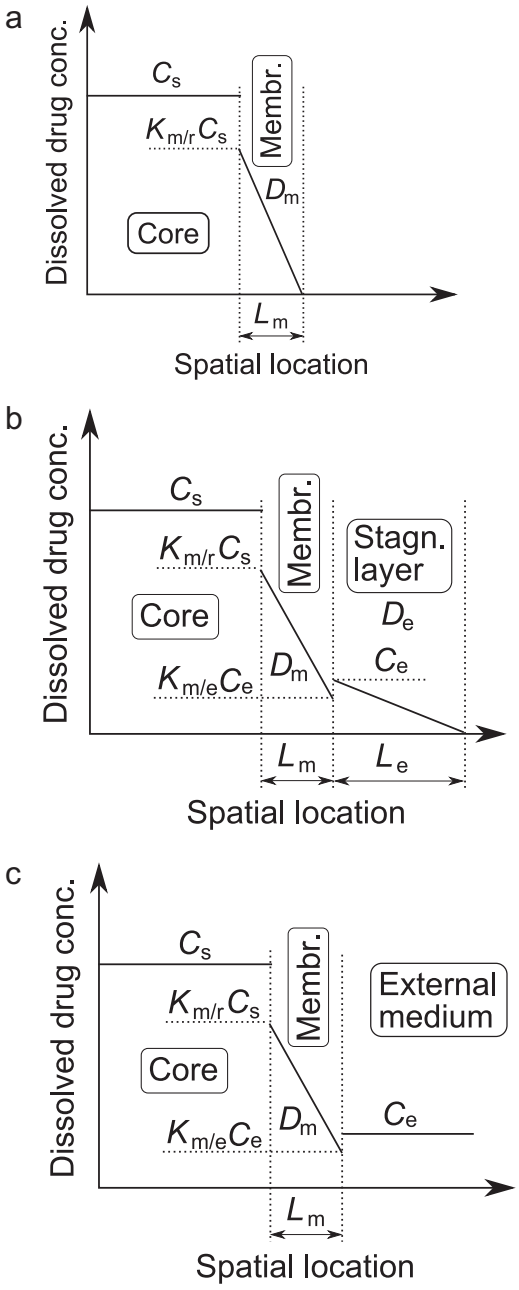

Fig. 2. Effects of boundary conditions on drug release, exemplified by reservoir systems: (a) sink conditions, (b) stagnant layers and (c) dissolution media of finite volumes.

sink conditions, the outward flux of drug, J_0, is readily determined from Fick's first law (1) as

$$J_0 = \frac{D_m K_{m/r} C_s}{L_m}. \quad (2)$$

Hence a constant release rate is obtained (zero-order release).

When a stagnant layer exists, the concentration will no longer be zero at the interface between the membrane and the external medium (Fig. 2b). Again one needs to include a partition coefficient, so that the drug concentration in the membrane at the interface can be written as $K_{m/e}C_e$, where $K_{m/e}$ is the membrane/external medium partition coefficient, and C_e is the drug concentration in the external medium at the interface. Assuming steady state,

and using Fick's first law (1), the flux J_m across the membrane is expressed as

$$J_m = \frac{D_m(K_{m/r}C_s - K_{m/e}C_e)}{L_m} \tag{3}$$

whereas the flux J_e across the stagnant layer becomes

$$J_e = \frac{D_e C_e}{L_e}. \tag{4}$$

No accumulation of drug can occur at the interface during steady state, implying that these two fluxes must be equal. Solving Eq. (3) for C_e and substituting the result in Eq. (4), one finds that

$$J_m = J_e = \frac{J_0}{1 + (D_m K_{m/e} L_e)/(D_e L_m)}. \tag{5}$$

A stagnant layer reduces the release rate, but in this particular example does not affect the release kinetics that continue to be zero order.

A stagnant layer is often said to correspond to an external mass-transfer resistance, because mass transfer across interfaces is often analysed in terms of mass-transfer coefficients (Cussler, 1997, pp. 211–244), in this case $T_m = D_m/L_m$ for the membrane and $T_e = D_e/L_e$ for the stagnant layer. The overall mass transfer coefficient T is defined in such a manner that the total flux $J = TC_s$. A mass transfer coefficient is analogous to an electrical conductance (the reciprocal value of the corresponding resistance) and the overall mass transfer coefficient can be calculated in a similar manner to the conductance of two electrical resistors in series (with partition coefficients being taken into account). If $K_{m/r}$ and $K_{m/e}$ both equal unity, the overall mass transfer coefficient can be determined from the equation $1/T = 1/T_m + 1/T_e$.

