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Mathematical model for controlled diffusional release of dispersed solute drugs from monolithic implants

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ABSTRACT: New mathematical models are formulated and analytical solutions are presented for the diffusional release of a solute from both non-erodible and biodegradable multi-layered slab matrices in which the initial drug loading c_0 is greater than the solubility limit c_s. A Stefan problem with moving boundaries results from this formulation. An inward moving diffusional front separates the reservoir (unextracted region) containing the undissolved drug from the partially extracted region. The cumulative mass released is determined as a function of time. The ultimate goal of such an investigation is to provide a reliable design tool for the fabrication of specialized implantable capsule/drug combinations to deliver pre-specified and reproducible dosages over a wide spectrum of conditions and required durations of therapeutic treatment. Such a mathematical/computational tool may also prove effective in the prediction of suitable dosages for other drugs of differing chemical or molecular properties without additional elaborate animal testing.

INTRODUCTION

Controlled-release drug delivery is a subject of keen interest world-wide at this time. National and international pharmaceutical concerns and biomedical device developers are actively interested in exploiting this rapidly evolving and potentially lucrative market. Some of the many state-of-the-art applications may conceivable include:

- sustained release of estrogen and progesterone for menopausal women
- programmed release of antibiotics for patients recovering from surgical repair of bone fractures and/or installation of articular prostheses
- encapsulation of ovarian cells which themselves may continue to produce estrogen

- slow release of contraceptive chemicals for both men and women, particularly in third-world countries where the discipline of taking daily doses may be lacking
- drug delivery to targeted organs: e.g. slow release of insulin for diabetics
- encapsulation of pancreatic cells which may themselves trigger the natural production of insulin on a long term self-sustainable basis for diabetic patients.

Recent technical advances now permit one to control the rate of drug delivery. The required therapeutic levels may thus be maintained over long periods of months and years through implanted rate-controlled drug release capsules. Two such novel drug delivery systems currently employed are implantable polymeric and ceramic erodible monoliths.

Mathematical models developed over the past 35 years for controlled-release have recently been reviewed by Collins[1]. A simple practical model is presented here for the diffusional release of a solute from a biodegradable slab matrix in which the initial drug loading c_0 is greater than the solubility limit c_s. An inward moving diffusional front separates the reservoir (unextracted region) containing the undissolved drug from the partially extracted region. This front is followed by an inward propagating erosion front. The positions of these fronts are not known *a priori*. The mathematical formulation of such moving boundary problems (Stefan problem) has wide application to heat transfer with melting phase transitions and diffusion-controlled growth of particles, in addition to our topic of controlled-release drug delivery.

Additional applications of an industrial, agricultural or environmental nature, involving the diffusional release of a dispersed or dissolved solute from a polymeric monolith in which a pre-programmed dose-time schedule is necessary, further extend the interest in this problem to international levels. Examples of such applications may include the removal of solvent from polymer solutions during the dry spinning of fibres (Vrentas *et al.*[2]), photoresist technology and microlithography (Thompson *et al.*[3]) diffusional release of pollutants and additives from polymers into the environment (Wang *et al*.[4]) and controlled release of agricultural chemicals (Neogi & Allan[5]).

The rate-limiting property of the controlled drug delivery system resides in the design properties of the implanted drug delivery device itself, and is not necessarily dependent upon the physiology (e.g. the diffusion of the drug across biological membranes) of the subject. Drug release kinetics may depend on a number of intrinsic properties of the drug delivery implant: drug solubility, molecular weight and partition coefficient, matrix swelling, osmotic pressures, ion exchange, local electromagnetic force fields, etc. In what follows, we will focus on two specific properties of the drug delivery system: drug diffusion and matrix erosion. By the term erosion, we mean to denote the process by which material which is intrinsically insoluble in water can be converted into one that is water-soluble. In a pendant chain system for example, one may imagine a drug which is covalently bound to insoluble molecules and is then released by scission of its bonds either by water or by enzymatic action[6,7]. As the surface of the matrix is exposed to the surrounding extracellular fluids, its structure erodes and the drug impregnated within its walls and pores escapes.

