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Controlled release from a coated particle – Effects of initial conditions and methods of solution

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Abstract

The exact effects of three initial conditions – time lag, burst release, and steady state concentration profile – on drug release from a coated spherical matrix containing dissolved drug into a finite amount of well stirred elution liquid have been analyzed. The degree of the effect of initial conditions on drug release depends on the diffusivity ratio of coating layer to core matrix and the radius ratio of the coated particle to the core. For the case where drug concentration in the core is dependent on time only, the differences between the exact and the pseudo-steady state solutions are computed, therefore, pros and cons for the pseudo-steady state solution, which is simple and direct, can be anchored on exact comparison.

Keywords: Drug release; Initial condition; Exact solution; Pseudo-steady state

1. Introduction

A reservoir-type controlled release particle consists of a core and coating. The core may be a pure solid drug, a matrix with dissolved drug, or a matrix with dispersed drug. The coating can be of different material and thickness. Drug release from a particle then depends on the drug, the core, the coating characteristics, and the environment into which the drug is released.

One of the conditions that is always present in the problem of drug release is the initial condition. For particles that are put to drug release soon after the completion of coating, the drug concentration in the coating is negligible and time will be taken to establish a concentration profile in the coating layer. This is the time lag problem. For particles that are either stored for a period of time or fabricated at elevated temperature, the coating layer may become saturated with drug and thus the initial drug release rate will be very large. This is the burst release problem. Analytical solutions for several problems of drug release from a coated particle containing dissolved drug are available in the literature. For example, exact solutions for the time lag and burst release problems each with the conditions of constant drug concentrations at both surfaces of the coating layer have been given by Carslaw and Jaeger (1959); exact

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solutions for time lag problems with the conditions that drug concentration in the core is time dependent but space independent and that the elution liquid is either finite or a perfect sink have been provided by Christensen et al. (1982); and exact solutions for time lag problems with the conditions that drug concentration in the core is time and space dependent and that the elution liquid is either finite or a perfect sink have been given by Lu and Chen (1993). Time lag and burst release problems with the conditions that the drug concentration in the core is constant and that the elution liquid acts as a perfect sink have been reviewed by Baker and Lonsdale (1974) and Good and Lee (1984). A matter of present concern is then the exact extents of the effects of different initial conditions on drug release. Such exact comparison has not been made so far. Knowing exact answers to the problems may be important when questions regarding the initial dosages arise.

In contrast to the exact solutions cited above, an approximate solution for drug release from a coated pure drug bead has been solved by Lu and Lee (1992) using pseudo-steady state assumption. Lu (1994) generalized the above solution by introducing dimensionless variables and parameters into the problem. The results were then modified to the cases of time lag and burst release. A matter of present concern is how the initial condition and particle conditions interact on the exact difference between the pseudo-steady state solution and the exact solution. A preliminary comparison has been made for the time lag case (Lu, 1994). It appears that a thorough comparison, if made available, will provide precise information for the interaction of initial conditions and particle condition on drug release.

The purpose of this paper is to provide exact answers to the questions raised above. First, the release of drug from a spherical coated particle containing dissolved drug and releasing drug through a stable, permeable, and non-swelling coating layer into a well stirred elution liquid of a given volume is analyzed exactly for different initial conditions. The effects of initial conditions and particle conditions on drug release are then compared. Second, for the case that drug concentration in the core is dependent on time only, the pseudo-steady state solutions and the exact solutions are compared for different initial conditions and particle conditions.

2. Problems and basic equations

Drug release from a coated particle of radius a containing a core of radius b is considered. The core is either a pure dissolved drug or a matrix with dissolved drug. Drug release takes place in a well stirred elution liquid of volume V_e. The basic dimensionless equations for the core matrix and for the coating layer are as follows

$$\frac{\partial(\eta\theta_m)}{\partial\tau} = \frac{\partial^2(\eta\theta_m)}{\partial\eta^2}, \quad 0 \le \eta < 1, \tag{1a}$$

$$\frac{\partial(\eta\theta_f)}{\partial\tau} = D_r\frac{\partial^2(\eta\theta_f)}{\partial\eta^2}, \quad 1 < \eta < l. \tag{1b}$$

The dimensionless quantities in the above equations are defined as follows

$$\theta_m \equiv \frac{C_m}{C_0}, \quad \theta_f \equiv \frac{C_f}{C_0}, \quad \theta_e \equiv \frac{C_e}{C_0}, \tag{2a,b,c}$$

$$\tau \equiv \frac{D_m t}{b^2}, \quad \eta \equiv \frac{r}{b}, \tag{2d,e}$$

$$D_r \equiv \frac{D_f}{D_m}, \quad V_r \equiv \frac{V_e}{4\pi a^3/3}, \quad l \equiv \frac{a}{b}, \tag{2f,g,h}$$

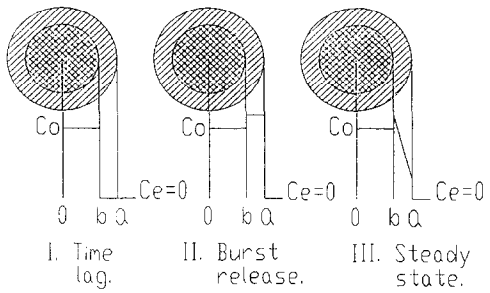

Fig. 1. Initial conditions.

where θ and C denote, respectively, the dimensionless concentration and concentration of drug, with subscripts m, f, and e representing the core, coating, and elution liquid. C_0 is the initial loading concentration of drug in the core. D_r denotes the ratio of drug diffusivity in coating layer, D_f, to that in the core matrix, D_m. V_r is the volume ratio of the elution liquid to the particle. η is the dimensionless radius and l the radius ratio.

