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Theoretical analysis of release kinetics of coated tablets containing constant and non-constant drug reservoirs

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ABSTRACT

A detailed theoretical analysis of drug release from a two-dimensional membrane-reservoir tablet into a sink is presented. An entire process of drug release was modeled including a phase of drug release from a constant reservoir followed by a phase of non-constant reservoir. Explicit theoretical solutions were obtained for the first time for the two phases and integrated seamlessly to describe a drug release process from a non-steady state to a steady state. The theoretical solutions were useful for the prediction of release kinetics and analysis of formulation variables as demonstrated by various examples including tablets with varying coating thickness, material properties, drug solubility and partition coefficient, anisotropy and temporal idiosyncrasies.

1. Introduction

Matrix tablets are often coated with a functional polymer such as ethylcellulose or an acrylic polymer to achieve sustained release (Felton, 2002; McGinity, 1997). Coated dosage forms, e.g. coated pellets and mini-tablets are widely used (Ishida et al., 2008; Seattone et al., 1995) to keep drug plasma concentration at therapeutic levels for a prolonged duration, reduce dose frequency, and to minimize side effects. Moreover, good patient compliance to mini-tablets in young children has been demonstrated in a recent clinical trial (Thomson et al., 2009). Owing to their smaller sizes, mini-tablets can be packed in capsule shells as a multi-unit dosage form. They offer advantages in dosing flexibility, ease of swallowing, and lower risk of dose-dumping as compared to regular tablets.

Coated dosage forms are often classified as a membrane-reservoir system when drug diffusion through the coating is a limiting step and drug dissolution is much faster than diffusion. The entire release process of such a system can be divided into two distinctive phases. The first phase is typified by a zero-order release profile due to the presence of a constant reservoir, i.e., the drug concentration in the core is above drug solubility C_s. The second phase is characterized by a first-order release profile owing to a non-constant reservoir, i.e., only dissolved drug exists in the system which is gradually depleted. A noticeable phenomenon, termed temporal idiosyncrasies, is initial burst or time lag in the beginning of drug release from a membrane-reservoir system. Initial burst is induced by drug penetration into the coating, due to long time storage or manufacturing at elevated temperatures, or intentionally prepared by adding a drug in the coating (Baker and Lonsdale, 1974; Kuu et al., 1992). In contrast, lag time is often observed when little or no drug is in the coating and drug diffusion through the coating is slow. In this case a finite interval of time is required to establish a steady state of drug concentration, during which the drug release rate gradually increases towards the steady state value.

The currently available theoretical (exact or approximate) solutions, reported in literature, are only for drug release from one-dimensional (1D) membrane-reservoir dosage forms such as slabs, cylinders and spheres in a perfect sink or a well-stirred external volume (Fan and Singh, 1989 and the references there in). Exact solutions were presented for constant membrane-reservoir 1D slabs, 1D cylinders and spheres in a sink with consideration of time lag and initial burst (Crank, 1975; Good and Lee, 1984). An exact solution for coated spheres with constant reservoir and initial burst in a well-stirred finite volume was also reported (Abdekhodie, 2002). For the 1D dosage forms of non-constant membrane-reservoir, analytical solutions were derived based on a pseudo-steady state assumption (Good and Lee, 1984).

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Despite the usefulness of coated tablets, in particular mini-tablets, up to now no attempt has been made yet to formally present an analytical solution to describe an entire course of drug release from a constant reservoir changing to a non-constant reservoir in a simple but sufficient rigorous manner. This paper is therefore intended to extend the previous analyses of 1D membrane-reservoir dosage forms and to derive analytical solutions for coated tablets with two-dimensional drug release, i.e., release from both the axial and the radial directions. Analytical solutions of drug release from a constant reservoir and a non-constant reservoir were derived separately and then integrated seamlessly as per mass balance. The initial burst and time lag phenomena were included in the model. Anisotropic coating materials or thickness were simulated for sophisticated applications. The analytical solutions were compared with exact solutions of 1D coated slab and cylinder as special cases. They were also verified with the numerical results of a 2D coated tablet calculated with the finite element method based on a partial differential equation of Fick's second law as a general case. Numerical analyses of various examples of coated tablets were conducted using the analytical solutions presented here.

