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Review

Modeling of drug release from matrix systems involving moving boundaries: Approximate analytical solutions

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ABSTRACT

The purpose of this review is to provide an overview of approximate analytical solutions to the general moving boundary diffusion problems encountered during the release of a dispersed drug from matrix systems. Starting from the theoretical basis of the Higuchi equation and its subsequent improvement and refinement, available approximate analytical solutions for the more complicated cases involving heterogeneous matrix, boundary layer effect, finite release medium, surface erosion, and finite dissolution rate are also discussed. Among various modeling approaches, the pseudo-steady state assumption employed in deriving the Higuchi equation and related approximate analytical solutions appears to yield reasonably accurate results in describing the early stage release of a dispersed drug from matrices of different geometries whenever the initial drug loading (A) is much larger than the drug solubility (C_s) in the matrix (or $A \gg C_s$). However, when the drug loading is not in great excess of the drug solubility (i.e. low A/C_s values) or when the drug loading approaches the drug solubility ($A \to C_s$) which occurs often with drugs of high aqueous solubility, approximate analytical solutions based on the pseudo-steady state assumption tend to fail, with the Higuchi equation for planar geometry exhibiting a 11.38% error as compared with the exact solution. In contrast, approximate analytical solutions to this problem without making the pseudo-steady state assumption, based on either the double-integration refinement of the heat balance integral method or the direct simplification of available exact analytical solutions, show close agreement with the exact solutions in different geometries, particularly in the case of low A/C_s values or drug loading approaching the drug solubility ($A \to C_s$). However, the double-integration heat balance integral approach is generally more useful in obtaining approximate analytical solutions especially when exact solutions are not available.

Contents

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1. Introduction

Matrix systems, where the drug is dispersed or dissolved in a carrier in the form of ointment, tablets, granules, microspheres, transdermal patches, stent coatings, etc., have been very popular in pharmaceutics and drug delivery applications due to their relative ease of fabrication as compared to the more complex membrane-reservoir type of delivery systems. A variety of excipients based on wax, lipid, as well as natural and synthetic polymers have been used as carrier material in the preparation of such matrix-type of drug delivery systems. The drug release from such matrix systems is mainly controlled by the diffusion process. However, depending on the physicochemical properties of the carrier material, drug release from the resulting matrix system may also be accompanied by concomitant swelling and/or erosion processes, e.g. when hydrophilic polymer excipients are present. The diffusional release of a dispersed or dissolved drug from a carrier matrix generally involves the presence of a moving diffusion front separating the unaffected core and the partially extracted or depleted region, where the front moves toward the unaffected core with time as more extracted region is created from the continuous drug dissolution and release. When an erodible or swellable polymer matrix is involved, the drug release kinetics is further complicated by the presence of a second moving boundary, namely the swelling or eroding front which moves either opposite to or in the same direction as the diffusion front. The mathematical analyses of such mass transfer problems involving moving boundaries are generally known as moving boundary problems, free boundary problems, or Stefan problems. The presence of a moving boundary introduces a non-linearity so that only a few exact solutions are known (Crank, 1975; Ockendon and Hodgkins, 1975; Wilson et al., 1978). In addition to numerical schemes, various approximate analytical solutions have been employed over the years to solve such moving boundary problems encountered in the analysis of drug release from matrix systems. Despite the prevalence of numerical methods taking advantage of the ever increasing availability of computer power, approximate analytical solutions are still valuable because they are generally much easier to use and they provide explicit functional dependence of the drug release on various properties of the drug and the matrix system.

Five decades ago, Professor Takeru Higuchi was the first one in the pharmaceutical field to tackle this moving boundary mathematical problem for drug release from matrix systems. Through an elegant yet simple graphic mass-balance analysis employing a linear concentration profile based on the pseudo-steady state assumption, he derived the famous Higuchi equation for the release of a suspended drug from an ointment base (Higuchi, 1961). The amazingly simple analytical expression of the Higuchi equation is remarkable because it was derived without having to directly solve the complex differential equations governing this planar moving boundary problem. He subsequently extended the application of the Higuchi equation to drug release from planar solid dosage forms in both homogeneous and granular matrices and derived additional equations for the release of a suspended drug from spherical matrix systems under a similar pseudo-steady state assumption (Higuchi, 1963). Professor Takeru Higuchi's seminal work laid the foundation for the quantitative analysis of drug release kinetics and the understanding of factors affecting drug release from matrix-type pharmaceutical dosage forms. The purpose of this review is to provide an overview of the theoretical basis of the Higuchi equation and its subsequent improvements and refinements, as well as related approximate analytical solutions to the general but more rigorously formulated moving boundary problem in different geometries. More complicated cases involving heterogeneous matrix, boundary layer effect, finite release medium, surface erosion, and finite dissolution rate will also be discussed. The effect of a swellable matrix will not be addressed here as it will be reviewed by other authors in this issue. Exact solutions will only be cited to demonstrate the accuracy of the approximate solutions. For exact and numerical solutions to this problem, the readers should consult several excellent review articles (Siepmann and Göpferich, 2001; Arifin et al., 2006; Siepmann and Siepmann, 2008).

2. Planar matrix

2.1. The Higuchi equation

The Higuchi equation was originally derived to describe the drug release from an ointment layer containing suspended drug at an initial concentration A (or amount of drug loading per unit volume), which is substantially greater than the solubility of the drug per unit volume in the vehicle matrix, C_s (Higuchi, 1961). The drug concentration gradient in the matrix and the resulting diffusion flux all exist in the direction perpendicular to the interface between the ointment and the release medium thus representing a classical one-dimensional diffusion problem. The assumptions made, either explicitly or implicitly, in deriving the Higuchi equation are summarized as follows:

(a) The initial drug loading, A, is much higher than the drug solubility in the vehicle matrix, C_s ($A \gg C_s$); this is a key assumption which dictates the validity of the pseudo-steady state approach.
(b) The drug dissolution rate at the dispersed drug front in the matrix is rapid comparing with the drug diffusion process; this results in a sharp discontinuity in drug concentration at this moving front.
(c) The concentration gradient of dissolved drug in the planar matrix is essentially constant; this is equivalent to the pseudo-steady state assumption which results in a linear concentration profile of dissolved drug in the partially extracted region.
(d) A semi-infinite geometry applies; this limits the applicability of the analysis to the early stage drug release from one surface of the matrix before the advancing drug front reaches the back surface of the matrix.
(e) The drug diffusion coefficient (D) in the matrix can be treated as a constant.
(f) The distance between suspended drug particles is much smaller than the thickness of the ointment matrix; this reduces or eliminates the lag time to reach a pseudo-steady state.
(g) The area of the ointment matrix layer is sufficiently large that the edge effect can be neglected.
(h) No erosion or swelling occurs in the ointment matrix.
(i) Perfect sink conditions are maintained for the entire duration of drug release.