Initially, the particle is in the following conditions

$$\theta_m(\eta,0) = 1, \tag{3a}$$

$$\theta_f(\eta,0) = \theta_{f,0}(\eta), \tag{3b}$$

$$\theta_e(0) = 0, \tag{3c}$$

where $\theta_{f,0}(\eta)$ represents the initial drug concentration profile in the coating layer. According to Fig. 1, $\theta_{f,0}(\eta)$ are expressed by:

$$\text{IC I, time lag case: } \theta_{f,0}(\eta) = 0 \tag{4a}$$

$$\text{IC II, burst release case: } \theta_{f,0}(\eta) = 1/K_b \tag{4b}$$

$$\text{IC III, SSCD case: } \theta_{f,0}(\eta) = (l-\eta)/[K_b\eta(l-1)] \tag{4c}$$

where IC denotes initial condition and SSCD represents the steady state concentration distribution. SSCD is a case setup for investigating the effect of the method of solution (exact vs pseudo-steady state) on drug release.

The boundary conditions are:

$$\theta_m(0,\tau) \text{ is finite,} \tag{5a}$$

$$K_b\theta_f(1,\tau) = \theta_m(1,\tau), \tag{5b}$$

$$\left(\frac{\partial\theta_m}{\partial\eta}\right)_{\eta=1} = D_r\left(\frac{\partial\theta_f}{\partial\eta}\right)_{\eta=1}, \tag{5c}$$

$$K_a\theta_f(l,\tau) = \theta_e(\tau), \tag{5d}$$

$$\left(\frac{\partial\theta_f}{\partial\eta}\right)_{\eta=l} = -\frac{V_r l}{3D_r}\frac{\partial\theta_e}{\partial\tau}. \tag{5e}$$

K_a and K_b are the partition coefficients which are assumed to be constant.

3. Solutions

The solutions are presented as follows. Sections 3.1–3.3 show exact solutions for IC I, II, and III. These exact solutions are reduced to the case $D_m \gg D_f$, i.e., $D_r \to 0$, in section 3.4. In section 3.5, for the purpose of comparison, the pseudo-steady state solutions from Lu (1994) are rewritten in terms of the notations used in this work.

3.1. Exact solutions for IC I, time lag case

Solutions for this case have been given by Lu and Chen (1993). For the sake of completeness, they are listed in the Appendix.

3.2. Exact solutions for IC II, burst release case

The method of solution used is analogous to that used in section 3.1. Exact solutions are shown below. The dimensionless concentrations are:

$$\theta_m(\eta,\tau) = \frac{K_b + l^3 - 1}{K_b + l^3 - 1 + V_r K_a l^3} + \frac{V_r K_a l^3}{3} \sum_{n=1}^{\infty} \frac{\beta_n \sin\left(\sqrt{D_r}\beta_n \eta\right) \exp\left(-D_r \beta_n^2 \tau\right)}{\eta f(\beta_n)}, \tag{6a}$$

$$\theta_f(\eta,\tau) = \frac{K_b + l^3 - 1}{K_b\left(K_b + l^3 - 1 + V_r K_a l^3\right)} + \frac{V_r K_a l^3}{3 K_b D_r} \sum_{n=1}^{\infty} \frac{\exp\left(-D_r \beta_n^2 \tau\right)}{\eta f(\beta_n)} \cdot \left\{ \left[K_b \sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) + \left(D_r - K_b\right) \sin\left(\sqrt{D_r}\beta_n\right) \right] \sin\left[(\eta - 1)\beta_n\right] + D_r \beta_n \sin\left(\sqrt{D_r}\beta_n\right) \cos\left[(\eta - 1)\beta_n\right] \right\}, \tag{6b}$$

$$\theta_e(\tau) = \frac{K_a\left(K_b + l^3 - 1\right)}{K_b\left(K_b + l^3 - 1 + V_r K_a l^3\right)} + \frac{V_r K_a^2 l^2}{3 K_b D_r} \sum_{n=1}^{\infty} \frac{\exp\left(-D_r \beta_n^2 \tau\right)}{f(\beta_n)} \cdot \left\{ \left[K_b \sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) + \left(D_r - K_b\right) \sin\left(\sqrt{D_r}\beta_n\right) \right] \sin\left(\delta\beta_n\right) + D_r \beta_n \sin\left(\sqrt{D_r}\beta_n\right) \cos\left(\delta\beta_n\right) \right\}. \tag{6c}$$