2. Theoretical analysis

A coated membrane-reservoir tablet, as depicted in Fig. 1a, can be viewed as a drug-rich core enveloped in a hollow cylinder (Ω_1) and two circular slabs (Ω_2), connected by a ring (Ω_3) with a rectangular cross-section whose sides have dimensions equal to the thickness of the radial and the axial coating. The concentrations of dissolved drug at the interface between the reservoir and the coating are denoted as C' at the reservoir side and C_m at the membrane side, respectively, which are related by a partition coefficient, $K = C_m/C'$. It is assumed that drug dissolution in the core is much faster than drug diffusion across the membrane coating and thus C' remains constant until all the dispersed drug is dissolved at a critical time, t^*. In the following sections, analytical solutions are derived separately for two phases of a drug release process: a constant reservoir phase from time zero to t^*, during which C' maintains constant at the drug solubility C_s; and a non-constant reservoir phase with C' decreasing with time. For both phases, a uniform distribution of C' in the reservoir is assumed.

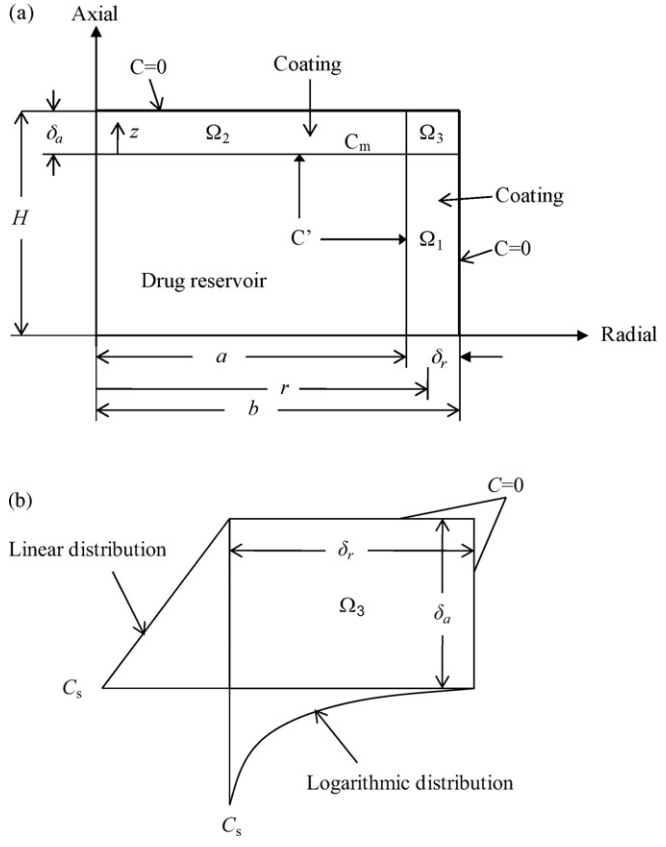

Fig. 1. (a) A schematic diagram for a 2D membrane-reservoir tablet. (b) Boundary conditions for domain Ω_3.

2.1. Analytical solution for a tablet with a constant reservoir

As long as the concentration of dissolved drug in the tablet is maintained at $C' = C_s$ by a constant reservoir, the total amount of drug released from a coated axisymmetric tablet is the sum of the amount of drug released from the cylindrical membrane Ω_1, the end membrane Ω_2 and the ring Ω_3. The amount of drug diffused through a unit area of a planar membrane, i.e., Ω_2, from a non-steady state to a steady state under a constant reservoir condition into a sink is described by Eq. (1) (Crank, 1975):

$$M_a = \frac{D_a K C_s t}{\delta_a} + \frac{2KC_s\delta_a}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\left[1-\exp\left(\frac{-D_a n^2\pi^2 t}{\delta_a^2}\right)\right] + \frac{4C_c\delta_a}{\pi^2}\sum_{m=0}^{\infty}\frac{1-\exp\left(\frac{-D_a(2m+1)^2}{\delta_a^2}\pi^2 t\right)}{(2m+1)^2} \quad (1)$$