4.2.3. Dissolution media of finite volumes

Let us now consider release into a finite medium of volume V_e while disregarding boundary-layer effects, using the same reservoir system as mentioned above (Fig. 2c). In this case Eq. (3) remains valid, but the external concentration C_e will increase with time and needs to be determined as part of the solution procedure. Problems of this type, with a 'free' boundary condition, are often referred to as free boundary value problems (Crank, 1984). If we let $M(t)$ be the amount of drug in the external medium, we can express its concentration as $C_e(t) = M(t)/V_e$. The time rate of change of $M(t)$ equals $A_e J_m$, where A_e is the total external surface area and J_m, as before, is the flux across the membrane. Hence we are led to a first-order differential equation, of the form

$$\frac{dM}{dt} + \lambda M = \lambda M_\infty, \tag{6}$$

where

$$\lambda = \frac{A_e D_m K_{m/e}}{L_m V_e} \tag{7}$$

is a rate constant and

$$M_\infty = \frac{K_{m/r} C_s V_e}{K_{m/e}} \tag{8}$$

is the asymptotic amount of drug released. Provided that the external media contains no drug initially, the solution can be stated as (Flynn et al., 1974)

$$M(t) = M_\infty(1 - e^{-\lambda t}). \tag{9}$$

Hence, the finite external volume (V_e) has caused a change in the release kinetics, from zero-order to first-order. Since initially, there is no drug in the external medium, the initial release rate equals $A_e J_0$. As soon as the drug concentration builds up in the external medium, the release rate reduces, until an equilibrium situation is obtained. Similar first-order kinetics are expected under sink conditions, where, due to the absence of solid drug in the core, the saturated concentration can no longer be maintained (Flynn et al., 1974).

4.3. Matrix geometry

In an ideal case, geometry affects drug release from matrix systems but not from reservoir systems (Siepmann and Siepmann, 2008). For the planar geometry, drug release truly is one-dimensional, simplifying the mathematical analysis. This geometry has therefore been the bases for many investigations (Higuchi, 1961; Roseman and Higuchi, 1970; Tojo, 1985; Paul and McSpadden, 1976; Lee, 1980; Bunge, 1998; Zhou and Wu, 2002; Frenning, 2003, among others). Other geometries that permit relatively straightforward analyses to be performed are the sphere (Higuchi, 1963; Lee, 1980; Frenning, 2004) and the cylinder with drug release occurring in the radial direction only (Roseman and Higuchi, 1970; Siegel, 2000; Huang et al., 2000). This is because the spherical and cylindrical symmetry makes it sufficient to retain one spatial coordinate in the analysis.

For general cylindrical systems, drug transport in both the axial and radial directions needs to be considered. Such an analysis has been performed by Fu et al. (1976) when no solubility limitations exist ($A_0 < C_s$). However, when there is an excess of drug ($A_0 > C_s$), the analytical treatment becomes considerably more involved. Cobby et al. (1974a,b) proposed a generic cubic equation in the square root of time for the release from matrix tablets. Zhou et al. (2005) have presented a pseudo-steady state analysis of drug release from cylindrical matrices containing an excess of solid drug (further elaborated upon by Frenning et al., 2005).

More detailed analyses typically rely on numerical methods, especially when additional factors are taken into account or when complex geometries are studied. The FD method has for example, been used in a series of papers devoted to the release of drug from swelling HPMC matrices by Siepmann and co-workers (Siepmann et al., 1999a,b, 2002; Siepmann and Peppas, 2000). The FE method has been used to investigate complex geometries (Zhou and Wu, 1997), inhomogeneous drug loadings and concentration/time-dependent diffusion coefficients (Wu and Zhou, 1998). The FE method has also been applied to investigate the effects of stagnant layers and finite volumes of release media (Wu and Zhou, 1999) and the implications of slow drug dissolution (Frenning et al., 2005).

5. Matrix systems: drug loading below solubility

In the absence of any solubility or dissolution limitations, the release of drug from an inert matrix system can be determined by solving the homogeneous diffusion equation (Fick's second law). When diffusion is unidirectional, the equation takes the form (Crank, 1979; Cussler, 1997)

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}, \tag{10}$$

where the diffusion coefficient D is assumed to be independent of concentration, and the drug concentration $C(x,t)$ is a function of the spatial coordinate x and time t. The diffusion equation is a partial differential equation (PDE), second-order in space and first-order in time, identical in form to the heat-conduction equation. A large number of solutions exist in the literature, for various geometries, initial and boundary conditions, and have been conveniently summarised in the textbooks by Crank (1979) and Carslaw and Jaeger (1986). Such solutions tend to be rather complex, and often take the form of an infinite series, as obtained by operational methods, in particular Laplace transforms (Carslaw and Jaeger, 1948).

One exception to this rule, which is of relevance in drug release, is the half-infinite system, occupying the spatial region $x > 0$, with constant surface concentration (usually zero). Assuming that the matrix initially contains a uniform amount A_0 of dissolved drug, the initial condition can be stated as

$$C(x,t) = A_0 \quad \text{for} \quad x \geq 0 \quad \text{and} \quad t = 0. \tag{11}$$

When sink conditions are enforced on the boundary at $x = 0$, one boundary condition is

$$C(x,t) = 0 \quad \text{for} \quad x = 0 \quad \text{and} \quad t > 0. \tag{12}$$

For a semi-infinite system, no change in concentration will occur sufficiently far away from the boundary, regardless of time. Hence one can postulate a boundary condition at infinity as

$$C(x,t) = A_0 \quad \text{when} \quad x \to \infty \quad \text{and} \quad t > 0. \tag{13}$$