Fractional cumulative release and dimensionless release rate are:

$$F(\tau) = 1 + \frac{K_a V_r l^2\left(K_b + l^3 - 1 + K_a V_r l^3\right)}{3 D_r\left(K_b + l^3 - 1\right)} \sum_{n=1}^{\infty} \frac{\exp\left(-D_r \beta_n^2 \tau\right)}{f(\beta_n)} \cdot \left\{ \left[K_b \sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) + \left(D_r - K_b\right) \sin\left(\sqrt{D_r}\beta_n\right) \right] \sin\left(\delta\beta_n\right) + D_r \beta_n \sin\left(\sqrt{D_r}\beta_n\right) \cos\left(\delta\beta_n\right) \right\}, \tag{7a}$$

$$R(\tau) = \frac{-K_a V_r l^2\left(K_b + l^3 - 1 + K_a V_r l^3\right)}{3\left(K_b + l^3 - 1\right)} \sum_{n=1}^{\infty} \frac{\beta_n^2 \exp\left(-D_r \beta_n^2 \tau\right)}{f(\beta_n)} \cdot \left\{ \left[K_b \sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) + \left(D_r - K_b\right) \sin\left(\sqrt{D_r}\beta_n\right) \right] \sin\left(\delta\beta_n\right) + D_r \beta_n \sin\left(\sqrt{D_r}\beta_n\right) \cos\left(\delta\beta_n\right) \right\}. \tag{7b}$$

$f(\beta_n)$ and β_n in the above equations are found by Eq. A3 and A4.

The above solutions are checked by reducing the equations to a special case for which the solution is available in the literature. The special case used is that core matrix and coating layer are completely the same, i.e., $D_r = 1$, and $K_b = 1$. This is the case of a particle without coating. The fractional cumulative release for this special case is found as

$$F(\tau) = \text{Eq.7a}|_{D_r=1,K_b=1} = 1 - \frac{V_r K_a(1+V_r K_a)}{3} \sum_{n=1}^{\infty} (l\beta_n)^2 \sin(l\beta_n)\exp(-\beta_n^2\tau) \Big/ \left\{ \left[\frac{1}{2\beta_n} + \frac{(V_r K_a + 1)l^2\beta_n}{2} \right] \sin(l\beta_n) - \left(\frac{l}{2} - \frac{V_r K_a l^3 \beta_n^2}{6} \right) \cos(l\beta_n) \right\}, \tag{8}$$

where β_n are the non-zero roots of the following equation which is reducd from Eq. A4

$$\left[1 + \frac{V_r K_a}{3}(l\beta_n)^2 \right] \sin(l\beta_n) - l\beta_n \cos(l\beta_n) = 0. \tag{9a}$$

By writing $q_n \equiv l\beta_n$ and $\alpha \equiv V_r K_a/3$, the above equation is rewritten as:

$$\tan(q_n) = \frac{3q_n}{3 + \alpha q_n^2}. \tag{9b}$$

Eq. 8 is rearranged into the following form by dividing both the numerator and the denominator of the second term on the right-hand side by $\cos(l\beta_n)$ and by substituting into it the expression for $\tan(q_n)$ in Eq. 9b:

$$F(\tau) = 1 - \sum_{n=1}^{\infty} \frac{6\alpha(1+\alpha)q_n^2 \exp(-q_n^2\tau/l^2)}{9 + 9\alpha + \alpha^2 q_n^2}. \tag{10}$$

This is the equation of fractional cumulative release for an uncoated spherical matrix releasing drug in a finite volume of well stirred elution liquid. Eq. 10 and 9b agree with Eq. 6.31 and 6.30 of Crank (1975).

3.3. Exact solution for IC III, SSCD case

This case is different from the pseudo-steady state solution to be discussed in section 3.5 in that steady state concentration distribution exists only initially while the latter assumes a steady state concentration profile in coating layer at any instant throughout the release of drug. To determine the difference between the pseudo-steady state solution and the solution of the present case for which an analytical solution is unknown, this case is solved by using the method analogously to that used in section 3.1. The expressions for drug concentrations are found as follows

$$\theta_m(\eta,\tau) = \frac{K_b - 1 + l(l+1)/2}{K_b + l^3 - 1 + V_r K_a l^3} + \frac{l}{\delta} \sum_{n=1}^{\infty} \frac{\exp(-D_r\beta_n^2\tau)}{\eta\beta_n^2 f(\beta_n)} \cdot \left[\beta_n + (1 + V_r K_a l^2 \beta_n^2/3)\sin(\delta\beta_n) - l\beta_n \cos(\delta\beta_n) \right] \sin\left(\sqrt{D_r}\beta_n \eta\right), \tag{11a}$$

$$\theta_r(\eta,\tau) - \frac{K_b - 1 + l(l+1)/2}{K_b(K_b + l^3 - 1 + V_r K_a l^3)} + \frac{l}{K_b D_r \delta} \sum_{n=1}^{\infty} \frac{\exp(-D_r\beta_n^2\tau)}{\eta\beta_n^2 f(\beta_n)} \cdot \left\{ \left[D_r \sin\left(\sqrt{D_r}\beta_n\right) + K_b\left(\sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) - \sin\left(\sqrt{D_r}\beta_n\right)\right) \right] \sin[(\eta - 1)\beta_n] \right.$$

