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A mechanism on the drug release into a perfect sink from a coated planar matrix with a super-saturation loading in the core

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Abstract

A comprehensive model is proposed to accurately describe drug release kinetics from a coated plane sheet when drug loading in the core is above its saturation level. The general solutions are acquired in a dimensionless form by the Laplace transform and the solution for the special case-a perfect sink condition, is derived from these general ones. On the basis of the model calculations, the effects of the diffusion ratios and thickness ratios of the coatings to the core, and drug loading entrapped in the core during the release processes have been discussed over wide range of variables. To validate the model equations proposed, the coated systems, 5-fluoracilum/ethylene-vinyl alcohol copolymer (5-Fu/EVAL) core matrix coated with various polymeric materials such as EVAL, cellulose acetate (CA), poly(2-hydroxyethyl methacrylate) (PHEMA) and poly(methyl methacrylate) (PMMA), having different diffusivities, are designed, experimentally investigated and graphically and quantitatively compared with the theoretical values. The results show a good correlation between the theory and experiment.

Keywords: Coated planar matrix; Controlled release; Mathematical analysis; In-vitro release

1. Introduction

Controlled release of a drug is important not only for attaining the most effective use of the drug but also for the prevention of side-effects. There are many ways to design controlled release dosage forms: from film coated pellets, tablets or capsules, to more sophisticated and complicated delivery systems (Chien, 1982; Buri et al., 1985). Nowadays a coated form is of popularity in the market. It is used not only to attain the zero-order release, but to eliminate the burst release at initial period as well. A coated matrix, or plane sheet, may include two parts, a core matrix which is loaded with a drug initially, and a coating film which is coated on the core. The initial drug concentration in the core may be above or below

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saturation. If above, the core concentration will be at the saturation until a sufficient amount of drug has been released. If below, the core concentration decreases continuously with time. For the coating, the initial drug concentration may be zero or a function of position that results from manufacturing or diffusion during storage. The release of a drug from such a coated matrix has been investigated by various researchers under different conditions. Flynn et al. (1974) used the pseudo-steady state assumption and obtained the solution. Christensen et al. (1980) used the same assumption to solve the sub-saturation release problem for core concentration varying with time but being uniform within the core and variable extraction medium concentrations. Lu and Lee (1992) used the pseudo-steady state assumption and solved the case of core concentration over and below saturation-variable extraction medium concentration. The core concentration is also assumed to be time dependent and space independent. Special cases that were derived from their solutions agreed with the results of Flynn et al. (1974) and Christensen et al. (1980), respectively. Christensen et al. (1982) later gave exact solutions to three diffusion problems. The first exact solution is for their previous problem. The other two are for constant core concentration-variable extraction medium concentration and variable core concentration-sink condition in extraction medium. Lu and Chen, 1993 have investigated this kind of topic for more general case of various coating to core diffusivity ratios but with the limit of drug loaded below the saturation level. Moreover, all of the above have concerned a coated spherical particle release system which is immersed in a well stirred extraction medium and diffusivity was assumed to be constant. There are some other literature coping with the coated system. Tojo et al. (1983) simulated the membrane-moderated controlled release of active agent from the core matrix. Fan and Singh (1989) presented the problems that have been encountered and solved in controlled release. Carslaw and Jaeger (1959) and Crank (1975) described various kinds of diffusion problems. Recently, the authors (Xu et al., 1997) have coped with the problem of drug release from a coated plane sheet with a sub-saturation in the core and obtained a generalized solution for this case. This topic is extended in this paper for the super-saturation loading in the core with the whole system immersed in a well stirred extraction medium and for the more general cases of various coating to core diffusivity and thickness ratios and variable core concentration-variable coating concentration-variable extraction medium concentration.

2. Theoretical considerations

2.1. General case

A drug is dissolved uniformly-in a slab matrix with thickness, L_m. This matrix is coated uniformly with a material so that the thickness of coating is L_f. The drug is loaded in the core initially with a concentration of C_d, which is greater than C_s, the drug saturability in the core material. Coating film is initially free of drug. This coated matrix is then immersed in a well-stirred medium of volume V_e. Thus the boundary layer is assumed to be negligible. Moreover, following the results of monolithic device (Higuchi, 1963), a sharp interface will be produced which divides the core into two sections: the unreleased region and the released region with a distance, L_t. As the drug is released, the released region expands and thus L_t will increase with time. Drug concentrations in the released region of the core, coating and extraction medium are represented, respectively, by C_m, C_f and C_e. Diffusivities of drug in the core and coating are represented by D_m and D_f, which are assumed to be constant. A schematic drawing of this case is shown in Fig. 1.

The basic mass transfer equations for the core and the coating are as follows

$$\frac{\partial C_m}{\partial t} = D_m \frac{\partial^2 C_m}{\partial x^2}, \quad -L_t < x < 0 \tag{1a}$$

$$\frac{\partial C_f}{\partial t} = D_f \frac{\partial^2 C_f}{\partial x^2}, \quad 0 < x < L_f \tag{1b}$$

With the boundary conditions

$$C_m(-L_t,t) = C_s, \quad C_m(0,t) = K_b C_f(0,t) \tag{2a, 2b}$$

$$-D_m\frac{\partial C_m}{\partial x}_{x=0} = -D_f\frac{\partial C_f}{\partial x}_{x=0} \quad (2c)$$

$$C_f(L_f,t) = K_a C_e(t), \qquad -SD_f\frac{\partial C_f}{\partial x}_{x=L_f} = V_e\frac{\partial C_e}{\partial t} \quad (2d,\ 2e)$$

where K_a and K_b are the partition constants of coating-medium and core-coating, respectively, and S is the released area. The initial conditions are:

$$C_m(x,0) = C_s, \quad C_f(x,0) = 0, \quad C_e(0) = 0 \quad (3a,\ 3b,\ 3c)$$

Eq. (1a) and Eq. (1b) can be solved in dimensionless forms defined as follows by the Laplace transform for the purpose of generality.