A schematic concentration profile considered by Professor Takeru Higuchi in deriving his famous equation for drug release from matrix systems containing suspended drug in contact with a perfect sink is represented in Fig. 1, where the diffusion front at a distance h from the ointment surface is shifted by a small distance Δh during a corresponding time interval of drug release, Δt. Also in Fig. 1, the drug concentration profile in the partially extracted region containing dissolved drug is assumed to be linear. This is equivalent to the well known "pseudo-steady state" assumption commonly employed in engineering applications.

By performing a simple graphic mass-balance analysis based on Fig. 1, Higuchi obtained the following equation for the amount of drug depleted or released per unit area, dM, due to the movement of the front by Δh:

$$\mathrm{d}M = (A - C_s)\mathrm{d}h + \tfrac{1}{2}C_s\,\mathrm{d}h = A\,\mathrm{d}h - \tfrac{1}{2}C_s\,\mathrm{d}h \quad (1)$$

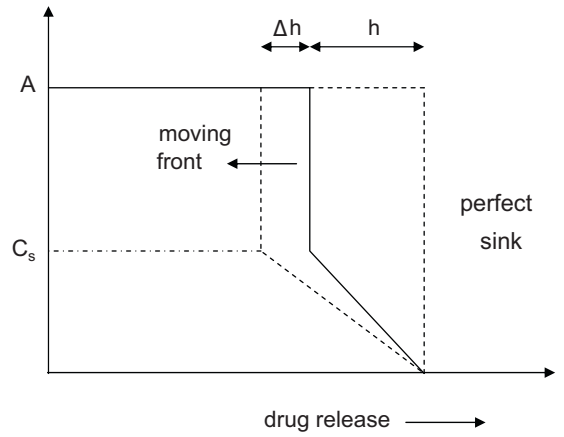

Fig. 1. Schematic concentration profile during drug release from an ointment containing suspended drug as considered by Higuchi (1961).

Also, from Fick's first law, the diffusion flux per unit area can be expressed as:

$$\frac{dM}{dt} = \frac{DC_s}{h} \tag{2}$$

Combining Eqs. (1) and (2) to eliminate dM, Higuchi obtained the following expression describing the progression of the moving front during drug release:

$$h = \sqrt{\frac{DC_s t}{2A - C_s}} \tag{3}$$

From Fig. 1, it is apparent that the total amount of drug release per unit area, M, can also be calculated from a simple mass balance:

$$M = hA - \frac{hC_s}{2} \tag{4}$$

Combining Eqs. (3) and (4), results in the well-known Higuchi equation for drug release per unit area from a planar matrix:

$$M = \sqrt{(2A - C_s)C_s Dt} \tag{5a}$$

this can also be written as:

$$M = \sqrt{2\left(\frac{A}{C_s}\right) - 1}\left[C_s\sqrt{Dt}\right] \tag{5b}$$

This is a remarkably simple equation considering the complexity of the physical situation treated. The amount of drug released per unit surface area from the planar matrix containing a large excess of drug (initial drug loading ≫ drug solubility, or $A \gg C_s$) is proportional to the square root of time with the proportionality constant relating to measurable parameters such as the drug loading, drug solubility, and diffusion coefficient. It should be emphasized that Eq. (5) is strictly valid for the early stage of drug release before the advancing drug front reaches the back surface of the matrix in the case of drug release from one side of the matrix such as from an ointment layer, or before the advancing drug fronts meet at the center of the matrix in the case of drug release from both sides of a solid matrix.

The rate of drug release from a planar matrix per unit area can be obtained by differentiating Eq. (5) with respect to time:

$$\frac{dM}{dt} = \frac{1}{2}\sqrt{\frac{(2A - C_s)C_s D}{t}} \tag{6}$$

Using the assumption of $A \gg C_s$, Eqs. (5) and (6) can be further simplified to:

$$M = \sqrt{2AC_s Dt} \tag{7}$$

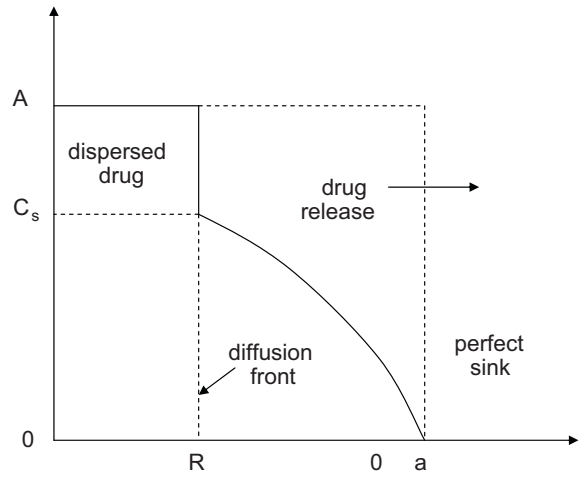

Fig. 2. General schematic concentration profile during the release of a dispersed drug from a planar matrix.

and

$$\frac{dM}{dt} = \sqrt{\frac{AC_s D}{2t}} \tag{8}$$

Rigorously, the real concentration profile in the partially extracted region is non-linear in the planar matrix. Thus, as will be shown later, the pseudo-steady state solution to this diffusion problem exhibits varying degrees of deviation from the exact solution depending on the magnitude of the drug loading to drug solubility ratio.

2.2. Exact analytical solution

For drug release from a planar matrix containing suspended drug at an initial concentration A and an equilibrium drug solubility in the matrix, C_s, the governing diffusion equation describing the kinetics of drug release is given below. This is identical to the problem considered by Higuchi including all the above listed assumptions (except without introducing the pseudo-steady state linear concentration profile and the assumption of $A \gg C_s$):

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{9}$$

where D is the constant diffusion coefficient, $x = 0$ at either the back surface of an ointment layer or the center of a solid matrix, and $x = a$ at the drug-releasing matrix surface. The initial and boundary conditions involved are:

$$R(t) = a, \quad \text{at} \quad t = 0 \tag{10a}$$

$$C(x, t) = 0, \quad \text{at} \quad x = a \tag{10b}$$

$$C(x, t) = C_s, \quad \text{at} \quad x = R(t) \tag{10c}$$

$$D\frac{\partial C}{\partial x} = (A - C_s)\frac{dR}{dt}, \quad \text{at} \quad x = R(t) \tag{10d}$$

Here $R(t)$ is the time dependent position of the moving drug diffusion front. As long as $A > C_s$, the moving boundary condition of Eq. (10d) introduces a nonlinearity which makes this diffusion problem more difficult to solve. The physical situation considered here is depicted in the schematic drawing of Fig. 2, where the sharp concentration discontinuity at the dispersed drug front implies that the drug dissolution is rapid comparing with the drug diffusion process; in other words, the dissolution step is not rate-limiting.

