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Drug Release into External Absorber: Concentration-Dependent Diffusivity

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Introduction

Release of drug dispersed in polymer matrix into external absorber is of essence in drug delivery applications, for example, ointment and oral drug delivery system.[1–8] When drug is loaded in polymer matrix, it dissolves and diffuses subsequently into an external absorber through the polymer matrix on application. In general, drug is initially loaded in excess of its solubility in polymer matrix for long-term effect. Depending on the dissolution rate of drug, there are two important subjects which are frequently discussed: diffusion controlled release[1–6] and dissolution/diffusion controlled release.[7,8] In the former, dissolution rate of drug is assumed so fast that time of dissolution can be ignored; in the latter, diffusion rate is comparable to dissolution rate, and dissolution should be taken into account in mathematical model. In regime of diffusion controlled release, two distinct zones will appear due to dissolution of excess drug in polymer matrix, and complexity will arise from a mobile saturation front in mathematical modeling. The relevant theoretical model was pioneered by Higuchi.[1] Considering drug dispersed in a planar polymer matrix, Higuchi[1] discussed drug delivery when matrix was in contact with a perfect sink. Analytically approximate solution was given by Higuchi[1] using pseudo steady state approximation. The model of Higuchi[1] was solved by Paul and McSpadden.[2] Based on analytically exact solution, the applicability of pseudo steady state approximation was examined in their work. Using a refinement of integral method proposed by Volkov and Li-Orlov,[9] Lee solved extended model concerning conditions of finite external volume, spherical geometry, erodible surface, and so forth.[3] Wu and Zhou considered polymer matrix of several geometries in a finite external medium.[5] The effect of boundary layer covering the polymer matrix was analyzed by finite element method in their work. Considering a planar polymer matrix, similar analysis was also made using pseudo steady state approximation by them.[6] The integral method originates in the boundary-layer theory,[10] where, based on the assumption that the velocity profiles inside the boundary-layer all come from one approximate profile family, some important parameters like boundary-layer thickness, displacement thickness, momentum thickness, and wall shear stress, can be recovered from the integral equation. In the first integral method ever used, called the Karman-Pohlhausen method, a polynomial velocity profile of degree four was introduced in the momentum integral equation. Motivated by this method, Goodman[11–13] suggested the heat-balance integral method in heat conduction based on mathematical analogue. Using the heat-balance integral method, the heat conduction problems concerning infinite slab,[11,13] phase of change,[11,13] variable thermal properties,[12,13] and so on, were solved. Volkov and Li-Orlov proposed a refinement of integral method for heat conduction.[9] For elimination of the error possibly introduced by the temperature derivative term in Goodman's integral equation, they suggested a double integral technique, and a refined integral equation, called the integro-differential equation, was used in substitution for Goodman's integral equation. Using this refinement, accuracy of the approximate solution was found improved significantly in comparison with that by the heat-balance integral method, especially for the heat conduction problems concerning variable thermal properties.

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The refinement of integral method by Volkov and Li-Orlov[9] is applicable for the release systems of drug in polymer matrix in conditions of moving saturation front, erodible matrix surface, external finite absorber, variable physical properties, and so forth. In this contribution, diffusion controlled release of drug dispersed in excess of drug solubility in polymer matrix into an external absorber is under consideration based on Volkov and Li-Orlov's method.[9] For practicality, both effects of concentration-dependence of drug diffusivity and finite volume of external absorber are also considered. A semi-analytically approximate solution can be derived, and in addition, applicability and limitation of this method will be discussed under various system parameters, including excess quantity of drug in polymer matrix and volume of external absorber.

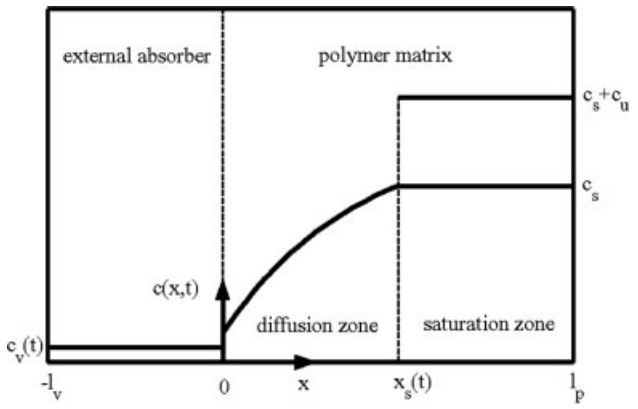

Figure 1. Schematic representation of diffusion controlled moving boundary model.