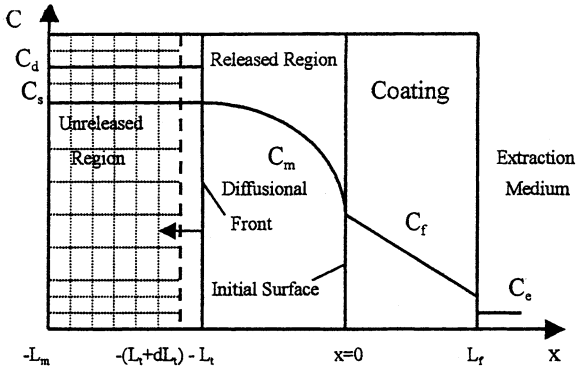

Fig. 1. Schematic Diagram of solute release from a coated matrix system with a super saturation in the core ($C_d > C_s$).

$$\theta_i = C_i/C_s, \quad i = m, f, e, d \quad (4a,4b,4c,4d)$$

$$\tau = D_m t/L_t^2, \quad \eta = x/L_t \quad (4e,4f)$$

$$D_r = D_f/D_m, \quad l = L_f/L_t, \quad V_r = V_e/SL_f \quad (4g,4h,4i)$$

The procedures seem to be sophisticated and omitted here and the results are given as follows [Detailed solution processes can be referred to the dissertation paper (Xu, 1995)]

$$\theta_m = 1 + \sum_{n=1}^{\infty}\frac{2\sqrt{D_r}[\sin(l\beta_n) + (V_r l/K_a)\beta_n\cos(l\beta_n)]\sin[\sqrt{D_r}(1+\eta)\beta_n]}{\beta_n\varphi(\beta_n)}e^{-D_r\beta_n^2\tau} \quad (5a)$$

$$\theta_f = \frac{1}{K_b} + \sum_{n=1}^{\infty}\frac{2\cos(\sqrt{D_r}\beta_n)[\cos(l\beta_n - \eta\beta_n) - (V_r l/K_a)\beta_n\sin(l\beta_n - \eta\beta_n)]}{\beta_n\varphi(\beta_n)}e^{-D_r\beta_n^2\tau} \quad (5b)$$

$$\theta_e = \frac{1}{K_a K_b} + \sum_{n=1}^{\infty}\frac{2\cos(\sqrt{D_r}\beta_n)}{K_a\beta_n\varphi(\beta_n)}e^{-D_r\beta_n^2\tau} \quad (5c)$$

where:

$$\varphi(\beta_n) = -\cos(\sqrt{D_r}\beta_n)\left[\left(D_r + K_b l + \frac{V_r l K_b}{K_a}\right)\sin(l\beta_n) + \left(\frac{V_r D_r}{K_a} + \frac{V_r l K_b}{K_a}\right)l\beta_n\cos(l\beta_n)\right] + \sin(\sqrt{D_r}\beta_n)\left[\left(\frac{V_r\sqrt{D_r}l}{K_a} + \frac{V_r\sqrt{D_r}K_b}{K_a}\right)l\beta_n\sin(l\beta_n)\right] - \left(\sqrt{D_r}l + \frac{V_r\sqrt{D_r}l}{K_a} + \sqrt{D_r}K_b\right)\cos(l\beta_n) \quad (6)$$

and β_n are the roots of the following equation:

$$\sqrt{D_r}\sin(\sqrt{D_r}\beta_n)\left[\sin(l\beta_n) + \frac{V_r l}{K_a}\beta_n\cos(l\beta_n)\right] - K_b\cos(\sqrt{D_r}\beta_n)\left[\cos(l\beta_n) - \frac{V_r l}{K_a}\beta_n\sin(l\beta_n)\right] = 0 \quad (7)$$

The release rate, R_t is obtained by differentiating (Eq. (5b)) with respect to dimensionless distance l at the coating-medium interface, i.e.

$$R_t = \frac{-D_f}{L_t L_m\theta_d}\left(\frac{\partial\theta_f}{\partial\eta}\right)_{\eta=1} = \frac{-2D_f V_r l}{L_t L_m\theta_d K_a}\sum_{n=1}^{\infty}\frac{\beta_n\cos(\sqrt{D_r}\beta_n)}{\varphi(\beta_n)}e^{-D_r\beta_n^2\tau} \quad (8)$$

Here, $\theta_d = C_d/C_s$ F_t, the fractional cumulative release at time t, is easily obtained by integrating of Eq. (8) at the specified time intervals

Eq. (5a)–Eq. (5c) and Eq. (8) represent the general solutions for concentrations, release rate in dimensionless forms. These solutions can be

simplified in special cases, which are derived as follows.