The only exact solution to this moving boundary problem (defined by Eqs. (9) and (10)) was originally derived for melting and solidification (Carslaw and Jaeger, 1959). The first adaptation of this

exact solution to the analysis of drug release from a planar matrix containing dispersed drug was actually Koizumi et al. (1975). Their contribution in this regard has largely been overlooked in the literature over the years as almost all the citations attribute Paul and McSpadden (1976) for adapting this exact solution to drug release. As will be discussed later, Koizumi et al. also provided fairly accurate simplified analytical expressions to this exact solution. The available exact solution for drug release per unit area from such a planar matrix of semi-infinite geometry is:

$$M = \frac{2}{\sqrt{\pi}\,\mathrm{erf}(\xi)}\left[C_s\sqrt{Dt}\right] \tag{11}$$

where

$$\sqrt{\pi}\xi\,\exp(\xi^2)\mathrm{erf}(\xi) = \frac{C_s}{A - C_s} \tag{12}$$

When $A \to C_s$ (as well as when $A < C_s$), the drug is in the dissolved state. In this case, Eq. (11) reduces to:

$$M = \frac{2}{\sqrt{\pi}}\left[C_s\sqrt{Dt}\right] \tag{13}$$

This Eq. (13) is identical to the early time approximation of the exact solution describing the diffusion of dissolved drug from a planar matrix (Baker, 1987).

2.3. Approximate analytical solutions

Based on a double-integration refinement of Goodman's heat balance integral method (Goodman, 1958) due to Volkov and Li-Orlov (1970), Lee (1980) derived approximate analytical solutions for the drug release from matrix systems of different geometries containing dispersed drug, which better approximate the exact solutions at all drug loading to drug solubility ratios (A/C_s) without assuming pseudo-steady state or $A \gg C_s$. The original approach of Goodman is based on the concept that instead of finding a solution satisfying the partial differential equation for heat conduction (identical in form for diffusion) at every point, the partial differential equation can be reduced to an ordinary differential equation by integrating it once over the space domain. This procedure is equivalent to the well-known Karman–Pohlhausen momentum integral method in boundary layer theory (Goodman, 1958; Bankoff, 1964). Briefly, it involves the integration of the diffusion equation once with respect to the space variable followed by the substitution of a suitable approximating temperature (or concentration) profile with undetermined coefficients. The resulting ordinary differential equation can be solved for undetermined coefficients satisfying available boundary conditions. The double-integration method of Volkov and Li-Orlov (1970) employs an additional integration with respect to the space coordinate which further eliminates the spatial derivatives, thereby markedly improves the accuracy of the approximate analytical solutions.

Double integration of Eq. (9) with the application of boundary condition Eq. (10d) yields the following equation (Lee, 1980):

$$a - R(t) = \sqrt{\frac{Dt}{g}} \tag{14}$$

where

$$g = \int_1^0 \mathrm{d}\eta \int_1^\eta \left(1 - \frac{C}{C_s}\right)\mathrm{d}\eta + \frac{1}{2}\left(\frac{A}{C_s} - 1\right) \tag{15}$$

Selecting a trial quadratic approximating concentration distribution of the form:

$$1 - \frac{C}{C_s} = a_1 + a_2\eta + a_3\eta^2 \tag{16}$$

and substituting it into Eqs. (14) and (15), the unknown coefficients a_1, a_2 and a_3 can be determined by applying the boundary conditions defined in Eqs. (10a)–(10d).

Once the concentration profile of Eq. (16) is determined, the amount of drug release can then be calculated. Using the above described approach, Lee (1980) obtained the approximate analytical solution for this moving boundary problem of drug release from a planar matrix in the following form:

$$M = \frac{1 + H}{\sqrt{3H}}\left[C_s\sqrt{Dt}\right] \tag{17}$$

where

$$H = 5\left(\frac{A}{C_s}\right) - 4 + \sqrt{\left(\frac{A}{C_s}\right)^2 - 1} \tag{18}$$

Eq. (17) also predicts the familiar square root of time dependence for the amount of drug release per unit area, similar to the Higuchi equation (Eq. (5)) and the exact solution (Eq. (11)).

These equations are compared in Table 1 at various A/C_s values. It is clear that the deviation from the exact solution is consistently one order of magnitude smaller for the approximate analytical solution of Lee than those of Higuchi's results. In the limit of drug loading approaching the drug solubility ($A \to C_s$) or the dissolved drug case, the Higuchi equation gives a result 11.38% smaller that the exact solution whereas Lee's result is only 2.33% over. In fact, as $A/C_s > 1.04$, Lee's result is within 1% of the exact solution and as $A/C_s > 4.5$, it is virtually identical to the exact solution (within 0.1%).

The selection of approximate concentration profile in this approach can significantly affect the accuracy of the resulting approximate analytical solution. Langford (1973) showed that a trial quadratic profile as adopted in Lee's approach (Eq. (16)) generally gives a higher degree of accuracy in the heat balance integral approach than using higher degree polynomials as trial profiles. Reconfirmation of this aspect particularly for the case of drug loading approaching the drug solubility ($A \to C_s$) or the dissolved drug case has recently been attempted by Lin (2008). Despite this, a related earlier analysis of Lin et al. has been criticized (Lee, 2005).

2.4. Other approximate solutions

Approximate solutions to this problem have also been derived by simplifying the exact solutions. Koizumi et al. (1975) were the first ones to adopt the exact solution of Eqs. (11) and (12) to the analysis of drug release from a planar matrix containing dispersed drug. They further expressed the transcendental functions of Eqs. (11) and (12) into series expansions of ξ followed by rearranging and eliminating ξ terms to yield the following expression:

$$M = \sqrt{\left\{2A - \frac{2}{3}C_s - \frac{1}{45}\frac{C_s^2}{A - C_s} + \frac{2}{189}\frac{C_s^3}{(A - C_s)^2} - \cdots\right\}C_s Dt} \tag{19}$$

Truncating and keeping only the linear term in C_s, Koizumi et al. obtained the following approximate solution:

$$M = \sqrt{2\left(\frac{A}{C_s}\right) - \frac{2}{3}}\left[C_s\sqrt{Dt}\right] \tag{20}$$

They showed that the accuracy of the approximation can be further improved by keeping the first three terms of Eq. (19) and assumed that the higher order terms can be represented by a single term through undetermined coefficients α and β:

$$M = \sqrt{\left(2A - \frac{2}{3}C_s + \frac{\beta C_s^2}{A - \alpha C_s}\right)C_s Dt} \tag{21}$$

Table 1
Comparison of various analyses of drug release from a planar matrix.