Diffusion Controlled Moving Boundary Model

Here, we consider release of drug dispersed excessively in a polymer matrix into an external absorber, of which volume is comparable to that of polymer matrix. Initially before diffusion, drug is dispersed uniformly in polymer matrix by $c_s + c_u$ in quantity per unit volume, where c_s and c_u are, respectively, drug solubility in polymer matrix and quantity of undissolved drug per unit volume. The thickness of polymer matrix is $2l_p$, with l_p being distance between central plane of polymer matrix and polymer matrix/external absorber interface, cross-section area of polymer matrix is a_{ps}, and volume of external absorber is v. And for convenience, equivalent length of external absorber is defined as $2l_v$ with $l_v = v/2a_{ps}$. For mathematical simplicity, some assumptions are made as followed:

(1) The polymer matrix is a thin, planar lamella.

(2) The dissolution rate of drug is fast and release is diffusion controlled.

(3) The diffusivity of drug is strongly dependent on concentration of drug.

By assumptions 1 and 2, analysis here can be confined to an one-dimensional, diffusion controlled, moving boundary problem. For symmetry, only half of release system needs to be considered. Referring to Figure 1, abscissa x originates from polymer matrix/external absorber interface, and extends to central plane of polymer matrix located at $x = l_p$. Because of fast dissolution of undissolved drug, polymer matrix has two distinct regions: diffusion zone and saturation zone, which are separated by moving saturation front located at $x = x_s(t)$, as shown in this figure. In diffusion zone, where $x \in [0,x_s(t)]$, drug dissolves completely, and in saturation zone, where $x \in [x_s(t), l_p]$, drug is saturated, together with excess, undissolved drug of c_u in quantity per unit volume. The drug concentration in diffusion zone is denoted by $c(x,t)$ and that in external absorber is c_v(t). Hence, relevant mathematical equations can be summarized as followed:

$$\frac{\partial c}{\partial t} - \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right) = 0, \quad 0 \le x \le x_s \tag{1}$$

$$-\left(D\frac{\partial c}{\partial x}\right)\bigg|_{x=x_s} + c_u\frac{dx_s}{dt} = 0, \quad 0 \le x_s \le l_p \tag{2}$$

$$-\int_0^{x_s} c\,dx + (c_s + c_u)x_s - l_v c_v = 0 \tag{3}$$

$$c = kc_v, \quad x = 0 \tag{4}$$

$$c = c_s, \quad x = x_s \tag{5}$$

$$x_s = 0, \quad t = 0 \tag{6}$$

where t is time elapsed, D is concentration-dependent diffusivity of drug, and k is distribution coefficient. In these equations, Eqs. 4 and 5 denote boundary conditions, and Eq. 6 denotes initial condition. For convenience, Eqs. 1–6 are rewritten, respectively, in scaled forms as followed:

$$\frac{\partial C}{\partial T} - \frac{\partial}{\partial X}\left(D^*\frac{\partial C}{\partial X}\right) = 0, \quad 0 \le X \le X_s \tag{7}$$

$$-\frac{1}{C_u}\left(D^*\frac{\partial C}{\partial X}\right)\bigg|_{X=X_s} + \frac{dX_s}{dT} = 0, \quad 0 \le X_s \le 1 \tag{8}$$

$$-\int_0^{X_s} C\,dX + (C_u + 1)X_s - L_v C_v = 0 \tag{9}$$

$$C = kC_v, \quad X = 0 \tag{10}$$

$$C = 1, \quad X = X_s \tag{11}$$

$$X_s = 0, \quad T = 0 \tag{12}$$

where $X = x/l_p$, $L_v = l_v/l_p$, $X_s = x_s/l_p$, $T = D_{max}t/l_p^2$, $C = c/c_s$, $C_u = c_u/c_s$, $C_v = c_v/c_s$, and scaled diffusivity D^* is defined by

$$D^*(C) = \frac{D}{D_{max}} \tag{13}$$

where D_{max} is maximum value of D for full range of drug concentration. When diffusivity is known, resolution of Eqs. 7–9 subject to Eqs. 10–13 needs numerical method, for example finite difference method. Mathematical complexity due to