2.2. Special case — a perfect sink

The case of a perfect sink may be obtained by setting the volume of extraction medium to be infinite. Then $Vr \to \infty$ and Eq. (5a)–Eq. (5c) and Eq. (8) are simplified as follows

$$[\theta_m]_{V_r \to \infty} = \frac{K_b l - D_r \eta}{D_r + K_b l} + \sum_{n=1}^{\infty} \frac{2\cos(l\beta_n)\sin[\sqrt{D_r}\beta_n(1+\eta)]\, e^{-D_r\beta_n^2\tau}}{\beta_n A(\beta_n)} \quad (9a)$$

$$[\theta_f]_{V_r \to \infty} = \frac{l - \eta}{D_r + K_b l} + \sum_{n=1}^{\infty} \frac{-2\cos(\sqrt{D_r}\beta_n)\sin[\beta_n(1-\eta)]\, e^{-D_r\beta_n^2\tau}}{\sqrt{D_r}\beta_n A(\beta_n)} \quad (9b)$$

$$[\theta_e]_{V_r \to \infty} = 0 \quad (9c)$$

$$R_t = \frac{D}{L_t L_m \theta_d}\left(\frac{1}{D_r + K_b l} - \sum_{n=1}^{\infty} \frac{2\cos(\sqrt{D_r}\beta_n)}{\sqrt{D_r}\beta_n A(\beta_n)} e^{-D_r\beta_n^2\tau}\right) \quad (10)$$

where

$$A(\beta_n) = -\left(\sqrt{D_r} + \frac{K_b l}{\sqrt{D_r}}\right)\cos(\sqrt{D_r}\beta_n)\cos(l\beta_n) + (K_b + l)\sin(\sqrt{D_r\beta_n})\sin(l\beta_n) \quad (11)$$

and β_n are the non-zero roots of Eq. (12):

$$\sqrt{D_r}\sin(\sqrt{D_r}\beta_n)\cos(l\beta_n) + K_b\cos(\sqrt{D_r}\beta_n)\sin(l\beta_n)] = 0 \quad (12)$$

If, in addition to $V_r \to \infty$, the diffusivity in core is infinity, that is, $D_m \to \infty$, the coated matrices behave the same as the reservoir system and if the diffusivity in coating is infinity, i.e. $D_r \to \infty$, it becomes the monolithic matrix (Xu and Wang, 1995).

In the above cases, the cumulative release fraction, F_t can be obtained by integrating the R_t equations at specific time intervals.

3. Experimental description

3.1. Materials

Ethylene-vinyl alcohol copolymer (EVAL) with vinyl alcohol/ ethylene (VAL/E) molar ratio of 56/44 was obtained from Kori company (Japan),5-fluoracilum (5-Fu) was analytically pure and used as target drug, 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA) were chemically pure and purified prior to use. Cellulose acetate (CA) was from the market and without purification. n-Propanol, acetone and alcohol were used as solvents and $K_2S_2O_4$ and benzoyperoxide (BPO) as initiators. These agents were all analytically pure and used as received.

3.2. Preparation of the core matrices

The preparation of a core matrix follows the same procedures as those described in the previous work (Xu and He, 1998).

3.3. Preparation of coating solutions

CA coating solution was obtained by dissolving the desired amount of CA in acetone at 55°C. Poly-2-hydroxyethyl methacrylate (PHEMA) and Poly-methyl methacrylate (PMMA) solutions were obtained by the following procedure: monomer MMA or HEMA, diluted with alcohol to 10–20% previously, was placed in a flask. The solution was flushed with nitrogen for about 10 min, and then the initiator with the amount of 1‰ monomer (BPO for MMA and $K_2S_2O_4$ for HEMA) was added and kept 60–65°C for 2.5 h to get the coating solutions. These solutions were cooled to 30°C prior to use. For detailed information, our previous works (Xu et al., 1996, 1997) are referred.

3.4. Preparation of coated matrices (Xu et al., 1997)

The coated matrices were prepared by casting coating solutions onto the core matrices or throwing the core matrices into coating solutions (leav-

Table 1
Some parameters of drug investigated in the coating films

Coating	K_a	K_b	D_f, cm^2 s^{-1}	D_r
EVAL	0.601	1.0	2.78×10^{-8}	1.0
CA	0.545	1.1	8.65×10^{-10}	0.031
PMMA	0.404	1.5	7.72×10^{-11}	0.003
PHEMA	0.750	0.8	4.12×10^{-6}	148.2

material balance equation is needed. For a perfect sink, the materials balance can be easily made between the released region in the eve and the core-coating interface. The final equation is (Xu and Wang, 1995)

$$\left(\theta_d-\int_{-1}^{0}\theta_m\,\mathrm{d}\eta\right)\frac{\mathrm{d}L_t}{\mathrm{d}t}=-\frac{D_m}{L_t}\frac{\partial\theta_m}{\partial\eta}\bigg|_{n=-1} \tag{13}$$

Substituting Eq. (9a)to Eq. (13), yields,

$$\left[\theta_d=\frac{0.5D_rL_t+K_bL_f}{D_rL_t+K_bL_f}-2\sum_{n=1}^{\infty}\frac{\cos\sqrt{D_r}\,\sin(l\beta_n)\,[1-\cos(\sqrt{D_r}\beta_n)]\,e^{-D_r\beta_n^2\tau}}{\sqrt{D_r}\beta_n^2A(\beta_n)}\right]\frac{\mathrm{d}L_t}{\mathrm{d}t}$$
$$=\frac{D_m}{L_t}\left[\frac{D_rL_t}{D_rL_t+K_bL_f}-2\sum_{n=1}^{\infty}\frac{\sqrt{D_r}\cos(l\beta_n)e^{-D_r\beta_n^2\tau}}{A(\beta_n)}\right] \tag{14}$$

ing one face exposing) for 5 min. The whole films were allowed to dry for 24 h at 30°C prior to use.

3.5. In-vitro release test

The In-vitro release test was described in detail in our previous job (Xu and He, 1998).

3.6. Determination of model parameters (Xu et al., 1997)

The parameters to be determined include: the partition constants of coating-medium (K_a) and core-coating (K_b), drug saturability in the core matrix (C_s), the diffusion coefficients of drug in the core (D_m) and different coatings (D_f). The methods and experimental set up for the measurements of these parameters were described in detail in my previous job (Xu et al., 1997). The salubility and diffusivity of 5-Fu in EVAL core was, respectively, determined to be about 7.815 mg cm^{-3} and 2.78×10^{-8} cm^2 s^{-1} (Xu and He, 1998) and the other parameters were accumulated in Table 1.