where D_a is the drug diffusion coefficient in the axial direction in Ω_2, δ_a is the thickness of Ω_2, C_c is the initial drug loading in the coating. The amount of drug released from a unit length of the cylindrical membrane Ω_1 at $r = b$ is given below (Good and Lee, 1984)

$$M_r = \frac{2\pi KC_s D_r t}{\ln\left(\frac{b}{a}\right)} + 4\pi\sum_{n=1}^{\infty}\left(\frac{KC_s J_0(b\alpha_n)}{J_0(a\alpha_n)-J_0(b\alpha_n)} + C_c\right) \times \frac{J_0(a\alpha_n)\left[1-\exp(-D_r\alpha_n^2 t)\right]}{\alpha_n^2[J_0(a\alpha_n)+J_0(b\alpha_n)]} \quad (2)$$

where α_n's are the positive roots of $J_0(a\alpha_n)Y_0(b\alpha_n) - J_0(b\alpha_n)Y_0(a\alpha_n)$, J_0 and Y_0 are Bessel function of the first and the second kind of order zero, D_r is the radial drug diffusion coefficient in Ω_1, a and b are respectively the inner and outer radius of the cylindrical coating with a thickness $\delta_r = b - a$. Note that anisotropic material properties and different coating thicknesses in the radial and the axial directions are considered in these formulas. In other words, the values of D_r and δ_r can be identical as or different from D_a and δ_a.

An exact solution for drug release through Ω_3 from a non-steady state to a steady state has not yet been reported. Hence an approximate solution based on pseudo-steady state assumption (Higuchi, 1961) is derived

$$C(r) = KC_s\frac{\ln(r/b)}{\ln(a/b)} \quad a \le r \le b \text{ in } \Omega_1 \quad (3)$$

$$C(z) = KC_s\frac{\delta_a - z}{\delta_a} \quad 0 \le z \le \delta_a \text{ in } \Omega_2 \quad (4)$$

where $C(r)$ and $C(z)$ are the drug concentrations in the cylindrical and the planar membranes at a steady state, respectively. Using these two distributions as the boundary conditions shown in Fig. 1b, the concentration distribution in Ω_3 can be determined using the previously reported approach (Zhou et al., 2004):

$$C(r,z) = KC_s\frac{(\delta_a - z)}{\delta_a}\frac{\ln(r/b)}{\ln(a/b)} \text{ in } \Omega_3 \quad (5)$$

The rate of drug release from the two-dimensional ring Ω_3 through a unit area of the membrane at $z=\delta_a$ and a unit length of the cylindrical membrane at $r=b$ is given by

$$\frac{\partial m}{\partial t} = -D_a \frac{\partial C(r,z)}{\partial z}\bigg|_{z=\delta_a} - D_r \frac{\partial C(r,z)}{\partial r}\bigg|_{r=b} \tag{6}$$

The corresponding rate of drug release through the entire corner ring is

$$\frac{\partial M_c}{\partial t} = \int_a^b 2\pi D_a \frac{KC_s \ln(r/b)}{\delta_a \ln(a/b)} r dr - \int_0^{\delta_a} 2\pi D_r \frac{KC_s(\delta_a - z)}{\delta_a \ln(a/b)} dz \tag{7}$$

Integrating Eq. (7) with respect to time t yields the amount of drug released from the ring

$$M_c = \frac{\pi K C_s t}{\ln\left(\frac{a}{b}\right)} \left\{ \frac{D_a}{\delta_a} \left[\frac{a^2-b^2}{2} - a^2 \ln\left(\frac{a}{b}\right) \right] - D_r \delta_a \right\} \tag{8}$$

Since only a half of a tablet is considered above, the total amount of drug released from the entire tablet with a constant reservoir is

$$M_{t1} = 2[\pi a^2 M_a + (H-\delta_a) M_r + M_c] \tag{9}$$

where M_a, M_r, and M_c are given respectively by Eqs. (1), (2) and (8). Eq. (9) describes the cumulative amount of drug released from a constant membrane-reservoir tablet up to time, t^*, when all dispersed drug is dissolved. The t^* can be determined from Eq. (9) based on mass balance: $M^*_{t1} = V(C_0 - C_s)$, where $V = 2\pi a^2 (H-\delta_a)$is the internal volume of the coated tablet and C_0 is the initial drug loading.