A/C_s	$M/\left[C_s\sqrt{Dt}\right]$										
	Exact (Eq. (11))	Higuchi(Eq. (5b))	Error (%)	Lee (Eq. (17))	Error (%)	Koizumi (Eq. (20))	Error (%)	Koizumi (Eq. (22))	Error (%)	Bunge (Eq. (23))	Error (%)
50.668	10.0333	10.0186	−0.15	10.0333	0	10.0334	+0.001	10.0334	+0.001	9.9636	−0.69
13.170	5.0667	5.0337	−0.65	5.0661	−0.013	5.0669	+0.004	5.0668	+0.002	5.0610	−0.11
6.230	3.4336	3.3853	−1.41	3.4317	−0.055	3.4341	+0.015	3.4340	+0.012	3.4254	−0.24
3.806	2.6340	2.5713	−2.38	2.6302	−0.14	2.6354	+0.053	2.6350	+0.038	2.6240	−0.38
2.086	1.8686	1.7812	−4.68	1.8605	−0.44	1.8723	+0.20	1.8708	+0.12	1.8561	−0.67
1.501	1.5205	1.4150	−6.94	1.5101	−0.68	1.5282	+0.51	1.5246	+0.27	1.5084	−0.80
1.246	1.3390	1.2217	−8.76	1.3306	−0.63	1.3510	+0.90	1.3442	+0.39	1.3286	−0.78
1.060	1.1849	1.0579	−10.72	1.1909	+0.51	1.2055	+1.74	1.1892	+0.36	1.1804	−0.38
1.00	1.1284	1.0000	−11.38	1.1547	+2.33	1.1547	+2.33	1.1282	−0.018	1.1284	0

Further requiring that Eq. (21) agrees with the exact solution (Eq. (13)) and its derivatives in the limiting case of dissolved drug (i.e. $A \to C_s$) allows the determination of α and β. From which Koizumi et al. obtained a more accurate approximation:

$$M = \sqrt{\left\{2\left(\frac{A}{C_s}\right) - \frac{2}{3}\left(\frac{(A/C_s) - 0.88}{(A/C_s) - 0.89}\right)\right\}}\left[C_s\sqrt{Dt}\right] \tag{22}$$

Taking a similar but more intuitive approach, Bunge (1998) modified the Higuchi equation to the following form such that it will satisfy the exact solution, Eq. (13), in the limiting case of dissolved drug (i.e. $A \to C_s$):

$$M = \sqrt{2\left\{\frac{A}{C_s} - \left(\frac{\pi - 2}{\pi}\right)\right\}}\left[C_s\sqrt{Dt}\right] \tag{23}$$

Again, all these equations predict M to be linear with the square root of time however the dependencies on A/C_s are not the same. Eqs. (20), (22) and (23) are compared with the exact solution, the Higuchi equation and Lee's approximate analytical solution in Table 1 at various A/C_s values. It is evident that the deviations from the exact solution are also one order of magnitude smaller for these approximate solutions than those of Higuchi's results. Also, Eq. (20) due to Koizumi shows similar accuracy profile as Lee's approximate analytical solution including the 2.33% deviation from the exact solution in the limit of drug loading approaching the drug solubility ($A \to C_s$) as compared with the 11.38% deviation of the Higuchi equation. Only the improved Koizumi solution (Eq. (22)) and the Bunge solution (Eq. (23)) show better agreement with the exact solution in the limit of $A \to C_s$. This is not surprising as both equations were derived by forcing a fit to the exact solution in the limit of $A \to C_s$. Furthermore, as $A/C_s > 1.1$, the deviation from the exact solution for the Bunge solution starts to exceed that of the Lee's approximate analytical solution and becomes progressively worse at higher A/C_s values. In fact as $A/C_s > 50$, the Bunge solution becomes less accurate than the Higuchi equation. Overall, the improved Koizumi equation (Eq. (22)) best approximates the exact solution at all A/C_s values. Again, this is to be expected as Eq. (22) is a direct truncation and fitting to the exact solution. Such simplifying approaches will not work if an exact solution is not available.

3. Spherical matrix

Higuchi also extended his pseudo-steady state analysis to the release of suspended drug from spherical matrix systems (Higuchi, 1963). Assumptions identical to those for the planar matrix were made in his derivation either explicitly or implicitly, except that the pseudo-steady state concentration profile of dissolved drug in the partially extracted region is no longer linear, rather it is of the following form for the spherical geometry:

$$C = C_s\frac{R}{r}\frac{(a - r)}{(a - R)} \tag{24}$$

where r is the radial coordinate, a the radius, and R the time dependent position of the moving drug diffusion front as shown in the schematic drawing of Fig. 3. A and C_s have the same physical meaning as in the planar matrix.

Performing a similar mass balance as in the planar matrix and integrating the diffusion flux equation in the dissolved or partially extracted region, Higuchi obtained the following equations for the release of dispersed drug from a spherical matrix:

$$\frac{M}{M_\infty} = 1 - \left(\frac{R}{a}\right)^3 + \frac{1}{2}\frac{C_s}{A}\left[2\left(\frac{R}{a}\right)^3 - \left(\frac{R}{a}\right)^2 - \left(\frac{R}{a}\right)\right] \tag{25}$$

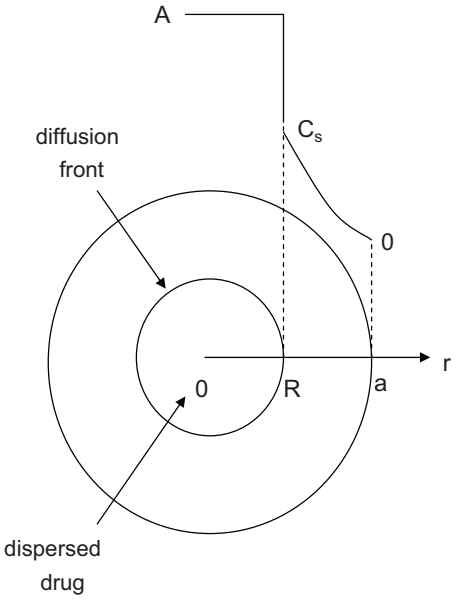

Fig. 3. General schematic concentration profile during the release of a dispersed drug from spherical matrix.

where M_∞ is the total amount of drug release per unit area, and

$$\frac{6C_sDt}{Aa^2} = 2\left(\frac{R}{a}\right)^3 - 3\left(\frac{R}{a}\right)^2 + 1 - \frac{C_s}{A}\left[2\left(\frac{R}{a}\right)^3 - 4\left(\frac{R}{a}\right)^2 + \left(\frac{R}{a}\right) + 1 + \ln\left(\frac{R}{a}\right)\right] \quad (26)$$