4. Results and discussion

4.1. Results from the model calculations

4.1.1. Computing procedure

Before the calculations can be conducted, the β_n and $A(\beta_n)$ are described as Eq. (11) and Eq. (12), respectively. It is easy to solve equation Eq. (14) by Runge–Kutta method for the distance in the released region at any time point and thus further calculations can be conducted for concentrations in the core and coating, the cumulative release fractions with the independently determined parameters. This calculation steps are described as below:

1. Input the independently determined parameters and permitted precision in the subroutine program.
2. Let $l=L_f/L_t$ (0) and solve the corresponding pole equation by the method of halving the interval.
3. Solve the material balance equation (14) as described below by use of R-K method to find L_t, the released distance at time t.
4. Calculate R_t, θ_m and θ_f according to the equations as derived above.
5. Integrating numerically R_t values at different released time, the cumulative release fraction can thus be obtained at a specified time.
6. If $L_t<L_m$, let $l=L_f/L_t$ and repeat from step 2; otherwise stop calculating and output the results.

It should be notified that a very small value such as 10^{-8} m is initially endowed with L_t (0) in our calculation because the theoretical value zero is not permitted in the above calculation. This initial value is much smaller than the magnitude

of core matrix thickness (in general it is 10^{-3} m) and thus this assumption does not affect the final results. In fact, we find that the results are very close to the calculated ones from different initial value for L_t (0) as long as it is small enough.

4.1.2. Profiles of release distance in the core

Profiles of released distances in the core are computed for the cases where $C_d = 15.45$, 50.0, 123.6, and $D_r = 100.0$, 1.0, 0.1, 0.01 and $L_f/L_m =$ 0.1, 1.0 and $K_a = K_b = 1$ which are illustrated in Fig. 2 for a thin coating and Fig. 3 for a thick coating, respectively. The effects of coating thickness and diffusivity ratio on the profiles of release distance can be easily obtained from these calculations and Figures.

For a thin coating (c.f. Fig. 2), the effect of the diffusivity ratio D_r on the rate at which the interfacial boundary moves is appreciable while D_r is less than 0.1, but is negligible otherwise. This is because the core controls mass transfer when D_r is greater than 1 and the diffusivity of core remains unchanged. If D_r is less than 1, two cases are necessary to be discussed. For the case of D_r greater than about 0.1, though the coating controls the mass transfer, the drug is easily released from the core through the coating film into the medium as a result of the high loading and thinner coating. But when D_r is less than about 0.1, resistance of coating to the release process is very appreciable and can't be compensated by drug loading and the coating thickness, and thus the release proceeds more slowly with a decrease in D_r values. It is interesting to note that a decrease in D_r causes an increase in linearity of the profiles between L_t and t (c.f curves denoted by 4 in Fig. 2). This implies that constant release rate (or zero release) is mainly dependent on the diffusivity ratio rather than the diffusivity in the core or coating and can be attained by decreasing the diffusivity ratio of coating to core, e.g. $D_r \leq 0.01$ as described in Fig. 2.

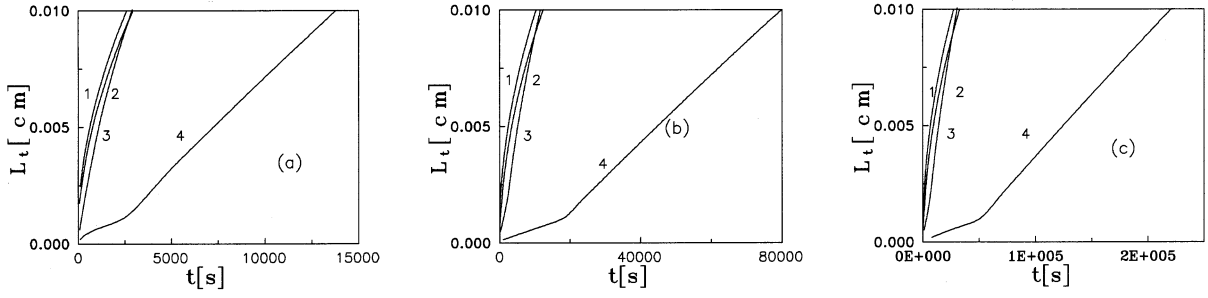

Fig. 2. Profiles of release distance versus time in the core for a coated matrix ($C_d > C_s$). For $L_f/L_m = 0.1$; $D_m = 2.78 \times 10^{-8}$ cm^2 s^{-1}, C_d: (a) – 15.45; (b) – 50; (c) – 123.6 mg cm^{-3}; D_r:1–100, 2–1, 3–0.1, 4–0.01.

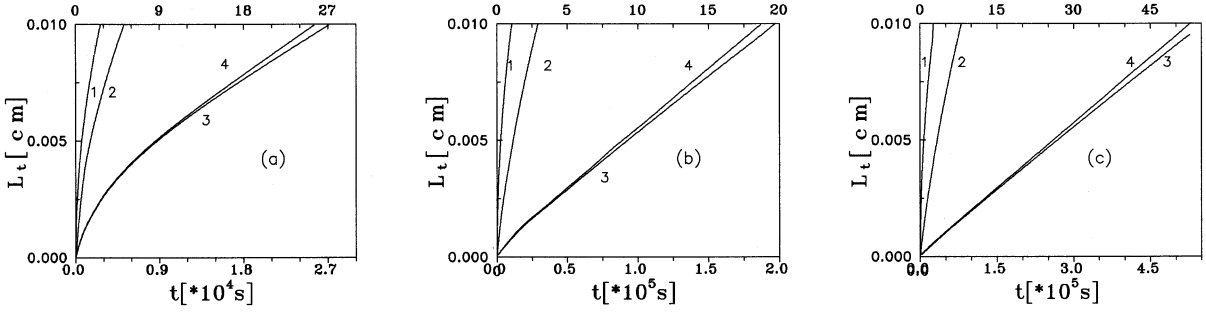

Fig. 3. Profiles of release distance versus time in the core for a coated matrix ($C_d > C_s$) For $L/L_m = 1.0$; $D_m = 2.78 \times 10^{-8}$ cm^2 s^{-1}; Cd: (a) – 15.45; (b) – 50; (c)123.6 mg cm^{-3}; D_r:1–100, 2–1, 3–0.1, 4–0.01.