For the half-infinite system, the Boltzmann transformation (Crank, 1979)

$$\eta = \frac{x}{2\sqrt{Dt}}, \tag{14}$$

reduces the PDE (10) to an ordinary differential equation (ODE) in the reduced variable η. This transformation is consistent with the initial and boundary data, because the initial condition (11) and the boundary condition (13) can be translated into a single condition at $\eta = \infty$ (the boundary at $x = 0$ corresponds to $\eta = 0$, at which point the sink condition (12) applies). The resulting ODE takes the form

$$C'' + 2\eta C' = 0 \tag{15}$$

where the prime indicates differentiation with respect to η. Noting that e^{η^2} is an integrating factor, Eq. (15) can be immediately integrated once, to show that C' is proportional to $e^{-\eta^2}$. A second integration produces the concentration profile,

$$C(\eta) = A_0 \operatorname{erf}(\eta), \tag{16}$$

where

$$\operatorname{erf}(\eta) = \frac{2}{\sqrt{\pi}} \int_0^{\eta} e^{-z^2}\, \mathrm{d}z \tag{17}$$

is the error function (Abramowitz and Stegun, 1965) [the factor $2/\sqrt{\pi}$ is included in the definition so that $\operatorname{erf}(\eta)$ approaches unity for large η]. The concentration profile (16) leads to the classical formula,

$$M(t) = 2A_0 \sqrt{\frac{Dt}{\pi}}, \tag{18}$$

for the amount of drug released after time t per unit interface area. Hence, the amount of released drug increases with the square root of time.

6. Matrix systems: drug loading above solubility

Drug release from matrix systems can generally be considered as diffusion-controlled, even when an excess of drug is present in the matrix ($A_0 > C_s$). However, the restrictions imposed by solubility cause a reduction in the concentration gradient, whereby resulting in slower drug release. The classical analysis of this situation is based on moving-boundary descriptions.

6.1. Moving-boundary descriptions

6.1.1. Problem formulation

Let us consider the same half-infinite system as was mentioned above, with the assumption that the initial drug loading $A_0 > C_s$. Provided that drug dissolution is not rate limiting, the matrix can be divided into an outer depleted region and an inner region containing solid drug. These two regions are separated by a boundary that moves inwards with time (see Section 4.1) (Higuchi, 1961). The spatial location of the moving boundary is denoted by $x_*(t)$. The homogeneous diffusion equation (10) continues to be valid in the depleted region, and the mathematical statement of the problem is as follows:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \quad \text{for} \quad 0 < x < x_*(t). \tag{19}$$

The sink condition (12) also applies in this case, but a new boundary condition is needed at $x = x_*(t)$, where

$$C(x,t) = C_s \quad \text{for} \quad x = x_*(t) \quad \text{and} \quad t > 0. \tag{20}$$

The motion of the boundary requires an additional condition for its determination. Thus, local mass conservation at the moving boundary requires that:

$$D\frac{\partial C}{\partial x} = S_0 \frac{dx_*}{dt} \quad \text{for} \quad x = x_*(t) \quad \text{and} \quad t > 0. \tag{21}$$

The above condition was first given in this form by Paul and McSpadden (1976). It is often referred to as a Stefan condition (Crank, 1984), in honour of Stefan (1891), who investigated this problem in relation to melting ice.

6.1.2. Exact analysis

It turns out that an exact analysis of the moving-boundary problem, formulated in the preceding section, is possible in terms of the reduced variable η defined by Eq. (14) (Paul and McSpadden, 1976). Hence, it immediately follows that the spatial location of the moving boundary increases with the square root of time, $x_* = 2\eta_*\sqrt{Dt}$, where η_* is the location of the boundary in the reduced description (when η rather than x and t is used as independent variable). Furthermore, the concentration profile becomes (Paul and McSpadden, 1976)

$$C(\eta) = C_s \frac{\operatorname{erf}(\eta)}{\operatorname{erf}(\eta_*)}, \tag{22}$$

and the amount of released drug per unit interface area is

$$M(t) = \frac{2C_s}{\operatorname{erf}(\eta_*)} \sqrt{\frac{Dt}{\pi}}. \tag{23}$$

Eqs. (22) and (23) are identical in form to Eqs. (16) and (18), but as a consequence of the restrictions imposed by solubility, the coefficient A_0 is replaced by $C_s/\operatorname{erf}(\eta_*)$ in the former. However, these formulae are not useful unless the value of η_* is known, and this requires the solution to be determined for the equation

$$\sqrt{\pi}\eta_* e^{\eta_*^2} \operatorname{erf}(\eta_*) = \frac{C_s}{S_0} = \mathrm{Ste}, \tag{24}$$

where the second equality defines the Stefan number (Ste). In general, this equation needs to be solved numerically.

6.1.3. Approximate analysis

The planar system is exceptional in the sense that an exact solution is obtainable, as outlined in the preceding section. For other geometries, one has to rely on approximate analytical or numerical methods. The two most commonly used analytical approximation methods are; the pseudo-steady state approximation, used by Higuchi (1961), and the (heat) integral balance method, originally devised by Goodman (1958) and refined by Volkov and Li-Orlov (1970).