In general, the amount of drug released from Ω_3 is small as compared with that from Ω_1 and Ω_2. Thus one may further simplify Eq. (9) by omitting the term M_c to obtain an expression of initial burst or time lag for a coated tablet. By letting $C_c = 0$ and $t \to \infty$ in a simplified format of Eq. (9), equations for the amount of drug released at the steady state and time lag can be derived as

$$M = 2\pi K C_s \left[\frac{a^2 D_a}{\delta_a} + \frac{2(H-\delta_a) D_r}{\ln\left(\frac{b}{a}\right)} \right] (t - t_{\text{lag}}) \tag{10}$$

$$t_{\text{lag}} = \frac{a^2\delta_a/6 + 4(H-\delta_a)\sum_{n=1}^{\infty} J_0(a\alpha_n) J_0(b\alpha_n)/\{\alpha_n^2 [J_0^2(b\alpha_n) - J_0^2(a\alpha_n)]\}}{a^2 D_a/\delta_a + 2(H-\delta_a) D_r/\ln(b/a)} \tag{11}$$

Similarly, letting $C_c = KC_s$ and $t \to \infty$ leads to the following equations for the initial burst case

$$M = 2\pi K C_s \left[\frac{a^2 D_a}{\delta_a} + \frac{2(H-\delta_a) D_r}{\ln\left(\frac{b}{a}\right)} \right] (t + t_{\text{burst}}) \tag{12}$$

$$t_{\text{burst}} = \frac{a^2\delta_a/3 + 4(H-\delta_a)\sum_{n=1}^{\infty} J_0^2(a\alpha_n)/\{\alpha_n^2 [J_0^2(a\alpha_n) - J_0^2(b\alpha_n)]\}}{a^2 D_a/\delta_a + 2(H-\delta_a) D_r/\ln(b/a)} \tag{13}$$

where t_{lag} and t_{burst} are often referred to time lag and initial burst, illustrated in Fig. 2 as the intercepts on the x-axis of the plot of M vs. t.

2.2. Analytical solutions for a tablet with a non-constant reservoir

When all of dispersed drug is dissolved, the reservoir in the tablet becomes non-constant, i.e., C' becomes a variable. As C' is governed by the release rate in both the axial and the radial directions, the total amount of drug released from the tablet is no longer a simple summation of the amount of drug released from Ω_1, Ω_2 and Ω_3. Instead, C' has to be calculated as a function of time based on mass balance from the following equation:

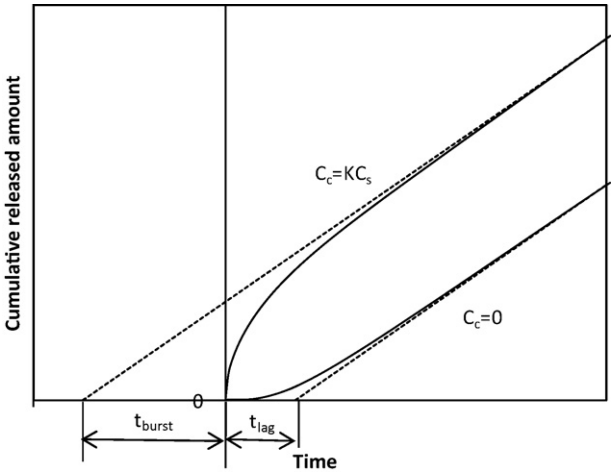

Fig. 2. Illustration of time lag and initial burst.