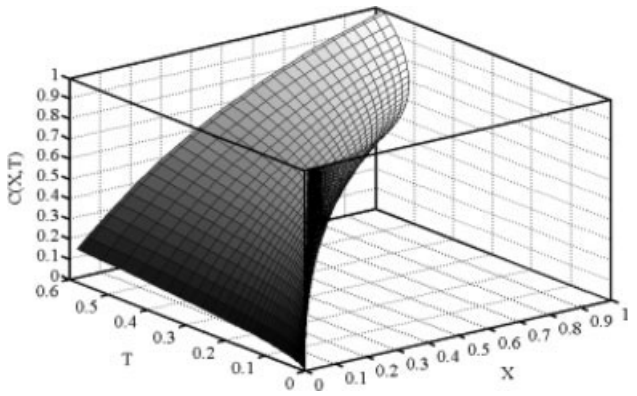

Figure 2. A typical solution surface of *C* as a function of both *X* and *T*.

moving boundary can be removed using special technique such as Landau transform.[14] A typical solution surface by numerical method is demonstrated in Figure 2. Numerical calculations for exact solution is generally laborious, hence a semi-analytically approximation is to be given in subsequent sections.

Derivation of Integral Equation

In refinement of integral method by Volkov and Li-Orlov,[9] an integral equation, called integro-differential equation, is suggested in substitution for governing partial differential equation. Here following the course of their work,[9] we starts from double integration of Eq. 7:

$$\int_0^{X_s}\int_{X_s}^{X}\left[\frac{\partial C}{\partial T}-\frac{\partial}{\partial X'}\left(D^*\frac{\partial C}{\partial X'}\right)\right]dX'dX=0 \tag{14}$$

With the aid of Eq. 8, we obtain an analog of integro-differential equation in Volkov and Li-Orlov's work[9] as

$$\int_0^{X_s}\int_{X_s}^{X}\frac{\partial C}{\partial T}dX'dX-\left(\int_0^{X_s}D^*\frac{\partial C}{\partial X}dX-C_uX_s\frac{dX_s}{dT}\right)=0 \tag{15}$$

Upon applying Leibnitz's rule on the first term, and integration by substitution on the second term, Eq. 15 becomes

$$\frac{d}{dT}\int_0^{X_s}\int_{X_s}^{X}CdX'dX+X_s\frac{dX_s}{dT}-\left(\int_{kC_v}^{1}D^*dC-C_uX_s\frac{dX_s}{dT}\right)=0 \tag{16}$$

Finally, after some rearrangement, Eq. 16 can be simplified further as the following integral equation:

$$\frac{d}{dT}\left[\left(\int_0^1\int_1^{\eta}Cd\eta'd\eta+\frac{1}{2}C_u+\frac{1}{2}\right)X_s^2\right]-\int_{kC_v}^{1}D^*dC=0 \tag{17}$$

where $\eta = x/x_s = X/X_s$. Equation 17 is key equation which is to be used later for approximate solutions.

Approximately Quadratic Polynomial Concentration Profile

An important assumption made in integral method is that variable profile in domain during process belongs to an approximate profile. Depending upon this assumption, calculation of solution is largely reduced in time and labor. Generally, polynomial profile is favorable. Here we use an approximately quadratic polynomial concentration profile which can be expressed as

$$C\cong a_2\eta^2+a_1\eta+a_0 \tag{18}$$

where in this equation, a_2, a_1, and a_0 are coefficients depending on time and parameters. For these coefficients, an additional subsidiary condition is needed and derived as follows. Upon applying total differentiation on Eq. 11 with respect to T, we have

$$\left.\frac{\partial C}{\partial T}\right|_{X=X_s}+\left.\frac{\partial C}{\partial X}\right|_{X=X_s}\frac{dX_s}{dT}=0 \tag{19}$$