Provided that the initial drug loading A_0 considerably exceeds the solubility C_s (implying a small Stefan number Ste), the movement of the boundary will be sufficiently slow, as to allow the time

derivative to be neglected in Eq. (19), so that $\partial^2 C/\partial x^2 \approx 0$.. The concentration C will therefore increase linearly from 0 at the origin to C_s at the moving boundary, so that the gradient $\partial C/\partial x \approx C_s/x_*$. When this expression is inserted in the Stefan condition (21), an ODE in $x_*(t)$ is obtained. This ODE can be solved by separation of variables, to produce the result

$$x_* \approx \sqrt{\frac{2DC_s t}{S_0}}. \tag{25}$$

If desired, this expression can be restated in terms of the reduced front position (η_*) and the Stefan number (Ste) as $\eta_* \approx \sqrt{\mathrm{Ste}/2}$. Having obtained the front position, the release rate $\mathrm{d}M/\mathrm{d}t$ per unit exposed area can be immediately evaluated as $D\,\partial C/\partial x \approx DC_s/x_*$ and hence the amount of released drug becomes

$$M(t) = \sqrt{2C_s S_0 D t}. \tag{26}$$

This expression was previously derived by Paul and McSpadden (1976). As noted by these authors, the classical Higuchi (1961) formula is recovered if $A_0 - C_s/2$ is substituted for $S_0 = A_0 - C_s$. This discrepancy originates from the fact that the Stefan condition (21) expresses mass conservation at the moving boundary, whereas, Higuchi (1961) considered mass conservation at the matrix boundary. Since both expressions were derived under the assumption that $A_0 \gg C_s$, this difference is insignificant for practical applications.

More accurate analytical results can be obtained using the (heat) integral balance method, in particular in its refined version, as was performed by Lee (1980) and later by Lin (2008). The underlying idea is to integrate the diffusion equation (19) once (for the original method by Goodman, 1958) or twice (for the refined method proposed by Volkov and Li-Orlov, 1970) with respect to space, in order to obtain an auxiliary balance equation. Next, a suitable functional form containing unknown parameters is postulated for the concentration profile in the depleted region. The unknown parameters are finally determined so that the concentration profile satisfies the boundary conditions and the auxiliary balance equation. With a carefully selected functional form, it is possible to achieve highly accurate results. Investigating a related problem, Sadoun et al. (2006) derived the expression

$$\eta_* \approx \frac{1}{2}\sqrt{\sqrt{(\mathrm{Ste}+6)^2 + 24\,\mathrm{Ste}} - (\mathrm{Ste}+6)}, \tag{27}$$

that gives the moving-boundary position with an error not exceeding 1% as long as Ste < 100 (Sadoun et al., 2006). The maximal error in the amount of released drug will be considerably smaller, however, because a Stefan number of 100 implies that initially more than 99% of the drug is present in dissolved form. Hence, the location of the moving boundary will have a marginal effect on the overall release profile. By applying the value of η_* provided by Eq. (27) in Eq. (23), a highly accurate formula for the amount of released drug is obtained.

The refined integral balance method has also been used by Lee (1980) to derive approximate analytical expressions for the amount of drug released from planar and spherical matrices into external media of finite volumes. This analysis was however restricted to the case of completely dissolved drug. In more complicated situations, both the pseudo-steady-state approximation and the integral-balance method may be applied in different regions of the same system. Such an approach was recently used in an approximate analytical analysis of the release of catanionic mixtures from gels (Frenning et al., in press), where the original model (Bramer et al., 2009) was based on regular solution theory (Holland and Rubingh, 1983).

6.2. Continuous-field descriptions

An alternative description, originally proposed by Ayres and Lindstrom (1977), utilises a continuously varying 'concentration' $S(x, t)$ of solid drug, defined so that $S(x, t)$ is the amount of solid drug present per volume unit matrix at spatial location x and time t. Dissolution acts as a source of dissolved drug, and the diffusion equation is modified to read

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \frac{\partial S}{\partial t}. \tag{28}$$

The negative sign on the right-hand-side of the equation is needed, because a decrease in S corresponds to a source for C. A major advantage of this continuous-field description is that the inhomogeneous diffusion equation (28) is valid everywhere in the matrix, regardless of whether solid drug is present or not. However, an additional equation is needed to determine the variation in solid drug concentration. This equation can be written as

$$\frac{\partial S}{\partial t} = -kF(S)(C_s - C) \tag{29}$$

where $F(S)$ is a function of the solid drug concentration, analogous to the area available for dissolution in the Noyes–Whitney equation (Noyes and Whitney, 1897). Also, when the dissolution rate is considered not to be rate-limiting, the factor $F(S)$ needs to be included on the right-hand-side of Eq. (29), to ensure that S always remains non-negative. If dissolution-rate effects are disregarded, one can use the unit step (Heaviside) function:

$$F(S) = \begin{pmatrix} 1 & \text{if } S \geq 0, \\ 0 & \text{if } S < 0. \end{pmatrix} \tag{30}$$

A more general model of this type has been considered by Lee et al. (1998). Related solution procedures, alternatively referred to as phase-field models (Caginalp, 1986, 1989) or level-set methods (Chen et al., 1997; Osher and Fedkiw, 2001), have attracted considerable interest in numerical analysis.