$$V\frac{dC'}{dt} = -KC' \left\{ \frac{D_r A_r}{a \ln\left(\frac{b}{a}\right)} + \frac{D_a A_a}{\delta_a} + \frac{\pi}{\ln\left(\frac{a}{b}\right)} \left[\frac{D_a}{\delta_a} \left(\frac{a^2-b^2}{2} - a^2 \ln\left(\frac{a}{b}\right) \right) - D_r \delta_a \right] \right\} \tag{14}$$

where $A_r = 4\pi a(H-\delta_a)$ and $A_a = 2\pi a^2$ are the cylindrical area and the areas of two flat ends, respectively. The left hand side of Eq. (14) is the reduced amount of drug in the core and the three terms on the right hand side represent the amount of drug released through Ω_1, Ω_2 and Ω_3, respectively. The variable concentration C' can then be determined

$$C' = C_s \exp\left[-\frac{K}{V} \left(\frac{A_r D_r}{a \ln(b/a)} + \frac{A_a D_a}{\delta_a} + \frac{\pi}{\ln(a/b)} \left\{ \frac{D_a}{\delta_a} \left[\frac{a^2-b^2}{2} - a^2 \ln\left(\frac{a}{b}\right) \right] - D_r \delta_a \right\} \right) t \right] \tag{15}$$

The cumulative amount released from a tablet with a non-constant reservoir tablet is $M_{t2} = V(C_s - C')$ and thus

$$M_{t2} = C_s V \left\{ 1 - \exp\left[\frac{-2KD_r}{a^2 \ln(b/a)} - \frac{KD_a}{\delta_a(H-\delta_a)} - \frac{\pi K}{V} \left(\frac{D_a}{\delta_a} \left(\frac{a^2-b^2}{2\ln(a/b)} - a^2 \right) - \frac{D_r \delta_a}{\ln(a/b)} \right) \right] t \right\} \tag{16}$$

2.3. Complete analytical solution for the entire release process

We now have a complete explicit solution, composed of Eqs. (9) and (16), for a coated tablet initially with a constant reservoir and then a non-constant reservoir. Eq. (9) is used for the period of $t \le t^*$ and Eq. (16) for the period of $t > t^*$. A series of data from M^0 to M^*_{t1} corresponding to $t=0$ to t^* is obtained from Eq. (9); while M^0_{t2} to M'_{t2} is calculated using Eq. (16) with corresponding $t_2 = t - t^*$ to the time at which M_{t2} reaches a plateau. Finally letting $t = t^* + t_2$ and $M = M^*_{t1} + M_{t2}$ results in a data set of a complete release profile.

Due to the relatively complex formulas and the existence of transcendental expressions therein, it would be very tedious to perform numerical analyses by simple software such as Excel spreadsheet. Hence a computer program subroutine was developed and inte-