Substitutions of both Eqs. 7 and 8 into Eq. 19, and after some rearrangement, additional condition is derived as

$$D^*(1)\left.\frac{\partial^2 C}{\partial X^2}\right|_{X=X_s}+\left(\left.\frac{dD^*}{dC}\right|_{C=1}+\frac{1}{C_u}D^*(1)\right)\left(\left.\frac{\partial C}{\partial X}\right|_{X=X_s}\right)^2=0 \tag{20}$$

Hence, according to Eqs. 10, 11, and 20, three coefficients can be solved. Solution of these coefficients strongly depends on the form of diffusivity, as is shown by Eq. 20. For monotonically increasing diffusivity, coefficients as followed is appropriate:

$$a_0=kC_v \tag{21}$$

$$a_1=-a_2-kC_v+1 \tag{22}$$

$$a_2=-\left(-kC_v+1+\frac{C_uD^*(1)}{C_u\left.\frac{dD^*}{dC}\right|_{C=1}+D^*(1)}\right)+\left[\left(-kC_v+1+\frac{C_uD^*(1)}{C_u\left.\frac{dD^*}{dC}\right|_{C=1}+D^*(1)}\right)^2-(-kC_v+1)^2\right]^{1/2} \tag{23}$$

The approximate quadratic polynomial concentration profile by Eq. 18 with coefficients in Eqs. 21–23 can be verified to be satisfactory for general use, and also, it satisfies condition that mass flux is negative in diffusion zone, that is, $-D^*\,\partial C/\partial X < 0$. Equations 21–23 show that approximately quadratic polynomial concentration profile used here is self-adjusting according to conditions of release system.

Example: Exponential Type Diffusivity

For illustration, a typical exponential type drug diffusivity expressed by

$$D^*=\frac{D}{D_{max}}=e^{C-1} \tag{24}$$

is used. Diffusivity defined in this equation varies significantly from e^{-1} to 1 during diffusion, and this is common in polymer matrix release system. The maximum value of diffusivity, D_{max}, exists at $c = c_s$. Substituting Eq. 24 into Eq. 23, it becomes

$$a_2 = -\left(-kC_v + 1 + \frac{C_u}{C_u + 1}\right) + \left[\left(-kC_v + 1 + \frac{C_u}{C_u + 1}\right)^2 - (-kC_v + 1)^2\right]^{1/2} \quad (25)$$

Hence, coefficients a_2, a_1, and a_0 are known by Eqs. 21, 22, and 25. In addition, from Eqs. 9 and 18, one has

$$X_s = \frac{L_v C_v}{-\int_0^1 C d\eta + C_u + 1} \cong \frac{L_v C_v}{\frac{1}{6}a_2 - \frac{1}{2}kC_v + C_u + \frac{1}{2}} \quad (26)$$

Substitutions of Eqs. 18, 21, 22, 24, and 26 into Eq. 17, one has from integration

$$\int_0^{C_v} \frac{\left[2L_v^2 C_v \Delta_1 + L_v^2 C_v^2\left(\frac{1}{12}\frac{da_2}{dC_v} - \frac{1}{6}k\right)\right]\Delta_2^2 + 2L_v^2 C_v^2 \Delta_1 \Delta_2\left(-\frac{1}{6}\frac{da_2}{dC_v} + \frac{1}{2}k\right)}{\Delta_2^4(-e^{kC_v - 1} + 1)} dC_v \cong T \quad (27)$$

where in this equation, Λ_1 and Λ_2 are, respectively, defined as

$$\Delta_1 = \frac{1}{12}a_2 - \frac{1}{6}kC_v + \frac{1}{2}C_u + \frac{1}{6} \quad (28)$$

$$\Delta_2 = \frac{1}{6}a_2 - \frac{1}{2}kC_v + C_u + \frac{1}{2} \quad (29)$$

From Eq. 27, approximation of C_v can be solved using simple numerical integration. And also approximation of fraction of drug released, fr, defined by

$$\text{fr} = \frac{c_v a_{ps} l_v}{(c_s + c_u) a_{ps} l_p} = \frac{L_v C_v}{C_u + 1} \quad (30)$$

can be obtained directly.