Although the non-linearity introduced by $F(S)$ generally precludes an exact analytical solution, a simplification can be made by introducing a new dependent variable $U(x, t)$, defined by (Delborghi et al., 1976; Frenning et al., 2005)

$$U(x, t) = \int_0^t C(x, t')\,\mathrm{d}t', \tag{31}$$

where t' is a dummy variable. As long as S is positive, so that $F(S)$ equals unity, integration of Eq. (29) shows that $S - S_0 = -k(C_s t - U)$; hence we can write

$$S = \begin{pmatrix} S_0 + k(U - C_s t) & \text{if } S_0 + k(U - C_s t) \geq 0, \\ 0 & \text{if } S_0 + k(U - C_s t) < 0. \end{pmatrix} \tag{32}$$

Integrating Eq. (28) with respect to time (from 0 to t), one finds that

$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} + G \tag{33}$$

where the source term

$$G = C_0 + S_0 - S. \tag{34}$$

Hence, the mathematical formulation reduces to a standard diffusion equation with a non-linear source term. The numerical solution of such equations has been extensively studied and can for instance be obtained via the FD or FE methods (LeVeque, 2007; Hughes, 2000). A number of commercially available software packages allow the solution for arbitrary geometry to be readily obtained. Numerical solution provides U (and hence $C = \partial U/\partial t$) as a function of the space and time variables. The concentration of solid drug, S, can be calculated via Eq. (32). Finally, the total amount of

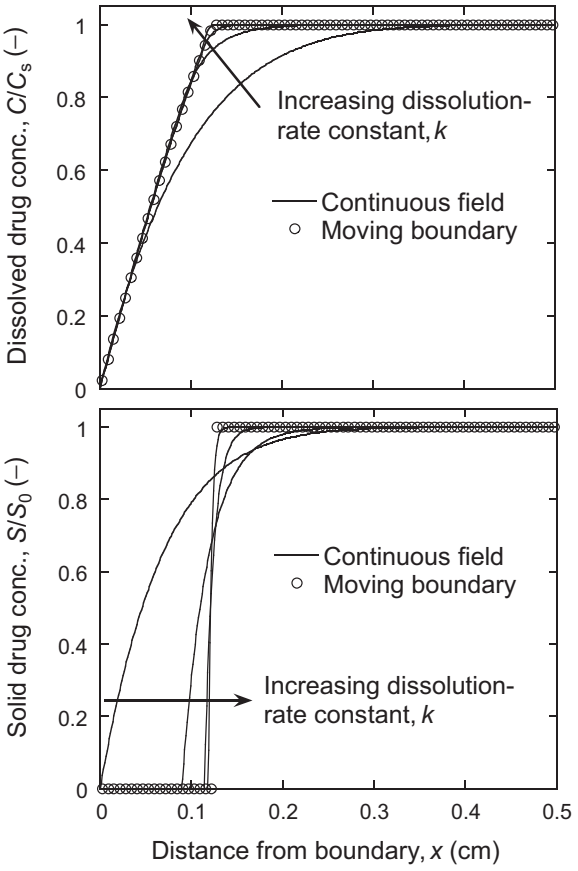

Fig. 3. Concentration profiles of dissolved (top) and solid drug (bottom) obtained by continuous-field (solid lines) and moving-boundary descriptions (open symbols).

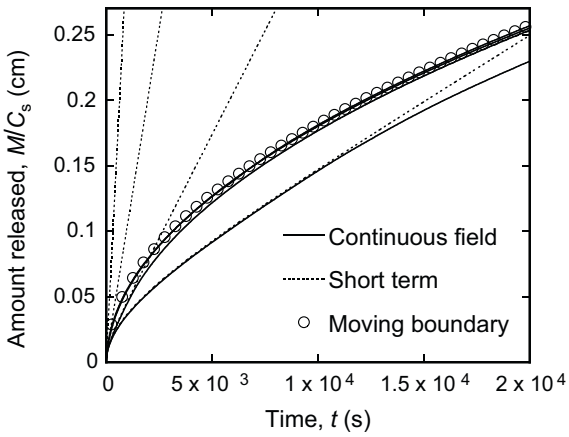

Fig. 4. Release profiles obtained by continuous-field (solid lines) and moving-boundary descriptions (open symbols). The dashed lines show the predictions of Eq. (35) (valid for short times).

drug that remains in the matrix is in the general case obtained by integrating $C+S$ over the spatial domain occupied by the matrix. For the planar system studied here, one can alternatively note that the magnitude of the outward flux is given by $D(\partial C/\partial x)_{x=0}$. As a consequence of Eq. (31), the amount of drug released per unit exposed area is thus obtained as $D(\partial U/\partial x)_{x=0}$.

To illustrate this procedure, we consider a system with a moderate excess of solid drug ($A_0 = 2C_s$, so that $S_0 = C_s$ and Ste = 1). The diffusion coefficient is kept fixed at 1×10^{-6} cm^2/s and calculations are performed for four different values of the dissolution rate constant k (1×10^{-4}, 1×10^{-3}, 1×10^{-2} and 1×10^{-1} s^{-1}). Concentration profiles obtained from a numerical solution of Eq. (33) are indicated by solid lines in Fig. 3 (the figure shows the situation after 1×10^4 s, i.e., slightly less than 3 h). As a comparison, the result obtained from a moving-boundary description, utilising the highly accurate value of η_* provided by Eq. (27) in Eq. (22), is indicated by open symbols. As expected, the numerical solution approaches the moving-boundary result when k increases. For the largest value of k considered, the concentration profile of the dissolved drug is almost identical with the one obtained from the moving-boundary analysis. However, for the solid drug, a transition zone can be seen, with a finite gradient in drug concentration.