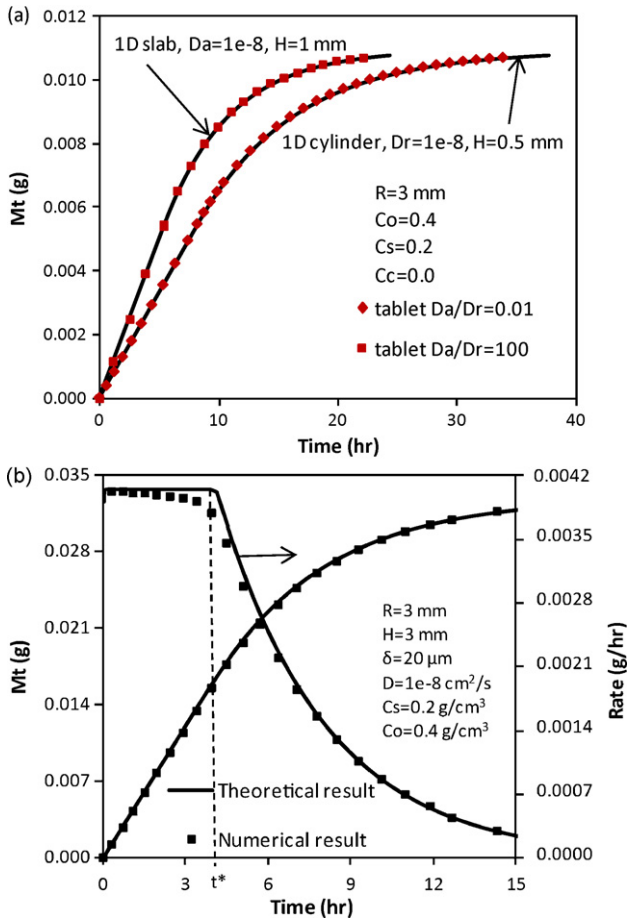

Fig. 3. (a) Comparison of theoretical results of 1D slab and 1D cylinder with this work. (b) Comparison of numerical results of 2D coated tablet with this work.

grated in the platform of a software package (AP-CAD©) for the following presented computations.

3. Results and discussions

3.1. Verification of the derived analytical solution

The derived analytical solution was first compared with well-recognized theoretical solutions of a 1D coated slab and cylinder (Fan and Singh, 1989). As the presented analytical solution includes anisotropic model parameters in the axial and the radial directions, one can easily apply the solution for a 2D tablet to a 1D coated slab by using a radial diffusion coefficient, D_r, much smaller than the axial diffusion coefficient, D_a. Similarly the solution can be applied to a 1D cylinder when the D_a is much smaller than D_r. If the solution for a 2D tablet is correct, it should agree with the previous analytical solutions in the two special cases, i.e., 1D slab and 1D cylinder. As illustrated in Fig. 3a, the release profiles calculated from this work agree very well with the solutions for 1D slab and 1D cylinder.

The cumulative amount of drug released and the release rate for a 2D table obtained in this work is then compared in Fig. 3b with the numerical results calculated using a software package (AP-CAD©) based on the finite element method (Zhou and Wu, 1997; Wu and Zhou, 1998, 1999). A good agreement is shown in Fig. 3b as well. These results suggest that the assumptions made in the derivation are acceptable.

3.2. Numerical analyses using the analytical solution

After having verified by previous analytical solutions for the special cases and by well-established numerical solutions, the utility of the analytical solution for a 2D coated tablet in the prediction of release profiles was demonstrated using several examples presented below.

3.2.1. Influence of coating thickness and tablet dimensions

The influence of coating thickness on the release profiles of a 2D tablet was examined by using the following variables:

$R = 3$ mm; $H = 1.5$ cm; $K = 1$; $C_0 = 0.4$ g/cm^3; $C_s = 0.2$ g/cm^3; $C_c = 0.0$ g/cm^3, $D_a = D_r = 1\text{e}{-8}$ cm^2/s.

The computed release profiles as a function of coating thickness is presented in Fig. 4a. It can be seen that the time corresponding to 50% of drug released, $t_{50\%}$, is almost linearly proportional to the coating thickness in this example.

Fig. 4b presents release profiles of mini-tablets of three different dimensions. With a fixed half thickness of 0.75 mm, drug release rate increases with decreasing tablet radius moderately. However drug release from mini-tablets (Fig. 4b) is much faster than the regular tablets (Fig. 4a). When the tablet dimensions are halved from $H = 1.5$ cm and $r = 3$ mm to $H = 0.75$ mm and $r = 1.5$ mm while all other parameters are kept the same, the time for drug release reaching ~97% of initial loading is about 16 h and 5 h for the reg-