MODEL DEVELOPMENT

For simplicity and without loss of generality, a constant erosion velocity is chosen[1], in the form ds/dt = - B, such that the position of the erosion front is given by the linear relation

$$s = s_0 - Bt \tag{1}$$

There would be no problem in principle in replacing the right-hand side of Eq. 1 with a more generalized form such as a polynomial in t. The distribution of drug concentration c(x,t) within the matrix at any time t and position x is governed by Fick's second law[8]:

$$\frac{\partial c}{\partial t} = \text{div}\,(\mathbf{D}\,\text{grad}\,c) = \frac{\partial}{\partial x}\left(D_x \frac{\partial c}{\partial x}\right) + \frac{\partial}{\partial y}\left(D_y \frac{\partial c}{\partial y}\right) + \frac{\partial}{\partial z}\left(D_z \frac{\partial c}{\partial z}\right) \tag{2}$$

where the flux is **D**grad c from Fick's first law and **D** is the diffusion coefficient for the drug contained within the pores of the matrix. In general, the matrix may be anisotropic and **D** will depend on position within the matrix and on time, due to possible spatial and temporal variations, respectively, in porosity, solubility, etc. In some instances, the diffusion coefficient **D** may also be concentration-dependent. However, for the purposes of this preliminary model, we will consider a homogeneous isotropic slab matrix with finite thickness $x = s_0$ and diffusion coefficient **D** = D, uniform within the monolithic matrix. Furthermore, we will treat the slab as semi-infinite, so that we may ignore variations in the y and z directions. Swelling of the polymer will not be considered.

Then, the three-dimensional unsteady diffusion Eq. (2) simply reduces to

$$\frac{\partial c}{\partial t} = \text{div}\,(\mathbf{D}\,\text{grad}\,c) = D\,\text{div}\,\text{grad}\,c = D\nabla^2 c = D\frac{\partial^2 c}{\partial x^2} \tag{3}$$

with the following initial and boundary conditions, respectively:

At $t = 0$ $\quad c(x, 0) = c_0$ set at the initial drug loading concentration
At $x = u(t)$ $\quad c(u, t) = c_s$ set at the solubility limit behind the diffusion front
At $x = s(t)$ $\quad c(s, t) = 0$ representing a perfect sink at the exposed erosion front surface

Were the matrix non-erodible, this initial and boundary value problem could be solved analytically in terms of transcendental functions (error functions) for the simple one-dimensional geometry of the idealized slab to yield the drug concentration distribution c(x,t) in the region $u < x < s$ between the diffusion front and the eroding outer surface of the slab. However, the resulting expressions for the eroding matrix will be difficult to integrate analytically for the subsequent determination of the position of the moving diffusion front. Therefore, a simpler preliminary solution for the release of drug from the matrix will be obtained by applying a straightforward mass balance across the diffusion front. The mass flux across the diffusion front is given as

$$D\left.\frac{\partial c}{\partial x}\right|_{x = u} = (c_o - c_s)\frac{du}{dt} \tag{4}$$

$$c(x) = c_s\left[1 - \frac{x-u}{s-u}\right] \tag{5}$$

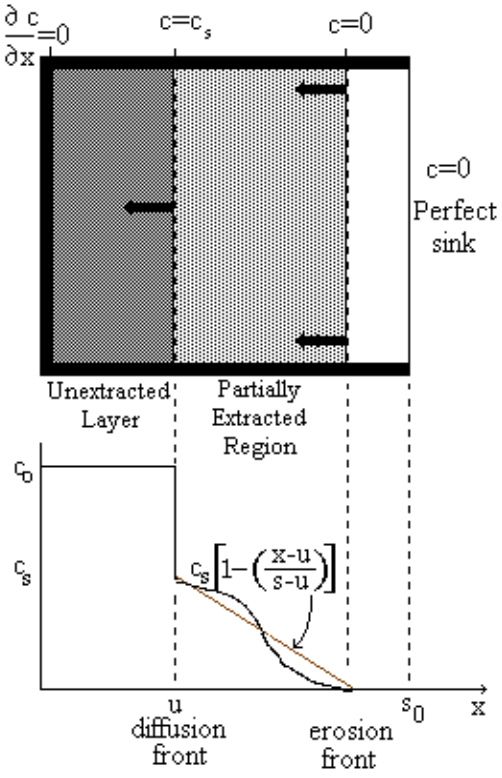
The mass balance Eq. (4) now yields the velocity of the diffusion front in dimensionless form as

$$\frac{dU}{dT} = \frac{\alpha}{(U-1)+\beta T} \tag{6}$$

where $\alpha = \frac{1}{(c_o - 1)}$ and $\beta = \frac{Bs_o}{D}$

and the corresponding expression for the position of the erosion front from relation (1) is

$$S(T) = 1 - \frac{Bs_o}{D}T = 1 - \beta T \tag{7}$$



We model a moving boundary problem. The outer surface of the matrix is considered to erode and to move inward at the same time as a diffusion front, starting at the exposed surface of the matrix, also moves inward towards the interior of the slab of initial thickness s_0, as shown here. In what we follows, we will adopt the general premises[9,10] that:

a) a perfect sink exists just outside the matrix, implying that drug is immediately removed from the region external to the matrix as soon as it arrives there, and

b) the drug concentration immediately behind the inward-moving diffusion front is fixed at the solubility limit c_s everywhere for all time. We denote the drug concentration as c(x,t) within the matrix, the thickness of the eroding slab at time t as x = s(t), the position of the diffusion front as x=u(t) and as $c = c_0$ the initial uniform drug loading concentration within the matrix.