$$+D_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\cos[(\eta-1)\beta_n]-D_r(1+V_rK_al^2\beta_n^2/3).\sin\left(\sqrt{D_r}\beta_n\right)\sin[(\eta-l)\beta_n]$$
$$-lD_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\cos[(\eta-l)\beta_n]\Big\}, \tag{11b}$$

$$\theta_e(\tau)=\frac{K_a(K_b-1+l(l+1)/2)}{K_b(K_b+l^3-1+V_rK_al^3)}+\frac{K_a}{K_bD_r\delta}\sum_{n=1}^{\infty}\frac{\exp(-D_r\beta_n^2\tau)}{\beta_n^2f(\beta_n)}$$
$$\cdot\left\{\left[D_r\sin\left(\sqrt{D_r}\beta_n\right)+K_b\left(\sqrt{D_r}\beta_n\cos\left(\sqrt{D_r}\beta_n\right)-\sin\left(\sqrt{D_r}\beta_n\right)\right)\right]\sin(\delta\beta_n)\right.$$
$$\left.+D_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\cos(\delta\beta_n)-lD_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\right\}. \tag{11c}$$

The equations for fractional cumulative release and dimensionless release rate are as follows:

$$F(\tau)=1+\frac{K_b+l^3-1+V_rK_al^3}{\delta D_r(K_b-1+l(l+1)/2)}\sum_{n=1}^{\infty}\frac{\exp(-D_r\beta_n^2\tau)}{\beta_n^2f(\beta_n)}$$
$$\cdot\left\{\left[D_r\sin\left(\sqrt{D_r}\beta_n\right)+K_b\left(\sqrt{D_r}\beta_n\cos\left(\sqrt{D_r}\beta_n\right)-\sin\left(\sqrt{D_r}\beta_n\right)\right)\right]\sin(\delta\beta_n)\right.$$
$$\left.+D_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\cos(\delta\beta_n)-lD_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\right\}, \tag{12a}$$

$$R(\tau)=\frac{K_b+l^3-1+V_rK_al^3}{\delta(K_b-1+l(l+1)/2)}\sum_{n=1}^{\infty}\frac{\exp(-D_r\beta_n^2\tau)}{f(\beta_n)}$$
$$\cdot\left\{\left[D_r\sin\left(\sqrt{D_r}\beta_n\right)+K_b\left(\sqrt{D_r}\beta_n\cos\left(\sqrt{D_r}\beta_n\right)-\sin\left(\sqrt{D_r}\beta_n\right)\right)\right]\sin(\delta\beta_n)\right.$$
$$\left.+D_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\cos(\delta\beta_n)-lD_r\beta_n\sin\left(\sqrt{D_r}\beta_n\right)\right\}. \tag{12b}$$

$f(\beta_n)$ and β_n in the above equations are found by Eq. A3 and A4.

3.4. Exact solutions for IC I, II, III with $D_r \to 0$

When $D_m \gg D_f$, then $D_r \to 0$, drug release is controlled by the coating layer and drug concentration in the core may be taken as time dependent and space independent. A new dimensionless time, τ_f, defined by

$$\tau_f = D_f t/b^2 = D_r\tau \tag{13}$$

was used to eliminate D_m from the problem. Then $F_i(\tau_f)$, i = I, II, III, exact fractional cumulative release for IC I, II, III with $D_r \to 0$, were derived respectively from Eq. A1, 7a and 12a. The results are:

$$F_I(\tau_f)=[\text{Eq.A1}]_{D_r\to 0}=1+(K_b+l^3-1+V_rK_al^3)\sum_{n=1}^{\infty}\frac{\beta_n\exp(-\beta_n^2\tau_f)}{3N(\beta_n)}, \tag{14a}$$

$$F_{II}(\tau_f)=[\text{Eq.7a}]_{D_r\to 0}=1-\frac{V_rK_al^2(K_b+l^3-1+V_rK_al^3)}{K_b+l^3-1}\sum_{n=1}^{\infty}\frac{\exp(-\beta_n^2\tau_f)}{3N(\beta_n)}$$
$$\cdot\left[(1-K_b\beta_n^2/3)\sin(\delta\beta_n)+\beta_n\cos(\delta\beta_n)\right], \tag{14b}$$

$$F_{III}(\tau_f)=[\text{Eq.12a}]_{D_r\to 0}=1-\frac{K_b+l^3-1+V_rK_al^3}{k_b-1+l(l+1)/2}\sum_{n=1}^{\infty}\frac{\exp(-\beta_n^2\tau_f)}{\delta\beta_n^2N(\beta_n)}$$
$$\cdot\left[(1-K_b\beta_n^2/3)\sin(\delta\beta_n)+\beta_n\cos(\delta\beta_n)-l\beta_n\right], \tag{14c}$$