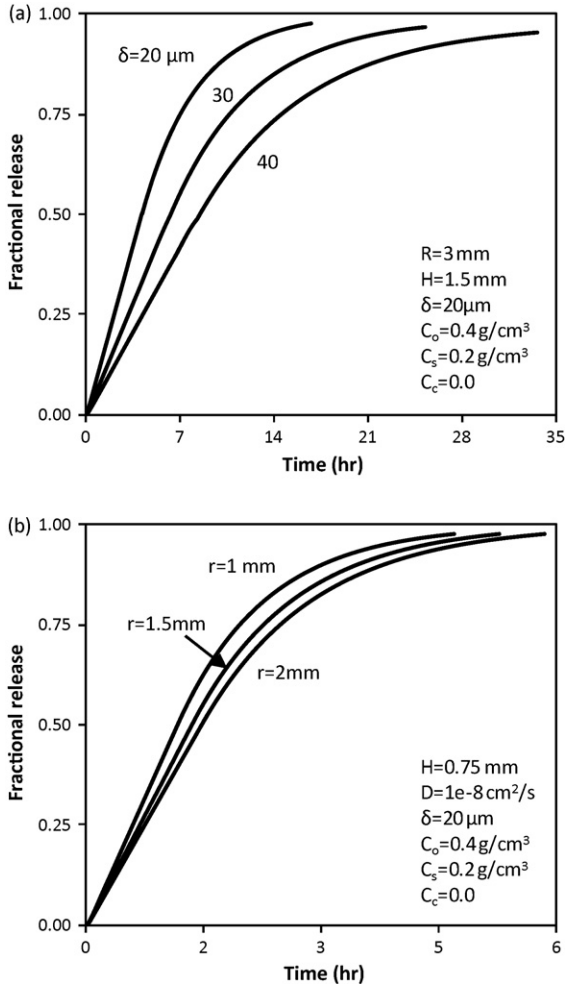

Fig. 4. (a) Effect of coating thickness on the drug release kinetics. (b) Effect of tablet dimension on the drug release kinetics.

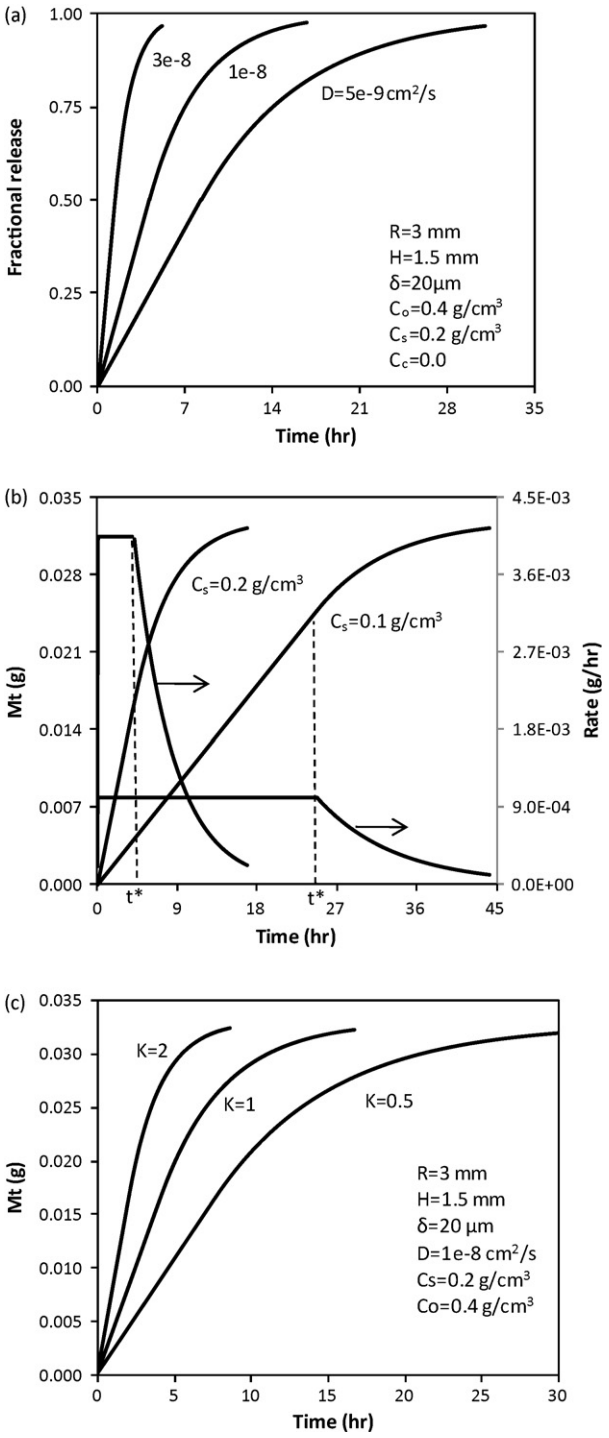

Fig. 5. (a) Effect of drug diffusion coefficient on the drug release kinetics. (b) Effect of drug solubility on the drug release kinetics. (c) Effect of partition coefficient on the drug release kinetics.

ular tablet and the mini-tablet, respectively. This result suggests that a thicker coating or a less permeable coating material should be applied to the mini-tablet if a similar release rate is required. Such adjustment of formulation parameters can be found by further computer simulation.