FIGURE 1. Schematic of slab matrix

Through a simple change in variables, setting $(U-1) + \beta T = V$, expression (6) becomes

$$\frac{dV}{dT} = \beta + \frac{\alpha}{V} \tag{8}$$

which may then be integrated directly to yield an implicit algebraic relation for the position U(T) of the diffusion front in the form

$$W - \alpha \ln\left(\frac{W+\alpha}{\alpha}\right) = \beta^2 T \qquad (9a)$$

where $W(T) = \beta V = \beta\,(U - 1 + \beta T)$. The solution (9a) satisfies the boundary condition $W(0) = 0$, equivalent to $U(0) = 1$. It yields an expression for the position of the diffusion front as a function of time in the dimensionless form

$$U = \frac{W(T)}{\beta} + 1 - \beta T \qquad (9b)$$

from which we can determine the time T_1 at which the diffusion front reaches the left boundary of the slab at $X = 0$ as

$$T_1 = T\big|_{U=0} = \frac{1}{\beta}\left[1 + \frac{W(T_1)}{\beta}\right] \qquad (9c)$$

CUMULATIVE MASS RELEASED

The amount of drug released per unit of exposed area of slab matrix at any time t is simply the difference between the original mass/unit area of drug in $u < x < s$, that is $c_0(s_0-u)$, and the amount remaining at time t, so that the resulting mass of drug released at the exposed surface of the slab can be expressed as

$$m(t) = c_o\,(s_o - u) - \int_u^s c(x,t)\,dx \qquad (10)$$

where c(x,t) is the concentration distribution in the region $u < x < s$ which is given by Eq. (5). The amount of drug released from the slab at any time t may then be expressed as

$$m(t) = c_o\,(s_o - u) - c_s \int_u^s \left[1 - \frac{x-u}{s-u}\right] dx = c_o\,(s_o - u) - c_s\left(\frac{s-u}{2}\right) \qquad (11)$$

which becomes in dimensionless variables

$$M(T) = (1 - U) - \frac{S-U}{2C_0} = (1 - U) - \frac{1 - \beta T - U}{2C_0} \qquad (12)$$

This expression (12) for the time course of cumulative drug release may be evaluated directly by substituting the corresponding expressions for S(T) and U(T) from equations (7) and (9b) respectively. The resulting mass release M(T) implicitly incorporates the design variables B, s_0, c_0, c_s, D, which may be optimized to produce a pre-specified therapeutic release rate of the drug into the body over a given period of time.

LIFETIME OF THE DRUG DELIVERY DEVICE

When the leftward progressing diffusion front reaches the edge X = 0 of the slab, $U \rightarrow 0$ (Fig. 1), not all the drug initially contained in the matrix is yet depleted. We will compute the time required for the remaining drug to be released.

But first, let us estimate the time needed for $U \rightarrow 0$. Eq. (9a) may be plotted and the implicit relation for W = W(T) can be determined graphically to yield, using Eq. (9c), the time at which U = 0. For purposes of illustration only, we have arbitrarily taken $C_0 = 2$, B = 1, D = 1, which gives a value of $T_1 = T\big|_{U=0} = 0.368$ for the dimensionless time at which the diffusion front reaches X = 0.

It now remains to compute the time required for all the drug to be released from the slab matrix during the period $T\big|_{U=0} < T < T_f$, where T_f is the lifetime of the device or the time for all the drug to be released from the slab matrix into the body. In the absence of the diffusion front which has penetrated completely through the thickness of the slab at $T = T\big|_{U=0}$, and maintaining the linear distribution of concentration with distance in the interval $0 < X < S$ in the form

$$C(X,T) = C_a\left(1 - \frac{X}{S}\right) \tag{13}$$

where $C = C_s$ at X = 0 for $T \leq T\big|_{U=0}$ and $C = C_a$ at X = 0 for $T > T\big|_{U=0}$. It is noted that the concentration C_a at X = 0 will decrease over time from its value of C_s at $T\big|_{U=0}$ to zero at T_f, the time at which all the drug has been released from the slab. During this process, the erosion front at X = S continues to progress leftward towards X = 0.