where

$$N(\beta_n) = \cos(\delta\beta_n)\left[\left(\frac{K_b l}{3} + \frac{K_b}{6} + \frac{l\delta}{2} + \frac{V_r K_a}{3} l^2 + \frac{V_r K_a}{6} l^3\right)\beta_n - \frac{V_r K_a K_b l^2 \delta}{18}\beta_n^3\right] + \sin(\delta\beta_n)\left[\frac{l^2+1}{2} + \frac{V_r K_a l^2}{3} - \frac{K_b}{3} - \left(\frac{K_b l\delta}{6} + \frac{V_r K_a l^2 \delta}{6} + \frac{2V_r K_a K_b l^2}{9}\right)\beta_n^2\right], \quad (15a)$$

and β_n are the non-zero roots of Eq. A4 at the limit, i.e.,

$$\cos(\delta\beta_n)\left[\left(\frac{K_b l}{3} + \frac{V_r K_a l^2}{3}\right)\beta_n^2 - \delta\right] + \sin(\delta\beta_n)\left[\frac{1}{\beta_n} + \left(l + \frac{V_r K_a l^2}{3} - \frac{K_b}{3}\right)\beta_n - \frac{V_r K_a K_b l^2}{9}\beta_n^3\right] = 0. \quad (15b)$$

3.5. Pseudo-steady state solutions, $D_r \to 0$

For this case C_m is dependent on time only. One such case is a coated pure drug bead releasing drug in a given amount of well stirred elution liquid. For this problem, Lu (1994) presented a pseudo-steady state solution in dimensionless form using dimensionless groups Y, X_1, X, p, s, ρ_u/C_s which are defined in the Nomenclature. The case of present concern is that the initial loading concentration of the dissolved drug is equal to the saturation concentration of the drug and that the elution liquid is pure initially. Then, by setting ρ_u/C_s to 1, the dimensionless cumulative release, Y, by pseudo-steady state solution is (Lu, 1994):

$$Y = \frac{s}{p(s+1)}\left[1 - \exp\left(-\frac{(s+1)}{s} p X_1\right)\right], \quad (16)$$

where $X_1 = X + m$ and $m = -1/6$, $a/(3b)$, 0 for IC I, II, and III. As $F = Y/Y_\infty$, and $Y_\infty = [s(\rho_u/C_s)]/[p(s+1)]$ (Lu, 1994), Y and F are related by the following equation

$$Y = F\frac{V_r l^2}{3(l-1)(1 + K_a V_r l^3/K_b)}. \quad (17a)$$

Also, from the definition of X, X and τ_f are related by

$$X = \frac{\tau_f}{K_a\left(\frac{a}{b} - 1\right)^2}. \quad (17b)$$

Thus, Eq. 16 written in terms of F, τ_f, m is

$$F_{(P.S.S.)_i}(\tau_f) = 1 - \exp\left[-\frac{3(K_b + V_r K_a l^3)}{V_r K_a K_b l^2 (l-1)}(\tau_f + mK_a(l-1)^2)\right]. \quad (18)$$

Subscript $(P.S.S.)_i$, i = I, II, III, represents solutions obtained by pseudo-steady state approach for initial conditions I, II, and III.

Table 1
The equations used for the figures

Figure	Legend	Equation no. for	
		F	R
2–5	I	(A1)	(A2)
	II	(7a)	(7b)
	III	(12a)	(12b)
6, 7	I	(14a)	
	II	(14b)	
	III	(14c)	
	P.S.S.	(18)	

4. Results and discussion

The following results and discussion, unless otherwise noted, are based on $V_r = 100$, $K_a = 1$ and $K_b = 1$. For convenience, the equations used for each figure are tabulated in Table 1.

Fig. 2 shows the exact effects of three IC on fractional cumulative release, F, for $a/b = 1.1$. For any D_r, F of the time lag case is the smallest and burst release the largest. The effect of IC on the F curve is dependent on the magnitude of D_r. The effect is negligible when D_r is large (core matrix controlling drug release). When D_r is small (coating layer controlling), the IC effect is substantial up to a greater value of τ. The effect, in any case, decreases as τ increases.

Fig. 3 shows the exact effects of three IC on dimensionless release rate, R, for $a/b = 1.1$. The IC effect similar to that shown in Fig. 2 is also observed for the release rate R. For any D_r, the initial rates are in accordance with the initial conditions, i.e., for the time lag case, the rate is zero initially and the rate increases to a maximum and falls; for the burst release case, the initial rate is infinite and the rate decreases monotonically with time; and for SSCD, the initial rate is finite and at the maximum but then decreases with time. R curves of the same D_r converge at large τ and the convergence occurs late when D_r is small. The extent of the effect of initial condition is, therefore, dependent on D_r.