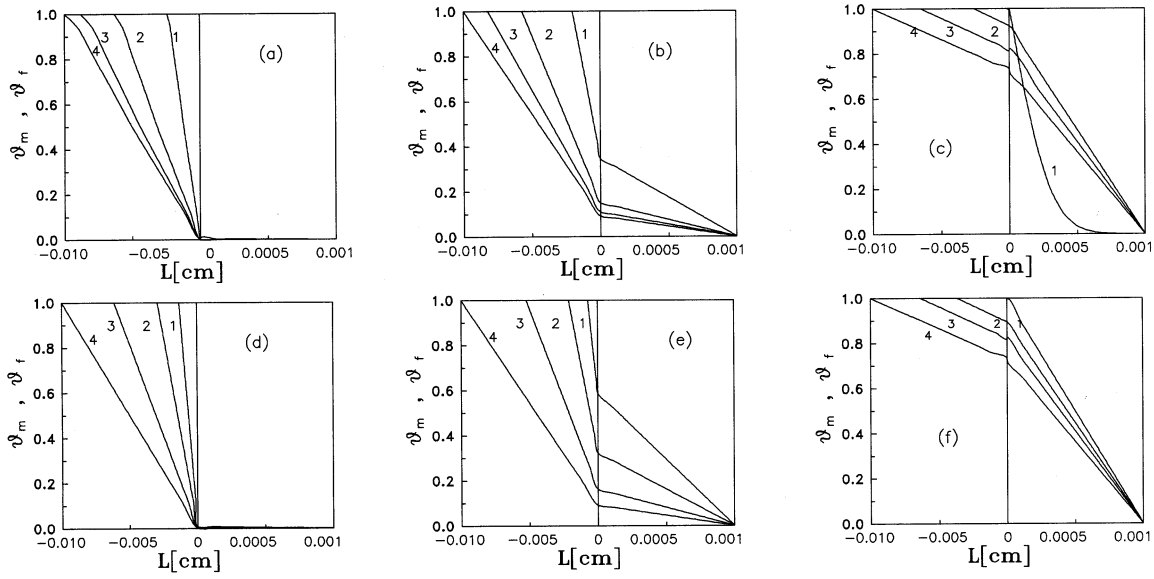

Fig. 4. Dimensionless concentration profiles in the core and coating versus time for a coated matrix system ($C_d > Ci_s$). For $L_t/L_m = 0$ 1: (a) $C_d = 15.45$ mg cm^{-3}, $D_, = 100$, t: 1–100, 2–1000, 3–2000, 4–2620 s; (b) $C_d = 15$ 45 mg cm^{-3}, $D_r = 1$ 0, t: 1–100, 2–1000, 3–2000, 4–2960 s; (c) $C_d = 15.45$ mg cm^{-3}, $D_r = 0.01$, t: 1–100, 2–4200, 3–9100, 4–13 800 s; (d) $C_d = 123.6$ mg cm^{-3}, $D_r = 100$, t: 1–200, 2–2000, 3–10 000, 4–27 360 s; (e) $C_d = 123.6$ mg cm^{-3}, $D_, = 1.0$, t: 1–200, 2–2000, 3–10 000, 4–32 700 s; (i) $C_d = 123.6$ mg cm^{-3}, $D_, = 0.01$, t: 1–10000, 2–100 000, 3–150 000, 4–220 000 s.

For a thick coating, e.g. a coating film as thick as the core matrix (Fig. 3), the above analyses are still applicable. The increase in coating thickness results in the changes of the shape and relative position of the profiles. In this case, the abrupt change in the release distance profiles occurs at $Dr = 1.0$ other than 0.1 for thin coating and constant release rate (or zero release) can be attained by decreasing the D_r value to 0.1 other than 0.01. Note that abscissas in Fig. 3 have a change in magnitude at $D_r = 0.01$ (lines labelled by, 4). This was done so that the release distance profiles at low D_r values can be shown clearly.

4.1.3. Concentration profiles in core matrix and coating film

Dimensionless concentration profiles across the coated matrix were computed for the cases where $C_d = 15.45$, 123.6 and $D_r = 100.0$, 1.0, 0.01 and $L_f/L_m = 0.1$, and $K_a = K_b = 1$ as illustrated in Fig. 4. Note that the abscissas in these panels have a change in the right so that the concentration in the coating can be shown clearly. Obviously, in the core matrix there exists a release interface just as behaved in a monolithic matrix (Xu, 1995). Concentration in the released region changes with time and keeps saturation value in the unreleased region. The concentration profiles are significant affected by the diffusivity ratio. When D_r is greater than unity, the core matrix concentration are steep in the region adjacent to the interface $L = 0$, i.e. the interface between the coating and the core (Fig. 4(a) and (c)). This is because that drug which is slowly released from the core is quickly passed over to the medium when diffusivity of the coating is high compared that in the core. Therefore, interface concentration is low in general. In addition, the slopes of concentration profiles both in matrix and coating are decreased as the release proceeds which elucidates that the release rate is decreased. If the diffusivity of core is the same as that of coating, the concentration profiles are continuous at $L = 0$ (c.f. Fig. 4(b) and (e)). The discontinuities that appear in the figures are due to the change in the abscissa. However, the situation is slightly different for the core when D_r is less than unity as shown in Fig. 4(c) and (f).