The complication that precludes an analytical solution of Eqs. (28) and (29), stems from the nonlinearity introduced by the function $F(S)$. However, as long as solid drug exists everywhere in the matrix (up to a certain time t_s), $F(S)$ equals unity, and a linear equation system is obtained that can be solved in closed form. Gurny et al. (1982) have demonstrated, building on results by Danckwerts (1950), that the amount of drug released per unit exposed area can be expressed as

$$M = C_s\sqrt{\frac{D}{k}}\left[\left(kt+\frac{1}{2}\right)\operatorname{erf}\left(\sqrt{kt}\right)+\sqrt{\frac{kt}{\pi}}\,e^{-kt}\right] \quad \text{for} \quad t < t_s. \tag{35}$$

It is intuitively clear that dissolution will proceed most rapidly at the boundary, where C and U are both zero under sink conditions. By inspection of Eq. (32) it is apparent that

$$t_s = \frac{S_0}{kC_s}. \tag{36}$$

Similar conditions must be fulfilled in order for related dissolution-controlled models to be valid, such as the one proposed by Peppas (1983). It is interesting to note that Eq. (35) predicts zero-order release in a limited time window for certain parameter values. The requirements for this are; that the product kt is sufficiently large that the exponential in Eq. (35) becomes small and the error function approaches unity, and at the same time kt is sufficiently small allowing the equation to remain valid. In light of Eq. (36), such a situation would occur, if there is a considerable excess of solid drug ($S_0 \gg C_s$). However, once a depleted region forms (at time t_s), a crossover occurs to a square root of time behaviour.

The drug release corresponding to the concentration profiles displayed in Fig. 3 is provided in Fig. 4, which also includes the predictions of Eq. (35) (dotted lines labelled as 'short term'). Again it is evident that the numerical solution approaches the moving-boundary result when k increases. For this drug loading, Eq. (35) is valid up to $t_s = 1\times10^{-4}$ s for the lowest value of k, and in this case, a time window with an approximate zero-order release is observed (between 5×10^3 and 1×10^4 s).

However, if the effects of a finite dissolution rate are to be included in the model, a slightly different function $F(S)$ is more appropriate. As noted by Hixson and Crowell (1931) and Edwards (1951), the surface area of the undissolved drug is proportional to the volume – and hence S to the power of 2/3 – provided that all solid drug particles initially have the same size, and retain their shape during the dissolution process. Thus, one can write

$$F(S) = \begin{cases} \left(\dfrac{S}{S_0}\right)^{2/3} & \text{if} \quad S > 0, \\ 0 & \text{if} \quad S < 0, \end{cases} \tag{37}$$

where S_0 is the initial concentration of solid drug. A function of this type has been used in a number of models (Ayres and Lindstrom, 1977; Lindstrom and Ayres, 1977; Frenning and Strømme, 2003;

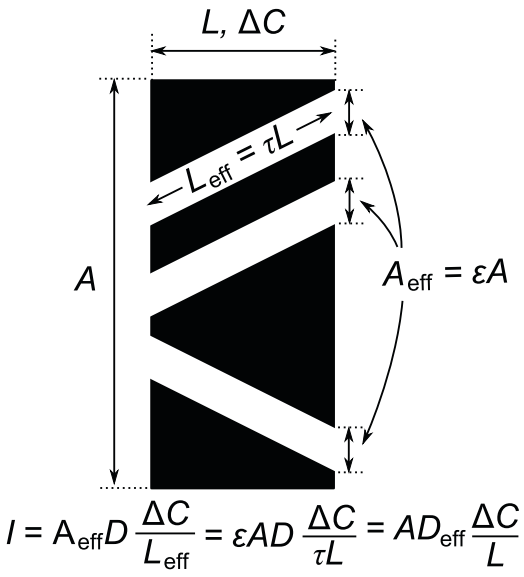

Fig. 5. Definition of effective diffusion coefficients: mass transport of magnitude I driven by a concentration difference ΔC across an idealised porous membrane of thickness L and cross-sectional area A. The effective diffusion coefficient D_{eff} accounts for porosity ε and tortuosity τ.

Frenning, 2003, 2004; Frenning et al., 2005; Blagoeva and Nedev, 2008).

7. Porous matrices

7.1. Effective diffusion coefficients

The drug-release rate from porous matrix structures is to a large extent determined by the matrix porosity. Since the porosity increases when drug dissolves, it is important to focuses on the porosity ε of the fully extracted matrix, as noted already by Higuchi (1963). Provided that the porosity is large enough such that percolation effects may be disregarded (see below), it is generally possible to describe diffusion through porous media with the normal diffusion equation (Eq. (10) for one-dimensional release), using an effective diffusion coefficient D_{eff}.