Fig. 4 and 5 show, respectively, the the exact effect of IC on F and R for different a/b and for $D_r = 0.1$. When a/b is large, the effect of IC becomes substantial. The effect in any case, however,

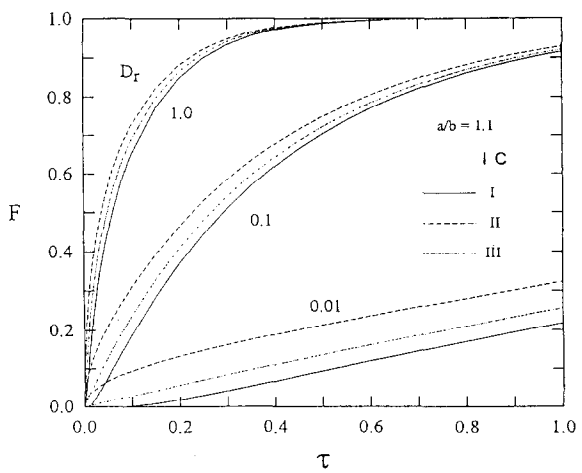

Fig. 2. The exact effect of initial conditions on fractional cumulative release, for various D_r and $a/b = 1.1$. $K_a = K_b = 1$, $V_r = 100$.

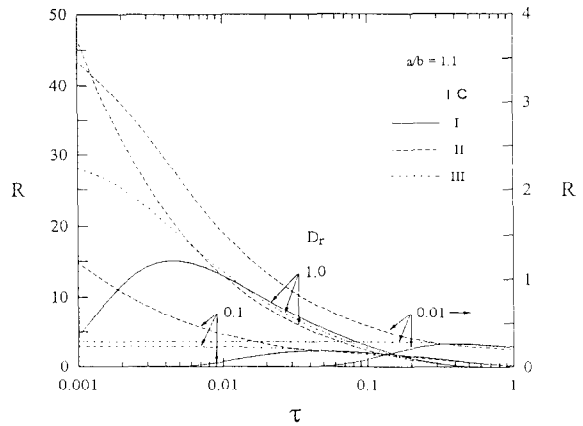

Fig. 3. The exact effect of initial conditions on dimensionless release rate, for various D_r and $a/b = 1.1$. $K_a = K_b = 1$, $V_r = 100$.

decreases as τ increases. Fig. 5 shows that as a/b increases, the IC effect on R persists to a greater τ, and that R for the time lag case eventually surpasses the others. In Fig. 4 and 5, as $D_r = 0.1$, the coating layer is in control of mass transfer. Therefore, with the increase in a/b, the effects of coating layer thickness and IC become more apparent.

Fig. 6 shows fractional cumulative release curves for $D_r \to 0$. The abscissa is in τ_f. For each a/b, five F curves are shown, three for exact solutions with IC I, II, and III, and two for pseudo-steady state solutions with IC I and II. The differences in the five F curves increase as a/b increases but decrease as τ_f increases.

Fig. 7 shows the relative percentage difference between the exact and pseudo-steady state solutions for three IC, three a/b, and $D_r \to 0$. The relative percentage difference is defined in the title of the ordinate. $F_{(P.S.S.)_i}$ is the pseudo-steady state solution given by Eq. 18 and F_i denotes the exact solution for

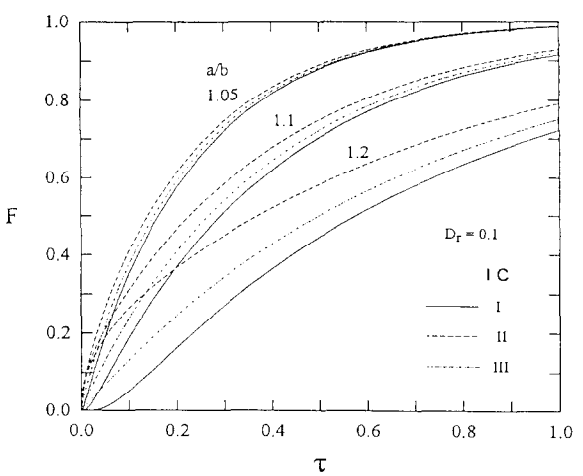

Fig. 4. The exact effect of initial conditions on fractional cumulative release, for various a/b and $D_r = 0.1$. $K_a = K_b = 1$, $V_r = 100$.

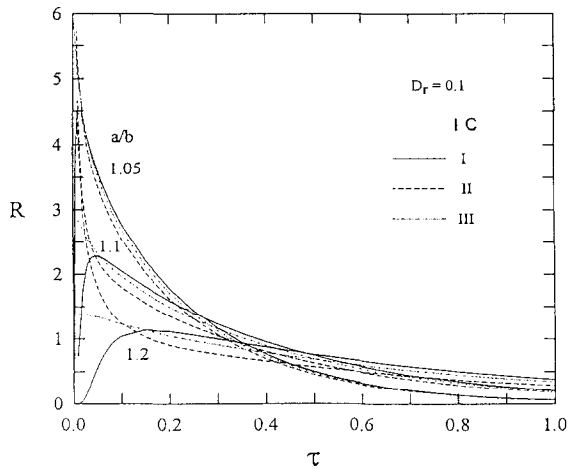

Fig. 5. The exact effect of initial conditions on dimensionless release rate, for various a/b and $D_r = 0.1$. $K_a = K_b = 1$, $V_r = 100$.