Because in this case, the coating controls the mass transfer, and the core matrix has enough time to uniformly distributed its concentration until the release region extends the whole core matrix thickness. Drug that is readily transferred to the interface at $L=0$ is transferred at decreasing rate through the coating film. Thus the changes in interface concentration at $L=0$ from the high to low values is more gradual when compared with those in Fig. 4(a) and (d), respectively. It should also be noted that for a given D_r, the larger the D_m, the larger the D_f and the shorter time for release.

The effects of loading on the release process can be obtained by compared Fig. 4(a–c) with Fig. 4(d–f), respectively. When D_r is greater than unity, the matrix control mass transfer and the core is nearly coatless. Therefore, concentration profiles approach zero in coating, linear in core for high loadings and curved in core for low loadings, which behave nearly the same as that in a monolithic system (Xu and Wang, 1995). As far as the D_r below unity is concerned, the concentration profiles both in the core and the coating approach more linear. The higher the loading, the more linear the profiles. This is because the coating is initially drug-free, the lag-time in the coating is shortened with an increase of loading.

It seems that almost the same results are obtained for the case of a thick coating, ea. $L_f/L_m=1.0$ These figures are not shown here for space saving. The main deviations are that concentration profiles approach more linear compared the thinned coating value at $D_r<1$ and slopes are gradually decreased. Because the ten times increase in thickness significantly causes an appreciable increase in the resistance of the coating and therefore the release process is slowed down.

4.1.4. The release rate

Fig. 5(a–c) show the plot of R_t, the release rate, versus time for various loadings and diffusivity ratios as shown in these figures. It should be noted that the time scales have compressed by their respective characteristic time t_m, the time which is needed when the release boundary extends to whole depth of the core matrix, i.e. $L_t=L_m$. Values of t_m can be easily obtained from Fig. 4(a–f) for different conditions. Take Fig. 4a as an example, if the release distance extends the whole core depth, it will take about 2620 s and thus $t_m=2620$ s at this condition. As shown in Fig. 5(a–c), there are two limiting cases. One is at large D_r which is represented by the case $D_r=100$ in this limit, the resistance to mass transfer due to coating film becomes negligible and the release rate attains the maximum value at the beginning and decreases with time thereafter. The other is at small D_r which is represented by the case $D_r=0.1$. In this limit, the release rate increases with time at the beginning and then decreased after attaining the maximum value at the time about $t/t_m=0.22$ due to the appreciable resistance of coating to mass transfer. Take Fig. 4(c) as an example, $t/t_m=0.22$ corresponds the real time $t=13\,800\times 0.22=3036$ s. Inspection of the corresponding Fig. 2(a) shows that the maximum rate occurs at the case when the release interface advances the depth around 1% core thickness. It is interesting

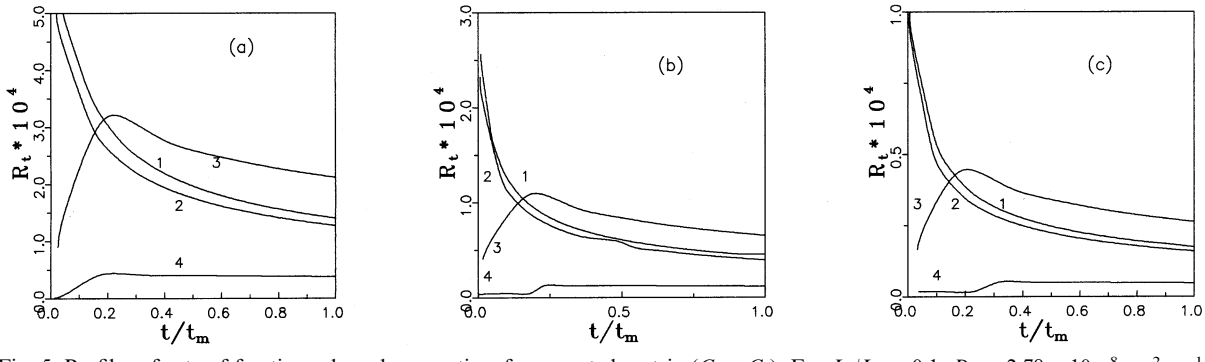

Fig. 5. Profiles of rate of fraction released versus time for a coated matrix ($C_d > C_s$). For $L_f/L_m=0.1$; $D_m=2.78\times10^{-8}$ cm^2 s^{-1}, C_D: (a), -15.45; (b), -50; (c), 123.6 mg cm^{-3}, D_r:1–100, 2–1, 3–0.1, 4–0.01.

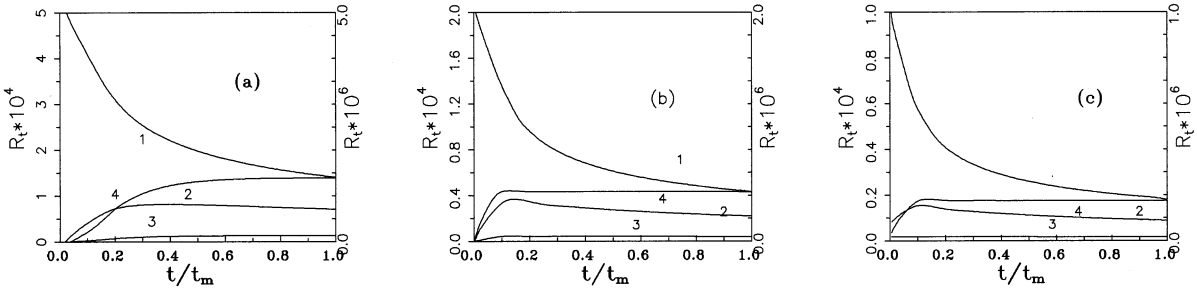

Fig. 6. Profiles of rate of fraction released versus time e for a coated matrix ($C_d > C_s$). For $L_f/L_m = 1.0$, $D_m = 2.78 \times 10^{-8}$ cm^2 s^{-1}, C_d: (a) -15.45; (b) -50; (c) 123.6 mg cm^{-3}; D_r: 1–100, 2–1, 3–1, 4–0.01.