3.2.2. Effect of drug solubility, diffusion coefficient and partition coefficient

Drug solubility and partition coefficient are material properties reflecting the interactions between drug and excipients, drug and medium, and excipients and medium. Diffusion coefficient of a given drug in a coating, on the other hand, is strongly determined by the base polymer, plasticizer, pore former and curing time. To differentiate the effect of each factor on the drug release profile, a sensitivity analysis by numerical simulation would be very effective. For the analysis of the effect of drug diffusion coefficient, the coating thickness is fixed at $\delta_a = \delta_r = 20\,\mu m$. Fig. 5a portrays that when the diffusion coefficient is varied from 3×10^{-8} to 5×10^{-9} cm^2/s, the release rate decreases significantly, which may result from the use of different amounts of a pore former in the coating formulation (Siepmann et al., 2007).

The effect of drug solubility on the profiles of cumulative amount released and release rate is depicted in Fig. 5b. For the tablets with the same initial drug loading, the higher the solubility, the shorter the zero-order release period and the smaller the t^*. It is conceivable that if $C_s = C_0$ the entire release profile will be the first order; and if $C_s \ll C_0$ a zero-order release profile will be dominant. As can be inferred from the results shown in Fig. 5c, the release rate increases with increasing partition coefficient due to a higher driving force solute diffusion towards the coating. Apparently the dependence of $t_{50\%}$ on partition coefficient K is non-linear in this particular case.

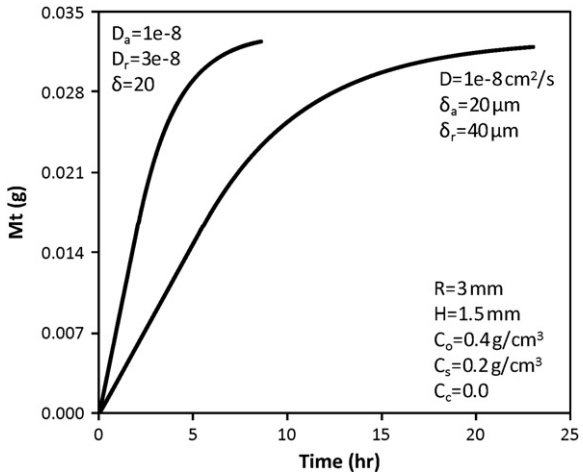

Fig. 6. Influence of different radial and axial coating materials and thicknesses.

3.2.3. Anisotropic coated tablets

In most cases the coating material and thickness are isotropic and uniform. However, defects and anisotropy in properties may occur during manufacturing or perhaps required by sophisticated applications. The application of the analytical solution derived in this work is demonstrated in Fig. 6 by analyzing two examples, one with different diffusion coefficients and the other with different coating thicknesses in the radial and the axial directions.

4. Conclusions

An analytical solution for drug release from 2D membrane-reservoir tablets has been derived and verified by numerical results. This solution has an explicit expression containing parameters associated with the physicochemical properties of ingredients, the formulation and the preparation of tablets. It can be readily used to predict release profiles of coated tablets with varying drug and excipient properties and to analyze their effects using computer software. It can predict release profiles with or without lag time and/or initial burst phenomena. It is able to handle coated tablets with different diffusion coefficient and coating thickness in the radial and the axial directions for sophisticated applications. The results in this work have demonstrated that various scenarios of

coated tablets can be analyzed and the presented analytical solution is effective for the prediction of release kinetics and for the design of this type of oral dosage form.

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