IC i, i = I, II, III. In the abscissa, $\tau_{f,99}$ represents τ_f at $F = 0.99$, thus, nearly the entire release life is covered. This figure shows that within about 5% time of life expectancy, the relative difference and its change with time are large in any case. After about 5% time of life expectancy, it may be said that: (1) relative differences for all cases decrease smoothly with time: (2) for a given a/b, the effect of IC on the relative difference becomes negligible, i.e., relative differences are about the same for the same a/b; (3) as a/b decreases, the relative difference decreases; and (4) relative differences are at most around 16, 8, and 4% for $a/b = 1.2$, 1.1, and 1.05, respectively. $a/b \cong 1.1$ may be taken as the criterion for the application of pseudo-steady state solutions. It should be borne in mind, however, that the above discussions are based on $V_r = 100$, $K_a = K_b = 1$. For $V_r = 10$, $K_a = K_b = 1$, results that are not much

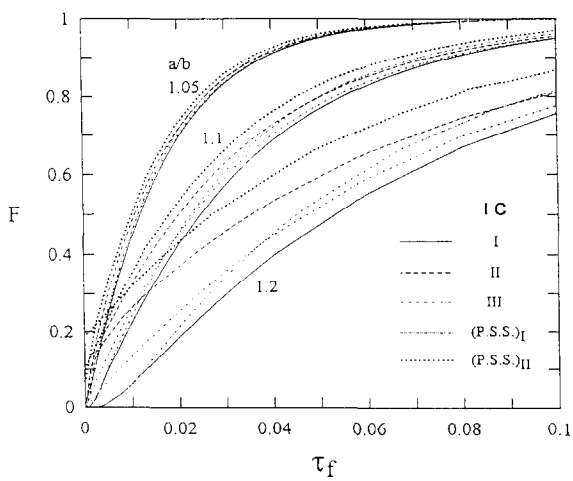

Fig. 6. Fractional cumulative release curves obtained by exact solutions and by pseudo-steady state solution for different initial conditions. $D_r \to 0$, $K_a = K_b = 1$, $V_r = 100$.

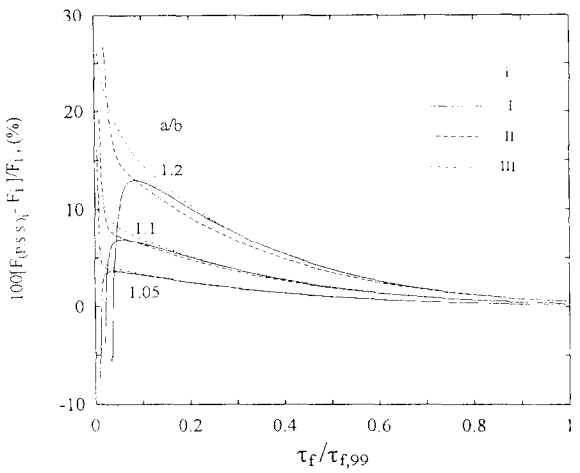

Fig. 7. Relative percentage difference between exact solutions and pseudo steady state solutions. For time lag, burst release, and SSCD. $D_r \to 0$, $K_a = K_b = 1$, $V_r = 100$.

different from Fig. 7 were obtained. In the case $V_r \ll 10$, i.e., a particle in a very small volume of liquid, the relative differences will be somewhat greater than those indicated by Fig. 7.

5. Conclusions

Drug release from a coated spherical particle containing dissolved drug has been analyzed exactly for time lag, burst release, and steady state concentration distribution in coating layer. The degree of the effect of initial conditions on release behavior is dependent on diffusivity ratio, D_r, and radius ratio, a/b. The effect of initial condition is sustained over a longer time for particles with small diffusivity ratio and large radius ratio.

For the case where drug concentration in the core is dependent on time only, pseudo-steady state solutions are compared with the exact solutions. The relative difference between the two is dependent on a/b. Excepting the cases of very small V_r and very small time, Pseudo-steady state solution is considered to apply for a/b less than around 1.1.

Nomenclature

a	radius of coated matrix, cm
b	radius of core matrix, cm
C_i	concentration: i = m, f, e, for core matrix, coating, and elution liquid; $i = 0$, for initial drug loading concentration in the core matrix; i = s, for saturation concentration of drug; gmol/cm^3
D_i	diffusivity; i = m, f, for core matrix and coating, cm^2/s
D_r	diffusivity ratio, $\equiv D_f/D_m$, –
$f(\beta_n)$	a function defined by Eq. A3, –
$F(\tau)$	fractional cumulative release, $\equiv M_t/M_\infty$, –
IC	initial condition,
K_i	partition coefficient, $i = a, b$. $K_a = C_e(t)/C_f(a,t)$; $K_b = C_m(b,t)/C_f(b,t)$, –