to note that if D_r is less than or equal to about 0.01, the drug is released at two different constant rates. Before the time about $t/t_m = 0.22$, the rate is very low while after this time, it is relatively high. This is because, in this case the resistance due to core matrix is neglected and the coating controls the whole mass transfer. Thus the coated system is well compared to the reservoir devices (Baker and Lonsdale, 1974) and the drug is released from this kind of system at a constant speed. However, it differs somewhat from the reservoir one that in the beginning the drug is not released into the medium but into coating and thus the process behaves as a two-constant-rate-stage release.

The loadings seem to exert no effect on the pattern of the curves but they actually affect the magnitude of release rate. The greater the loading is, the smaller the rate at the same dimensionless time t/t_m will be.

The effect of coating thickness on the release rate curves is investigated by comparing Fig. 5 with Fig. 6, respectively. Note that ordinates of curve four in Fig. 6 correspond the right and thus it is sited above curve three. Obviously, constant release is completely maintained when $D_r \leq 1$ after the dimensionless time reaches around 0.14. If $D_r \leq 0.01$, zero-order release is attained in the whole time range at cases of high loadings. No distinct maximum occurs in these figures. It should be pointed out that for a thin coating, a substantial change in rate curves occurs at D_r around 0.1; while for a thick coating, it is around 1.0. This result differ somewhat from the case of $C_d < C_s$ in that a substantial change in rate curves occurs at D_r around 1 for thin coating and around 10 for thick coating (Lu and Chen, 1993; Xu et al., 1997). Therefore, in the design of controlled release devices, a substantial change in the release rate curve maybe caused by choosing proper diffusivity ratio and the magnitude of this proper ratio is dependent on both the thickness of coating and the drug loading initially entrapped in the core matrix.

4.2. Comparison between the theoretical and the experimental

The coated systems investigated here are composed of same core, EVAL, but different coatings, such as EVAL, CA, PMMA and PHEMA. The coatings are drug free initially and the core contains 5-Fu with two loadings, 50.0 and 210.0 mg cm^{-3}, respectively, both of which are greater than the saturability of 5-Fu in EVAL(7.815 mg cm^{-3}). The diffusivity ratios which can be calculated from difusivities of core and coatings, were listed in Table 1. Obviously, they range from 0.003 to around 150 and thus are suitable for the analysis with the theory presented above.

With the independently determined parameters, theoretical values of cumulative release fraction F_t can be numerically integrated from those of release rate R_t at designated time intervals and compared with experimental ones. The results were shown in Fig. 7. These comparisons can also be done by the estimation of least square error which is defined as below (Husson et al., 1991):