When $A \gg C_s$, Higuchi's Eqs. (25) and (26) can be simplified to:

$$\frac{M}{M_\infty} = 1 - \left(\frac{R}{a}\right)^3 \quad (25a)$$

and

$$\frac{6C_sDt}{Aa^2} = 2\left(\frac{R}{a}\right)^3 - 3\left(\frac{R}{a}\right)^2 + 1 \quad (26a)$$

On the other hand, Lee (1980) obtained the following approximate analytical solution for the release of dispersed drug from a spherical matrix based on the double-integration heat balance integral method:

$$\frac{M}{M_\infty} = \left[1 - \left(\frac{R}{a}\right)^3\right]\left(1 - \frac{C_s}{A}\right) + 3\left(1 - \frac{R}{a}\right)\left(\frac{C_s}{A}\right)\left[\alpha_1 + \frac{\alpha_2}{2} + \frac{\alpha_3}{3}\right] \quad (27)$$

with

$$\frac{Dt}{a^2} = \frac{1}{12}\left[6\left(\frac{A}{C_s}\right) - 4 - \alpha_3\right]\left(1 - \frac{R}{a}\right)^2 - \frac{1}{3}\left(\frac{A}{C_s} - 1\right)\left(1 - \frac{R}{a}\right)^3 \quad (28)$$

where

$$\alpha_1 = 1, \quad \alpha_2 = -\alpha_3 - 1 \quad \text{and} \quad \alpha_3 = 1 + \left(\frac{A}{C_s} - 1\right)\left(\frac{R}{a}\right) - \sqrt{\left[1 + \left(\frac{A}{C_s} - 1\right)\frac{R}{a}\right]^2 - 1}$$

Here, the position of the moving front, R/a, is expressed as an implicit function of time in Eqs. (26), (26a) and (28). An elimination of R/a from either the Higuchi's solutions (Eqs. (25) and (26) and (25a) and (26a)) or the Lee's solution (Eqs. (27) and (28)) to obtain the fractional drug release as a direct function of time is very difficult. It is more convenient to correlate the fractional release with time at different R/a values.

Lee (1980) has demonstrated that similar to the case of a planar matrix, Higuchi's pseudo-steady state solution for the spherical

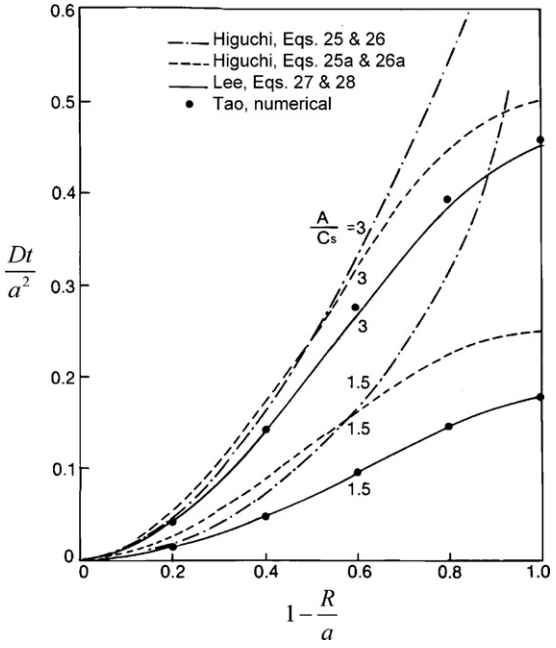

Fig. 4. Comparison of predicted diffusion front position in a spherical matrix at low A/C_s ratios.
Adapted with permission from Lee (1980).

matrix also fails at low A/C_s values (e.g. at $A/C_s = 1.5$ and 3), whereas Lee's solution for the spherical matrix exhibits excellent agreement with the numerical solution of Tao (1967) for an equivalent moving boundary freezing problem (see Fig. 4). Only at large A/C_s values (e.g. $A/C_s = 11$) does the Higuchi solution start to show better agreement with the numerical solution (drawing not shown). More recently, Frenning (2004) presented a careful analysis of both the Higuchi and Lee solutions for the spherical matrix and confirmed that Lee's approximate analytical solutions to the problem are more general than the Higuchi's results at all A/C_s values. And Higuchi and Lee solutions become identical only in the limit of $A/C_s \to \infty$.

Koizumi and Panomsuk (1995) took a very similar approach as Higuchi and obtained parametric equations containing an infinite series in terms of the reduced moving front position. Upon further simplification and partial elimination of the parametric reduced front position, they obtained the following expression for the release of dispersed drug from a spherical matrix:

$$M = 4\pi a^2\left[\sqrt{2(A - C_s)C_sDt} + \frac{4C_sDt}{9a}\left(\frac{C_s}{2A - C_s} - 3\right)\right] \quad (29)$$

This equation expresses the drug release as an explicit function of time and therefore is easier to use than the Higuchi's results of Eqs. (25) and (26). However, as shown by Koizumi and Panomsuk (1995) when comparing their results with the finite-difference numerical solutions, Eq. (29) suffers the same drawback as the Higuchi's results that it fails at low A/C_s values (e.g. $A/C_s = 2$); only at large A/C_s values (e.g. $A/C_s = 10$) does Eq. (29) start to show agreement with the numerical results.

4. Heterogeneous matrix

All the above mentioned results are strictly valid for homogeneous matrices. In treating a heterogeneous matrix such as a compressed or molded granular matrix where diffusion occurs only through the interstitial openings (or pores) produced by the leaching of drug particles, an effective diffusion coefficient defined as D^{liq}/τ should be inserted for D and an apparent solubility εC_s^{liq} should be inserted for C_s, where D^{liq} is the drug diffusion coefficient

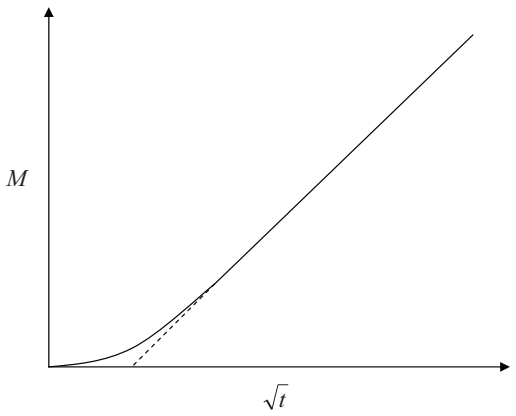

Fig. 5. Schematic representation showing deviation from square root of time dependence of drug release due to boundary layer effect.

in the pore fluid, C_s^{liq} the drug solubility in the pore fluid, ε the porosity expressed as the volume fraction of void space in the matrix, and τ the tortuosity factor defined as the ratio of the effective average path length in the porous matrix to the shortest distance in the direction of diffusion. Higuchi (1963) implicitly introduced such corrections in his analysis of drug release from granular matrices of both planar and spherical geometries. Foster and Parrott (1990) incorporated similar modifications in Lee's approximate analytical solution for planar matrix in analyzing their drug release data from inert and heterogeneous melt matrices. These corrections are necessary to take into account the reduction of drug solubility by the matrix porosity as well as the reduction of drug diffusion coefficient by the tortuosity factor of the matrix (Frenning et al., 2005). It should be noted that the present definition of effective diffusion coefficient in a heterogeneous drug-containing matrix is distinct from the commonly used effective diffusion coefficient defined as $D^{liq}\varepsilon/\tau$ for transport across porous membranes.