For evaluation, we examine final results when undissolved drug is exhausted. Two important parameters, Rft and Rffr, are defined, respectively, as

$$\text{RfT} = \frac{\text{approximate fT}}{\text{exact fT}} \quad (31)$$

$$\text{Rffr} = \frac{\text{approximate ffr}}{\text{exact ffr}} \quad (32)$$

where fT and ffr are, respectively, values of T and fr when moving saturation front just reaches central plane of polymer matrix, that is, when $X_s = 1$. Derivations of approximate fT and approximate ffr are as followed. Substitution of Eq. 25 into Eq. 26, and letting $X_s = 1$, value of C_v when $X_s = 1$ can be estimated using numerically finding root, and meanwhile approximate ffr can be read directly from Eq. 30. Subsequently, approximate fT is estimated from Eq. 27 using numerical integration. Based on definitions of these two parameters, if RfT is larger than unity, the time when $X_s = 1$ predicted by Eq. 27 is longer; if Rffr is larger than unity, the fraction of drug release when $X_s = 1$ predicted by Eq. 27 is larger. Applicability of approximate solution is determined by three system parameters: excess quantity of drug per unit volume C_u, distribution coefficient k, and half equivalent length of external absorber L_v. Distribution coefficient k depends on nature of polymer matrix and external absorber and is assumed unity for analysis. The variations of both RfT and Rffr for various values of C_u and L_v are demonstrated in Figures 3 and 4, respectively. As these two figures show, both RfT and Rffr are larger than unity for smaller C_u or larger L_v. When C_u increases or L_v decreases, both of these two get smaller, and may become smaller than unity when C_u is large, or L_v is small. If C_u continues increasing or L_v continues decreasing, Rffr will increase gradually after its minimum. The interesting phenomenon above can be realized by the following. When C_u increases, that is, quantity of undissolved drug increases, rate of moving saturation front will slow down, and concentration profile becomes flatter correspondingly; on the contrary when C_u decreases, rate of moving saturation front will speed up, and concentration profile becomes more curved. The effect of L_v is opposite to that of C_u. When L_v increases, that is, volume of external absorber increases, drug concentration in external absorber becomes smaller and which lead to faster rate of moving saturation front, and hence concentration profile becomes more curved correspondingly; on the contrary when L_v decreases, rate of moving saturation front will slow down, and concentration profile becomes more flatter. Therefore, for condition

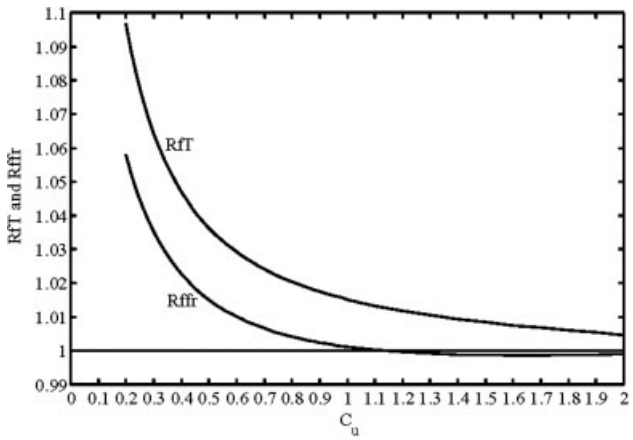

Figure 3. Variations of RfT and Rffr as functions of C_u when $L_v = 2.5$.

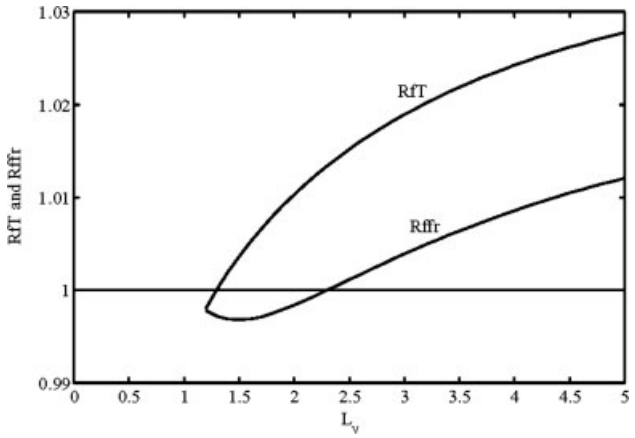

Figure 4. Variations of RfT and Rffr as functions of L_v when $C_u = 1.0$.