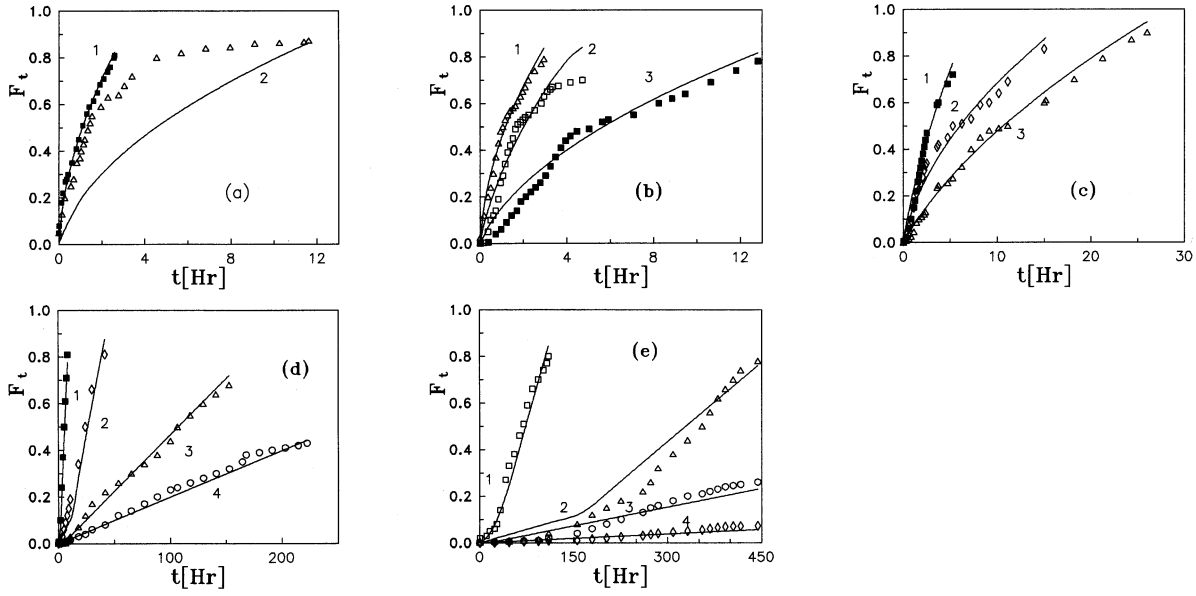

Fig. 7. Comparison between theory and experiment for the coated matrices with a super-saturation loading in the core. (a) Core matrix (coatless): $1-C_{\mathrm{d}}=50$; $2-C_{\mathrm{d}}=210$. (b) Coated with PHEMA: $1-C_d=50$, $L_f/L_m=0.09$; $2-C_d=50$, $L_f/L_m=0.11$; $3-C_d=210$, $L_f/L_m=0.52$. (c) Coated with EVAL:$1-C_d=50$, $L_f/L_m=0.51$; $2-C_d=210$, $L_f/L_m=0.09$; $3-C_d=210$, $L_f/L_m=0$ 51. (d) Coated with CA: $1-C_d=50$, $L_f/L_m=0$ 11; $2-C_d=210$, $L_f/L_m=0.11$; $3-C_d=50$, $L_f/L_m=0.09$; $4-C_d=210$, $L_f/L_m=$ 0.52. (e) Coated with PMMA: $1-C_d=50$, $L_f/L_m,=0$ 09; $2-C_d=210$, $L_f/L_m=0$ 09; $3-C_d=50$, $L_f/L_m=0.54$; $4-C_d=210$, $L_f/L_m=0.54$. Symbols represent the experimental points and solid lines stand for the theoretical simulation.

$$R=\left[\sum_{n=1}^{n}(F_{t.\mathrm{exp}}-F_{t.theo})^2/(n-1)\right]^{1/2} \qquad (15)$$

The calculated errors are listed in Table 2. The following is the discussion and important points based on these quantitative and graphical comparisons.

1. The quantitative comparisons labelled by the errors within 6% as listed in Table 2 show that there is a good correlation between the theory and the experiment in the investigated coated systems with different diffusivities and thickness ratios as well as drug loadings entrapped initially in the core matrix.
2. For comparison, release curves of uncoated matrices were shown in Fig. 7(a), which can also represent the case that the diffusivity ratio is infinity, i.e. $D_r\rightarrow\infty$. A good prediction to the experimental data has been observed at the case of a middle loading such as 50 mg cm^{-3}. But when the loading exceeds a critical value,

Table 2
Estimation of errors between the theory and the experimental for Fig. 7

Figure number	Curve 1		Curve 2		Curve 3		Curve 4	
	N	*R*,%	*N*	*R*,%	*N*	*R*,%	*N*	*R*,%
5a	29	3.124	35	28.51				
5b	22	3.146	22	5.489	22	5.73		
5c	15	5.155	19	4.204	19	2.488		
5d	18	4.741	18	4.629	21	2.002	21	1.547
5e	16	4.777	22	5.945	22	2.665	22	1.048

e.g. 210.0 mg cm^{-3}, the error is as large as 29% as observed from Table 2. Because for an uncoated matrix, the release is only matrix diffusion-controlled at relatively low loadings. But when the loading increases a designed value, release process will become both matrix and pore diffusion-controlled and thus causes large deviation from matrix diffusion-controlled theory. This has been intensively discussed in our previous paper (Xu and He, 1998).

3. As soon as the above monolithic matrices are coated, the situation is completely different. In all coated cases, the theoretical curves can give a good prediction to the experimental data as shown in Fig. 7(b)–(d). However, PHEMA is a kind of hydrophilic material and easy to be swollen in medium. When the core matrix coated with this material, it produces relative small additional resistance to the drug delivery and the release curves are almost the same as those of a non-coated matrix, which implies the core matrix entirely controls mass transfer. Therefore, the thickness of coating has nearly no effect on the experimental release curves due to high D_r value just as analyzed in the above. However, the existence of coating can eliminate surface release at the initial period and therefore a better correlation between theory and experiment has been made compared with the uncoated cases especially at the loading of 210 mg cm^{-3}.
4. When the matrix is coated with the same material, EVAL (c.f. Fig. 7(c)), the coated system becomes an integrity and acts as that in an monolithic one with a elongation of thickness free of drug initially. As described above, the burst release at the beginning is eliminated due to the existence of coating and thus the derived model proposed above can predict the experimental data in almost all the time range.
5. When the matrix is coated with PMMA or CA, values of D_r is much less than unity as shown in Table 1. The theoretical analyses tell us that in this limit, if the coating is thick enough, it will controls most the mass transfer and a pseudo-zero-order release curve will be brought about. Inspection of our experimental results as depicted in Fig. 7(d) and (e) for thick CA coatings and PMMA coatings shows a good consistence with the theoretical predictions.
6. As mentioned above, there is a transition in the theoretical release rate curves, because the drug is not released into the medium but into the coating at the first period. However, in practical experiments, a coated matrix has been laid wet aside for a long time before it is released, and thus this transition is not appreciable in the experimental observations.
7. Drug loading has little effect on the release curves by contrasting the cases of same coating, thickness ratio, but different drug loadings in Fig. 7(b–e). However, it actually affects the magnitude of release rate and the time needed to completely leach the drug. This fact is confirmed by previous theoretical calculations as depicted in Fig. 2.

5. Conclusions

Release of a drug from a coated planar matrix with a super-saturation loading in the core has been analyzed mathematically. Special case — a perfect sink is deduced from the general solutions. Based on the derived equations for a perfect sink, the effects of drug loading, diffusivity ratio, and the thickness of coating on release processes are computed and illustrated in detail. The results show that the drug loading, diffusivity ratio and the coating thickness are the most important factors in the design of a controlled release device and will determine the change in the release rate curve. By choosing the proper parameter combinations as discussed in the main text, a zero-release system can be obtained for the practical uses.

Four kinds of coated systems were designed and investigated experimentally to verify the theoretical predictions. From graphical and quantitative comparisons, the least square errors between them are observed to be within 6% for all coated cases and practical zero-release curves have been obtained for thick coatings with small diffusivity and thus the validity of the theoretical models proposed here is confirmed to some extent.

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