5. Boundary layer effect

The drug release from a matrix into an external aqueous medium may be complicated by the existence of a diffusion boundary layer at the matrix surface due to insufficient mixing. This stagnant aqueous boundary layer presents additional mass transfer resistance and causes deviation from the perfect sink assumption. As a result, the amount of drug release from a planar matrix shows an initial deviation (a delay) from the well known square root of time dependence as depicted in Fig. 5. Roseman and Higuchi (1970) incorporated the diffusion boundary layer effect in the Higuchi model based on the pseudo-steady state assumption and $A \gg C_s$. For a planar matrix, Roseman and Higuchi obtained the following analytical expressions:

$$h^2 + \frac{2D\delta h}{D_a} = \frac{2DC_s t}{A} \tag{30}$$

and

$$M = Ah \tag{31}$$

where δ is the thickness of the diffusion boundary layer, D_a the diffusion coefficient in the aqueous medium, and all other parameters have the same meaning as defined earlier. During the initial phase of drug release when the movement of the diffusion front is small (e.g. $h \ll 1$), the h^2 term of Eq. (30) will be much smaller than the h term and therefore can be neglected. This results in:

$$M = \frac{D_a C_s t}{\delta} \tag{32}$$

This predicts an initial release linear in t which will appear to be non-linear (or a delay) in the square root of time plot as illustrated in Fig. 5. As h increases with time, there will be a point when $h^2 >> 2D\delta h/D_a$ and Eq. (30) reduces to:

$$M = \sqrt{2AC_s Dt} \tag{7}$$

which is identical to Eq. (7), the simplified Higuchi equation for $A \gg C_s$. Similar analysis of this problem was also considered by Tojo (1985).

6. Finite release medium

Drug release into a finite release medium is often encountered in real life situation such as in vivo in a body cavity containing a drug delivery device where the accumulation of drug in the external finite volume of release medium tends to retard the subsequent drug release and change the overall drug release profile from that of under a sink condition. The exact analytical solutions to this problem are quite cumbersome and are only applicable to the case of dissolved drug (i.e. $A \leq C_s$). Lee (1980) first obtained approximate analytical solutions to this problem for both the planar and spherical matrices containing dissolved drug, and later extended it to the cylindrical matrices (Lee, 1992) using the double-integration heat balance integral method of Volkov and Li-Orlov (1970). Lee's solution for the planar matrix has the following form:

$$\frac{M}{M_\infty} = (1+\lambda)(1-\theta_b) \tag{33}$$

with

$$\frac{Dt}{a^2} = \frac{3\lambda^2}{4}\left[\ln\theta_b + \frac{1}{2}\left(\frac{1}{\theta_b}\right)^2 - \frac{1}{2}\right] \tag{34}$$

Lee's solution for the cylindrical matrix has the following expression:

$$\frac{M}{M_\infty} = (1+\lambda)(1-\theta_b) \tag{35}$$

with

$$\frac{Dt}{a^2} = \frac{3}{40}\lambda^3\left(\frac{1}{\theta_b}-1\right)^3 + \frac{3(3\lambda+5)}{160}\lambda^2\left(\frac{1}{\theta_b}-1\right)^2 + \frac{3\lambda^2(5-3\lambda)}{80}\left(\frac{1}{\theta_b}-1\right) - \frac{3\lambda^2(5-3\lambda)}{80}\ln\left(\frac{1}{\theta_b}\right) \tag{36}$$

And Lee's solution for the spherical matrix has the following form:

$$\frac{M}{M_\infty} = (1+\lambda) - \frac{\lambda(1+\lambda)}{(1+\lambda)-(1-0.5\delta)^2} \tag{37}$$

with

$$\frac{Dt}{a^2} = -\frac{\delta}{3} - \left(\frac{\lambda+2}{3}\right)\ln\left[\frac{4\lambda+4-(\delta-2)^2}{4\lambda}\right] + \frac{2}{3}(1+\lambda)^{0.5} \times \ln\left[\frac{[2(1+\lambda)^{0.5}+(\delta-2)][(1+\lambda)^{0.5}+1]}{[2(1+\lambda)^{0.5}-(\delta-2)][(1+\lambda)^{0.5}-1]}\right] \tag{38}$$

where the effective volume ration λ is defined as:

$$\lambda = \begin{cases} V/2K\sigma a, & \text{for a planar geometry,} \\ V/K\pi a^2 L, & \text{for a cylinder,} \\ 3V/4K\pi a^3, & \text{for a sphere,} \end{cases}$$

$$\theta_b = \frac{A - KC_b}{A} \quad \text{and} \quad \delta = 1 - \frac{R}{a}$$

Here V is the external finite volume, K the partition coefficient, σ the surface area of each side of the planar matrix, a the half thickness or radius of the matrix, L the length of the cylinder, C_b the bulk

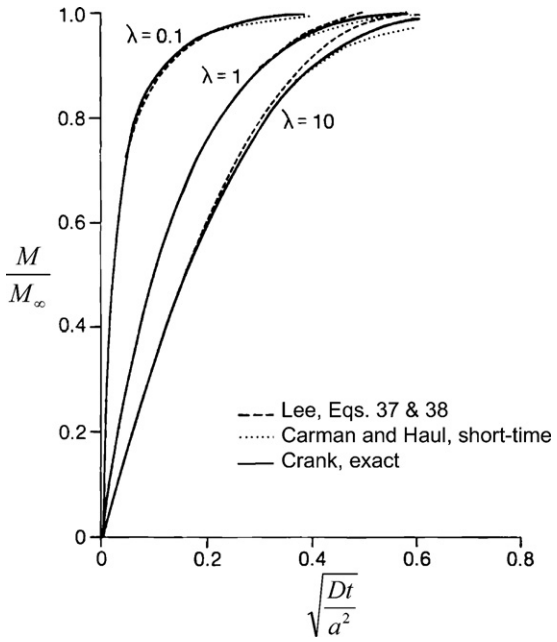

Fig. 6. Predicted fractional release of a dissolved drug ($A \leq C_s$) from a spherical matrix in a finite release medium at different λ values: (—) exact solution (Crank, 1975); (···), short time solution (Carman and Haul, 1954); (- - -) approximate analytical solution of Lee.
Adapted with permission from Lee (1980).