of smaller C_u or larger L_v, real concentration profile will becomes more curved than approximately quadratic polynomial concentration profile, and correspondingly real rate of moving saturation front is faster than that predicted by approximate solution. As a consequence, both RfT and Rffr appear positive deviation and vice versa. For comparison, concentration profiles for different values of L_v are demonstrated in Figure 5. Approximate solution is satisfactory for conditions of larger C_u or smaller L_v. When C_u is getting larger or L_v is getting smaller, both exact concentration profile and approximately quadratic polynomial concentration profile will approach to linear concentration profile, for rate of moving saturation front slows down. And therefore, both RfT and Rffr approach to unity. Applicable ranges of both C_u and L_v strongly depend on each other. If L_v changes, applicable range for C_u will be changed correspondingly; and contrarily, if C_u changes, applicable range for L_v will also be changed.

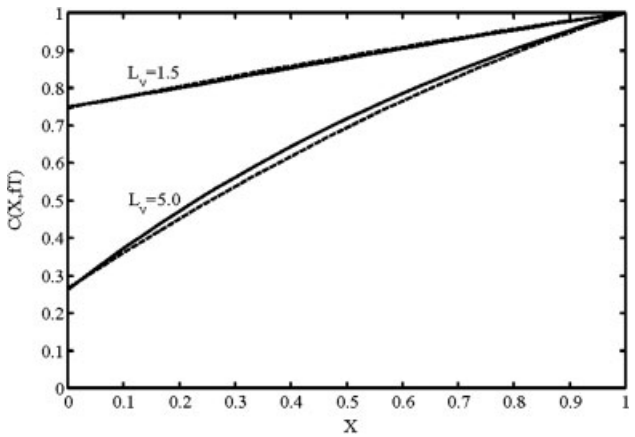

Figure 5. Spatial distribution of C at T = fT for various values of L_v.

In this figure, $C_u = 1.0$. Solid curves, exact solutions; dash-curves, approximate quadratic polynomial concentration profiles.

Conclusion

In this work, a semi-analytically approximate solution for release of drug dispersed excessively in a planar polymer matrix into an external absorber of finite volume is proposed based on refinement of integral method by Volkov and Li-Orlov.[9] Especially, condition when drug diffusivity is strongly dependent on its concentration is taken into account. From numerical results, approximate solution is found satisfactory for general conditions. Some important conclusions can be summarized as followed:

(1) For smaller C_u or larger L_v, approximate solution appears positive deviation.

(2) For larger C_u or smaller L_v, approximate solution appears negative deviation.

(3) Values of both C_u and L_v where approximate solution is applicable are interrelated.

Acknowledgments

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Notation

a_i = coefficients of approximate quadratic polynomial concentration profile, $i = 0$, 1, and 2
a_{ps} = cross-section area of polymer matrix
c = concentration of drug in diffusion zone
c_s = solubility of drug in polymer matrix
c_u = quantity of undissolved drug per unit volume
c_v = concentration of drug in external absorber
$C = c/c_s$
$C_u = c_u/c_s$
$C_v = c_v/c_s$
D = concentration-dependent diffusivity of drug in polymer matrix
D_{max} = maximum value of D
$D^* = D/D_{max}$
ffr = value of fr when $X_s = 1$
fr = fraction of drug released
fT = value of T when $X_s = 1$
k = distribution coefficient
l_p = half thickness of polymer matrix
l_v = half equivalent length of external absorber
$L_v = l_v/l_p$
Rffr = parameter defined in Eq. 31
RfT = parameter defined in Eq. 32
t = time
$T = D_{max}t/l_p^2$
x = abscissa of coordinate
x_s = position of moving saturation front
$X = x/l_p$
$X_s = x_s/l_p$
v = volume of external absorber

Greek letters

Δ_1 = variable defined in Eq. 28
Δ_2 = variable defined in Eq. 29
$\eta = x/x_s = X/X_s$

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