Basically, there are two effects that contribute to a reduction in the diffusion coefficient (Fig. 5). Firstly, since the drug cannot pass through the solid phase of the matrix, the cross-sectional area available for diffusion is reduced by a factor of ε. Secondly, pores channels tend not to be straight, and a drug molecule needs to, on average, diffuse a longer distance when going through a porous medium. The increased path length can be accounted for by reducing the diffusion coefficient by a tortuosity factor τ. Taking both effects into account, the effective diffusion coefficient is often defined as (see, e.g., Cussler, 1997, p. 173)

$$D_{\text{eff}} = \frac{\varepsilon D}{\tau} \tag{38}$$

where D is the diffusion coefficient of the dissolved drug in the liquid contained in the pores. It is apparent from Fig. 5 that the flux is obtained as the product of the effective diffusion coefficient D_{eff} and the (negative) gradient of the average drug concentration *in the liquid contained in the pores*. This definition is certainly the most suitable when diffusion occurs through a membrane, such as in reservoir systems, but may not necessarily be the most convenient one for matrix systems. For a matrix system, it appears most natural to define the initial drug loading (A_0) as the ratio between the amount of drug present in the matrix and the matrix volume (rather than as the ratio between the amount of drug and the pore volume), as performed by Higuchi (1963). Similarly, it is natural to calculate the concentration of dissolved drug as the ratio between the amount of the dissolved drug and the matrix volume. Such a procedure has two consequences. Firstly, the flux is obtained as the product of a 'reduced' diffusion coefficient D' and the negative gradient of the average drug concentration *in the matrix*, implying that

$$D' = \frac{D}{\tau}. \tag{39}$$

Secondly, a 'reduced' solubility C_s' in the matrix can be introduced as

$$C_s' = \varepsilon C_s, \tag{40}$$

where C_s is the drug solubility in the liquid within the pores. Although definitions (39) and (40) are less standard than (38), they are widely used in drug-release modelling. Their main advantage is that they enable expressions derived for a non-porous matrix to be immediately converted to the porous case, by substituting D' for D and C_s' for C_s. As an example, the expressions derived by Higuchi (1963) for the release from nonporous and porous matrices of planar and spherical geometries are related by these substitutions. However, slightly different adjustments for matrix porosity have sometimes been used (Miller and Peppas, 1983).

7.2. Percolation effects

In essence, percolation theory analyses clusters in lattices and there are two main types of percolation: site and bond percolation (Stauffer and Aharony, 1992; Sahimi, 1994). In site percolation, the lattice sites (alternatively referred to as nodes or vertices) are randomly occupied with a certain probability p and hence unoccupied with probability $1-p$. Two occupied neighbouring sites are considered to belong to the same cluster. Bond percolation focuses on the connections between neighbouring sites, referred to as bonds, that are randomly open with a certain probability p' and closed with probability $1-p'$ (transport can occur only through open bonds). Two neighbouring sites that are connected by an open bond belong to the same cluster. Percolation theory can be used to answer questions related to cluster size and structure. Of critical importance is the percolation threshold, i.e., the probability at which an infinite (or percolating) cluster forms. For site and bond percolation in a simple cubic lattice, the percolation thresholds are: $p_c = 0.3116$ and $p_c' = 0.2488$, respectively (Stauffer and Aharony, 1992). Implications of percolation theory on diffusion in disordered system have been discussed by Havlin and Ben-Avraham (1987) and a brief overview of percolation theory in relation to pharmaceutical science has been provided by Frenning and Alderborn (2009).

Percolation theory, introduced in pharmaceutical science by Leuenberger et al. (1987), has obvious implications for the release from inert matrix systems. This is because a pore network spanning the matrix is needed for satisfactory release of the drug. Typically, a site percolation model is used, with the porosity ε of the fully extracted matrix considered as being equivalent to the occupation probability p in the percolation model. The systematic study of percolation effects on drug release was initiated by Bonny and Leuenberger (1991), who observed a lower percolation threshold below which drug release was incomplete. In addition, an upper threshold was observed, above which the matrix no longer remained intact after drug release. Subsequent work in this field has focused on aspects such as the fractal dimensions of pore networks (Bonny and Leuenberger, 1993), particle size and drug/excipient particle size ratio (Caraballo et al., 1996; Millán et al., 1998) and three-dimensional release (Brohede et al., 2007).

Monte Carlo simulations can be used to study transport in pore networks when they are idealised as (site) percolation models.

Such analyses have been performed by Bunde et al. (1985) and Macheras and co-workers (Kosmidis et al., 2003a,b; Papadopoulou et al., 2006). Percolation theory is also closely connected to pore-network modelling, which can be considered as an extension of bond-percolation models.

7.3. Pore-network modelling

Pore-network modelling provides additional insights into diffusional transport through porous media. It relates the pore structure (pore-size distribution, connectivity and porosity) to its transporting capacity, which is typically expressed in terms of effective diffusion coefficients (Burganos and Sotirchos, 1987; Sahimi, 1992; Hollewand and Gladden, 1992; Sahimi, 1995). The basic setup is the same as for the bond-percolation model described above, with open or closed bonds connecting neighbouring sites in a lattice. However, whereas all open bonds are considered equivalent in bond percolation, pore-network modelling allows for a distribution in pores sizes. The analysis can for convenience be based on a regular lattice, such as the simple cubic lattice. This is because previous experience has shown that the choice of lattice has a minor influence on the results, as long as the average connectivity Z is kept constant (Arbabi and Sahimi, 1991). If the number of nearest neighbours in the lattice is N, the probability of having an open bond is calculated as $p' = Z/N$. Clearly, the connectivity cannot exceed the number of nearest neighbours, thus the use of the simple cubic lattice is limited to a maximum of 6 connections. The pore radii are typically determined from the pore-size distribution, under the assumption that all pores have the same length L (Sahimi, 1992). The length L is finally adjusted so that the porosity of the network equals the porosity of the matrix (attributing all volume to the pores and none to their junctions, i.e., the nodes).