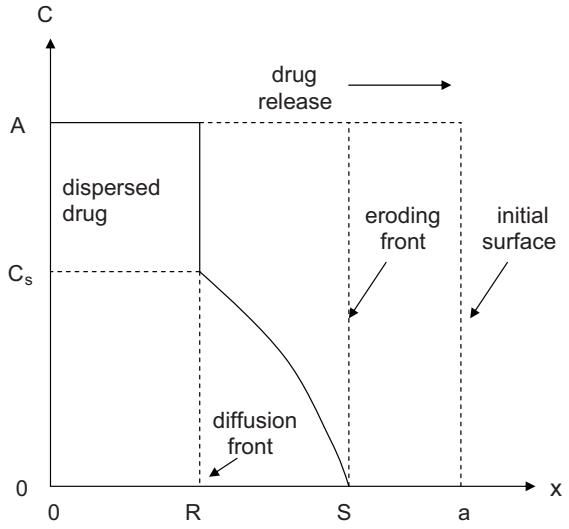

Fig. 7. General schematic concentration profile during diffusional release of a dispersed drug from a planar matrix undergoing surface erosion.
Adapted with permission from Lee (1980).

concentration in the finite release medium, and A the initial drug concentration ($A \leq C_s$); all other parameters have their usual meaning as defined in sections above. The direct elimination of θ_b from either Eqs. (33) and (34) or Eqs. (35) and (36), or the elimination of δ from Eqs. (37) and (38) to express the fractional drug release as a function of time is quite cumbersome. It is more convenient to correlate the fractional release with time at different θ_b or δ values.

Lee (1980, 1992) has shown that solutions obtained this way closely approximate the exact solutions (Crank, 1975) as well as the short time analytical solutions of Carman and Haul (1954) for an equivalent sorption problem. Such a comparison for the spherical case is illustrated in Fig. 6 at various values of the effective volume ratio λ; here the situation of λ greater than 10 corresponds to a near perfect sink condition. It should be emphasized that such a close agreement with the exact solutions, in both the dissolved case ($A \leq C_s$) discussed here and the dispersed cases with low A/C_s values discussed previously (Sections 2 and 3), is characteristic of approximate analytical solutions based on the double-integration heat balance integral method without making the pseudo-steady state assumption. As shown in previous sections, approximate solutions based on the pseudo-steady state assumption including the Higuchi equation tend to fail at low A/C_s values.

Zhou and Wu derived approximate analytical solutions based on the general approach of Higuchi for the case of a planar matrix (Zhou and Wu, 2002) and a spherical matrix (Zhou and Wu, 2003) containing dispersed drug in the presence of both the boundary layer effect and the finite release medium limitation. Because of the complexity of the mathematical problems, they employed the pseudo-steady state approximation in defining the concentration profiles. Similar to other pseudo-steady state approaches, their results are good for large A/C_s values but become less accurate at low A/C_s values (e.g. $A/C_s < 3$).

7. Surface erodible matrix

The release of a dispersed or dissolved drug from an erodible polymer system can be controlled by either a bulk-erosion or a surface-erosion mechanism. The physicochemical characteristics of these erodible drug delivery systems have been discussed in detail by Siepmann and Göpferich (2001). The situation where a planar matrix undergoes surface erosion (Fig. 7) is of special interest because the rate of drug release from such a system with near constant geometry (planar sheet) will be constant. In practice, a diffusional contribution would always be present in addition to surface erosion. In this case, exact analytical solutions are not available due to the inherent nonlinear nature of the problem. Lee (1980) first presented approximate analytical solutions for the drug release from such a surface erodible planar matrix, again using the double-integration heat balance integral method. When the eroding front moves at a constant velocity, Lee obtained the following solutions for the case of $A > C_s$:

$$\frac{M}{M_\infty} = \left[1 - \frac{1}{2}\left(\frac{C_s}{A}\right)\left(1 + \frac{a_3}{3}\right)\right]\delta + \left(\frac{Ba}{D}\right)\left(\frac{Dt}{a^2}\right) \tag{39}$$

and

$$\frac{Dt}{a^2} = \frac{1}{6h_1}\left[3\left(\frac{A}{C_s}\right) - 2 - \frac{a_3}{2}\right]\left[\delta - \frac{1}{2h_1}\ln(1 + 2\delta h_1)\right] \tag{40}$$

with

$$a_3 = \frac{A}{C_s} + \delta h_1 - \sqrt{\left(\frac{A}{C_s} + \delta h_1\right)^2 - (1 + 2\delta h_1)} \tag{41}$$

and

$$h_1 = \frac{1}{2}\left(1 - \frac{A}{C_s}\right)\left(\frac{Ba}{D}\right) \tag{42}$$

Here B is the surface erosion rate constant having the dimension of a velocity; δ is the relative separation between the diffusion and erosion fronts defined as $\delta = (S - R)/a$ (see Fig. 7), where S is the time dependent position of the erosion front defined as $S = a - Bt$ all other parameters have the same meaning as defined in previous sections. The parameter Ba/D is essentially the erosion rate to matrix permeability ratio which is a measure of the relative contribution of erosion and diffusion to drug release. Based on Eqs. (39)–(42), the predicted fractional release from an erodible matrix at $A/C_s = 5$ is plotted in Fig. 8 as a function of time and Ba/D together with the time when the diffusion fronts meet, where the drug release is seen to start with a with a typical first-order kinetics and later shift to a zero-order kinetics. When the erosion process dominates the diffusion process (i.e. large Ba/D values), almost complete zero-order

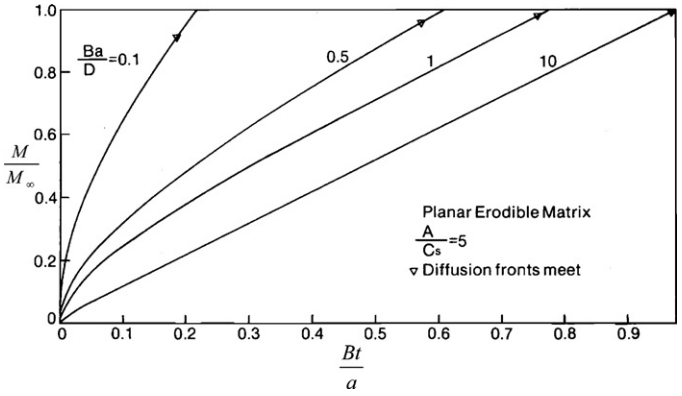

Fig. 8. Predicted fractional release of a dispersed drug from a planar matrix undergoing surface erosion at various ratios of erosion rate to matrix permeability (Ba/D). Adapted with permission from Lee (1980).

drug release will result. Eqs. (39)–(42) also predict that the drug release becomes more zero-order when the drug loading becomes much larger than the drug solubility in the matrix (i.e. $A \gg C_s$; drawing not shown). The appearance of such zero-order release region has been attributed to the synchronization of movement of the diffusing and eroding fronts at large times.