l dimensionless particle size, $\equiv a/b$; –
m a parameter, $m = -1/6$ for time lag case, $m = a/(3b)$ for burst release case, $m = 0$ for pseudo-steady state case, –
n index, –
M_t amount of drug released at time t, gmol
M_∞ amount of drug released at infinite time, or $M_{t\infty}$, gmol
$N(\beta_n)$ a function defined by Eq. 15a, –
P $\equiv 3(K_a/K_b)(a/b)(a/b-1)$, –
q^n roots of Eq. 9b, $\equiv l\beta_n$, –
r radius, cm
$R(\tau)$ dimensionless fractional cumulative release rate, $dF/d\tau$, –
s $\equiv (K_a/K_b)V_r(a/b)^3$, –
SSCD steady state concentration distribution in coating layer, –
t time, s
t_s the time at which solid drug disappears, s
V_e volume of elution liquid, cm^3
V_r volumetric ratio of the elution liquid to the coated matrix, $\equiv V_e/(4\pi a^3/3)$, –
X $\equiv D_f t/[K_a(a-b)^2]$, –
X_1 $\equiv X+m$, –
Y $\equiv M_t/[4\pi ab(a-b)C_s(K_a/K_b)]$, –
Y_∞ Y at $t=t_\infty$, –
α $\equiv V_r K_a/3$, –
β_n roots of Eq. A4, 9a, 15b, –
δ dimensionless thickness of coating, $\equiv (a-b)/b$, –
η dimensionless radius, $\equiv r/b$, –
θ_i dimensionless concentration: i = m, f, e, for core matrix, coating, and elution liquid; i = f,0, for initial drug profile in the coating, –
π = 3.1416, –
ρ_u density of pure drug, g/cm^3
τ dimensionless time, $\equiv D_m t/b^2$, –
τ_f dimensionless time, $\equiv D_f t/b^2$, –

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Appendix

Exact solutions for time lag case (Lu and Chen, 1993)

The dimensionless cumulative release, $F(\tau)$, and the dimensionless cumulative release rate, $R(\tau)$, are listed below.

$$F(\tau) \equiv \frac{M_t}{M_\infty} = 1 + \frac{K_b + l^3 - 1 + V_r K_a l^3}{D_r} \sum_{n=1}^{\infty} \frac{\exp(-D_r\beta_n^2\tau)}{\beta_n f(\beta_n)} \cdot \left[\sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) - \sin\left(\sqrt{D_r}\beta_n\right)\right], \tag{A1}$$

$$R(\tau) \equiv \frac{dF(\tau)}{d\tau} = -\left(K_b + l^3 - 1 + V_r K_a l^3\right) \sum_{n=1}^{\infty} \frac{\beta_n \exp(-D_r\beta_n^2\tau)}{f(\beta_n)} \cdot \left[\sqrt{D_r}\beta_n \cos\left(\sqrt{D_r}\beta_n\right) - \sin\left(\sqrt{D_r}\beta_n\right)\right]. \tag{A2}$$

where

$$f(\beta_n) = \sin\left(\sqrt{D_r}\beta_n\right)\cos(\delta\beta_n)\cdot\left[-\frac{K_b}{2D_r\beta_n} + \left(\frac{V_rK_aK_bl^2\delta}{6D_r} - \frac{K_bl}{2} - \frac{l\delta}{2} - \frac{V_rK_al^2}{3} - \frac{V_rK_al^3}{6}\right)\beta_n\right]$$
$$+ \sin\left(\sqrt{D_r}\beta_n\right)\sin(\delta\beta_n)\cdot\left[\frac{K_b}{2} + \frac{K_bl\delta}{2D_r} + \frac{V_rK_aK_bl^2}{3D_r} - \frac{l^2+1}{2}\right.$$
$$\left. - \frac{V_rK_al^2}{3} + \frac{V_rK_al^2}{6}(K_b+\delta)\beta_n^2\right]$$
$$+ \cos\left(\sqrt{D_r}\beta_n\right)\cos(\delta\beta_n)\frac{1}{\sqrt{D_r}}\left[\frac{K_b}{2} + \frac{D_r\delta}{2} - \frac{V_rK_al^2}{6}(K_b\delta + D_r)\beta_n^2\right]$$
$$- \cos\left(\sqrt{D_r}\beta_n\right)\sin(\delta\beta_n)\frac{1}{\sqrt{D_r}}\left[\frac{D_r}{2\beta_n} + \left(\frac{K_bl\delta}{2} + \frac{V_rK_aK_bl^2}{3} + \frac{D_rl}{2} + \frac{D_rV_rK_al^2}{6}\right)\beta_n\right]. \quad \text{(A3)}$$

and β_n are the non-zero roots of the following equation:

$$K_b\left[\sqrt{D_r}\beta_n\cos\left(\sqrt{D_r}\beta_n\right) - \sin\left(\sqrt{D_r}\beta_n\right)\right]\left[-l\beta_n\cos(\delta\beta_n) + \sin(\delta\beta_n) + \frac{V_rK_a}{3}l^2\beta_n^2\sin(\delta\beta_n)\right]$$
$$- D_r\sin\left(\sqrt{D_r}\beta_n\right)\left[-\left(l\beta_n^2+1\right)\sin(\delta\beta_n) + \delta\beta_n\cos(\delta\beta_n)\right.$$
$$\left. - \frac{V_rK_a}{3}l^2\beta_n^2(\beta_n\cos(\delta\beta_n) + \sin(\delta\beta_n))\right] = 0, \quad \text{(A4)}$$

where $\delta \equiv (a-b)/b = l-1$ is the dimensionless thickness of coating.

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