When the network is created, attention is directed towards transport through its open pores. Consider an open pore of radius r_{ij} (cross-sectional area $a_{ij} = \pi r_{ij}^2$) connecting two nodes i and j. If the drug concentrations at these nodes are C_i and C_j, it immediately follows from Fick's law (1) that the amount of drug transported from i to j per unit time is

$$I_{ij} = -\frac{Da_{ij}}{L}(C_i - C_j), \tag{41}$$

where D is the diffusion coefficient of the drug in the liquid within the pores. The assumption of zero nodal volumes necessitates that no drug should accumulate at the nodes, implying that

$$\sum_{j \in nn(i)} I_{ij} = 0, \tag{42}$$

where the sum extends over all nearest neighbours to node i. An analogy with resistor networks may be useful at this point. Eq. (41) has the same form as the classical Ohm's law, with I corresponding to the electrical current, C to the electrical potential and Da_{ij}/L to the conductance (the reciprocal value of the corresponding resistance). Similarly, Eq. (42) is analogous to Kirchhoff's first law. Thus, in the steady-state situation, pore network models are isomorphic with the classical resistor networks investigated by Kirkpatrick (1973).

Assigning concentrations to the nodes at two opposite boundaries, a concentration gradient develops in one spatial direction. Thus, Eqs. (41) and (42) combine to form a linear equation system for the nodal concentrations C_i of all nodes in contact with either boundary. This equation system can be solved numerically, enabling the flux through the pore network to be determined. Knowing the applied concentration gradient and the resulting flux, the effective diffusion coefficient is readily obtained.

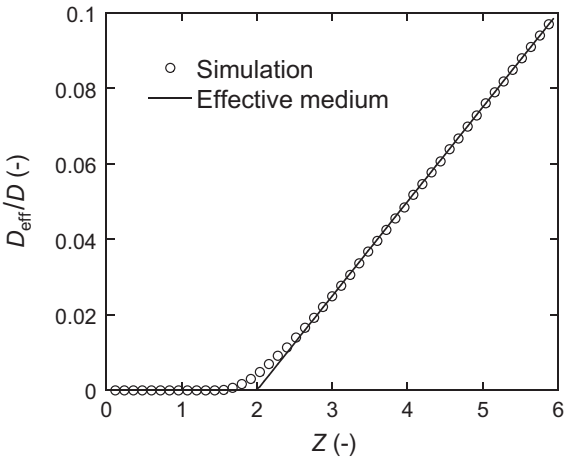

Fig. 6. Results obtained from pore-network modelling. Effective diffusion coefficient D_{eff} as a function of the network connectivity Z.

It is also possible to investigate pore networks by analytical methods, in particular, effective-medium theory, but the analysis tends to be rather complex (Sahimi et al., 1983). However, if all pores are monosized, one can use the methods described by Kirkpatrick (1973). The effective-medium approximation of the effective diffusion coefficient becomes

$$D_{eff} \approx \frac{\varepsilon D}{12}(Z - 2), \tag{43}$$

when the analysis is based on the simple cubic lattice with $N = 6$ nearest neighbours. This prediction is compared to simulated data in Fig. 6, assuming a matrix porosity ε of 30%, obtained using a simple-cubic network of size $30 \times 30 \times 30$ (in units of the pore length L). Percolation behaviour is evident in Fig. 6, with a critical connectivity $Z_c \approx 1.5$, which is in good agreement with percolation theory ($Z_c = 6p'_c \approx 1.49$ for the simple cubic lattice). From Fig. 6, it is apparent that the effective-medium approximation performs poorly close to the percolation threshold, but provides a good description of the simulated data once $Z \geq 3$. Such crossovers from percolation-type to effective-medium type behaviours are commonly encountered (Stauffer and Aharony, 1992; Sahimi, 1994).

8. Conclusions

Mathematical modelling of drug release from inert matrix systems has been reviewed, with the focus being directed towards general principles rather than particular applications. It is claimed that the overall drug release is the result of the combined effects of processes occurring on many different length scales, consequently drug release can be considered as a multiscale process. For inert porous matrices, pore network modelling can provide effective diffusion coefficients based on the pore structure (porosity, pore-size distribution and connectivity) that subsequently can be used in models of the overall release process. Although the effects of stagnant layers and finite volumes of release media have been briefly discussed, this review has elaborated mostly upon solution procedures for systems in which sink conditions provide reasonable approximations of reality. The most interesting situation occurs when the initial drug loading exceeds the drug solubility in the matrix. Here, our main message is that the Higuchi-type moving-boundary descriptions continue to be one of the most valuable tools for obtaining approximate analytical solutions, especially when coupled with integral-balance methods. However, continuous-field descriptions that utilise a continuously varying concentration of solid drug are advantageous when applying numerical methods. It is possible to derive a single diffusion-type equation with nonlin-

ear source terms, amenable to being solved by standard numerical packages, regardless of the geometry of the matrix. In this manner, drug release from matrices of arbitrary geometries can be determined without effort.

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