8. Finite dissolution rate

In all the modeling approaches described above, the drug dissolution rate at the dispersed drug front in the matrix is assumed to be rapid comparing with the drug diffusion process resulting in a sharp moving drug front. However, in real systems containing low solubility drugs, the dissolution rate of the suspended drug may become rate limiting which markedly affects the rate of drug release. Such dissolution-controlled drug release kinetics was first modeled by Ayres and Lindstrom (1977a,b) for one-dimensional drug release from a matrix of suspensions into a perfect sink. Through appropriate mass balance, they obtained the governing diffusion equation containing a source term to account for drug dissolution and crystallization processes. They then solved the limiting case relating to the analytical upper bound of the problem using the Laplace transform method. However, the analytical solutions of Ayres and Lindstrom are complicated which contain infinite series and require the determination of roots of transcendental equations. As a result, they resorted to numerical methods to evaluate the drug release kinetics. On the other hand, Chandrasekaran and Paul (1982) developed a simplified model for dissolution-controlled drug release by treating the matrix as a semi-infinite medium. However, the simplified analytical solution obtained is only applicable when there is undissolved drug at every point of the matrix. This arises because Chandrasekaran and Paul's approach does not include a mass balance for the suspended drug in their governing equations.

More recently, Frenning (2003, 2004) provided more rigorous analysis of the release of slowly dissolving drugs from both planar and spherical matrix systems. The drug release and dissolution processes are described by a set of coupled partial differential equations. One is the general diffusion equation with an extra source term resulting from drug dissolution, and the other is a reformulated Noyes–Whitney equation (Noyes and Whitney, 1897) taking into account changes in the surface area of undissolved drug. This latter equation will not be applicable once the dissolution process is complete, similarly the source term in the general diffusion equation will disappear once the dissolution process has ended. These coupled partial differential equations are nonlinear and cannot be solved analytically. In addition to numerical results,

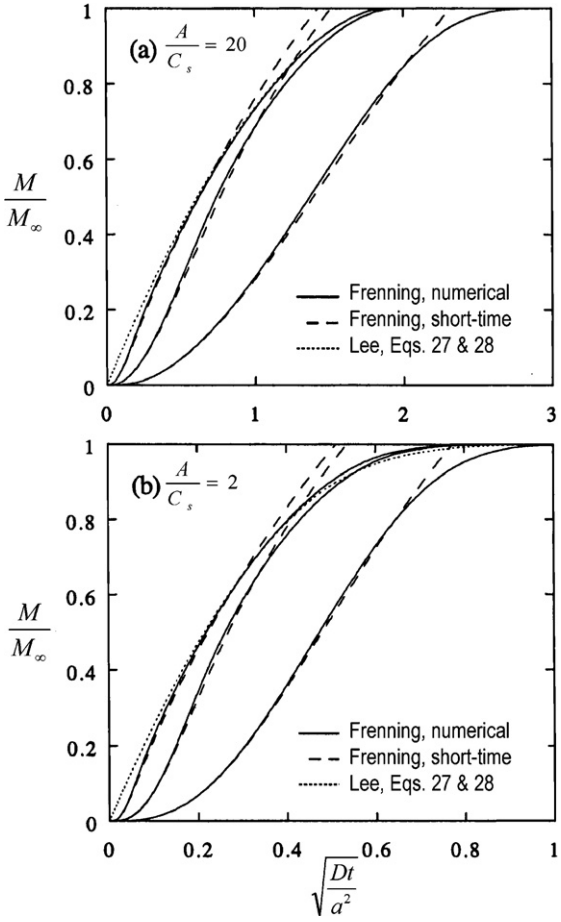

Fig. 9. Comparison of predicted fractional drug release profiles at different A/C_s ratios: (a) 20 and (b) 2, and different dissolution rate constants, κ: from left to right, κ = 1000, 100 and 10.
Adapted with permission from Frenning (2004).

Frenning (2003, 2004) derived approximate analytical solutions for this problem by first linearizing the coupled partial differential equations followed by the application of Laplace transform with the use of residue calculus for the inversion of the Laplace transform. The resulting analytical expression is essentially valid as a short time approximation however it still contains an infinite series which would be cumbersome to calculate for the drug release. A comparison of Frenning's numerical results with his short time approximation is shown in Fig. 9 for a spherical matrix at A/C_s values of 2 and 20 as a function of different dissolution rate constants (κ), where Lee's solution (Eqs. (27) and (28)) for drug release from a spherical matrix under the assumption of rapid dissolution at the drug front is also included as a limiting case. It is clear from Fig. 9 that the release profiles from both the numerical method and the short time approximation show an apparent delay or lag time in the square-root of time plots. This is due to the finite dissolution rate of the slowly dissolving drug where the apparent delay becomes more pronounced as the dissolution rate constant κ decreases. This deviation from the square root of time dependence is very similar to the effect of boundary layer as shown in Fig. 5. It should be noted that the release profiles calculated from Lee's solution (Eqs. (27) and (28)) exhibit no delay in the square-root of time plot. This is expected as Lee's solution was derived under the assumption of rapid dissolution. It is also observed from Fig. 9 that at early times, Frenning's short time approximation agrees well with the numerical results, but deviations start to develop at large times.

9. Conclusions

An overview of approximate analytical solutions to the general moving boundary diffusion problems encountered during the release of a dispersed drug from matrix systems has been provided. In addition to the theoretical basis of the Higuchi equation and its subsequent improvement and refinement, available approximate analytical solutions for the more complicated cases involving heterogeneous matrix, boundary layer effect, finite release medium, surface erosion, and finite dissolution rate have also been discussed. The Higuchi equation and other related approximate analytical solutions based on the pseudo-steady state assumption appear to be reasonably accurate in describing the early stage release of a dispersed drug from matrices of different geometries whenever the initial drug loading is much larger than the drug solubility (e.g. $A/C_s > 10$). However, when the drug loading is not in great excess of the drug solubility (low A/C_s values) or when the drug loading approaches the drug solubility ($A \rightarrow C_s$) which occurs often with drugs of high aqueous solubility, approximate analytical solutions based on the pseudo-steady state assumption tend to fail, with the Higuchi equation for planar geometry exhibiting a 11.38% error as compared with the exact solution. In contrast, approximate analytical solutions to this problem without making the pseudo-steady state assumption, based on either the double-integration heat balance integral method or the direct simplification of available exact analytical solutions, show close agreement with the exact solutions in different geometries, particularly in the case of low A/C_s values or drug loading approaching the drug solubility ($A \rightarrow C_s$). However, the double-integration heat balance integral approach is generally more useful in obtaining approximate analytical solutions especially when exact solutions are not available.

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