The amount of drug remaining in the matrix at any time $T > T\big|_{U=0}$ is given by the area under the curve (Fig. 2) as

$$1 - M(T) = \frac{1}{2} C_a S \tag{14}$$

The rate $\frac{dM}{dT}$ of mass release due to diffusion is then determined by Fick's first law as

$$\frac{dM}{dT} = D\,\frac{\partial C}{\partial x} \tag{15}$$

Using Eqs. (13) and (14),

$$\frac{1}{2}\left(C_a\frac{dS}{dT} + S\frac{dC_a}{dT}\right) = -D\frac{C_a}{S} \tag{16}$$

Substituting for S from the dimensionless equivalent of Eq. (1) and framing in dimensionless variables, we obtain a single first-order differential equation for the concentration C_a at X = 0 as a function of time T in the form

$$\frac{dC_a(T)}{dT} = -\left[\frac{2}{(\beta T - 1)^2} + \frac{\beta}{(\beta T - 1)}\right] C_a(T) \tag{17}$$

which is readily integrated to yield an expression for the drug concentration at X = 0 as

$$C_a(T) = \frac{Q}{1-\beta T} \exp\left[-\frac{2}{\beta}\left(\frac{1}{1-\beta T} - 1\right)\right] \tag{18}$$

where $$Q = \frac{(1-\beta T_1)}{\exp\left[\frac{2}{\beta(\beta T_1 - 1)}\right]}.$$

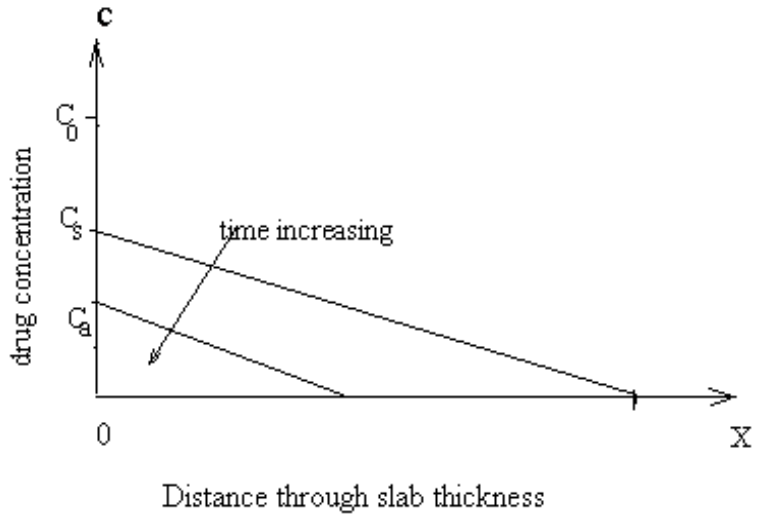


FIGURE 2. Approximated linear distribution of concentration C(X,T) for $T > T\big|_{U=0}$

In integrating Eq. (17) to obtain Eq. (18), we used the boundary condition $C_a(T_1) = 1$, where T_1 is given by Eq. (9c).

The second phase of mass M' (T) released during the interval $T_f > T > T\big|_{U=0}$ is simply given by

$$M'(T) = \frac{1}{2}\left[C_s S\big|_{U=0} - C_a S\right] \tag{19}$$

Note that as $S \to 0$, $M' \to \frac{1}{2} C_s S\big|_{U=0}$, which was the initial amount of drug present at $T\big|_{U=0}$. That is, all the drug is released by the time the erosion front U(T) approaches X=0. The time T_f required for the release of all the mass in the slab can now be computed from Eq. (18) with $C_a(T_f) = 0$ as

$$T_f = \frac{1}{\beta} = \frac{D}{BS_0} \tag{20}$$

Note from Eq. (18) that as $T \rightarrow T_f = \frac{1}{\beta}$, $C_a(T_f) \rightarrow 0$, because the exponential numerator decays to zero more quickly than does the linear denominator. Note also from Eq. (7) that the slab is fully eroded (S = 0) at T = $T_f = \frac{1}{\beta}$. The lifetime of the device can then be defined as the total time T_f required for release of all the original drug loading.

TIME TO ACHIEVE STEADY STATE MASS RELEASE

As the velocity $\frac{dU}{dT}$ of the diffusion front decreases with time and approaches the velocity $\frac{dS}{dT}$ of the erosion front, the distance $|(U\text{-}S)|$ separating the two fronts will reach a constant value and a steady state release rate will be established. By setting the velocity $\frac{dU}{dT}$ of the diffusion front equal to the velocity $\frac{dS}{dT}$ of the erosion front in Eqs. (6) and (7) of our one-layer eroding, we obtain

$$\frac{dS}{dT} = -\beta = \frac{dU}{dT} = \frac{\alpha}{(U-1)+\beta T} \qquad (21)$$

or

$$(U-1) + \beta T_{ss} = -\alpha / \beta \qquad (22)$$

Using Eqs. (7) and (9b), we find that steady state conditions defined by Eqs. 21 and 22 are achieved at time T_{ss} such that

$$|U - S| = \left| \frac{W(T_{ss})}{\beta} \right| = |(U-1) + \beta T_{ss}| = \alpha / \beta = \text{constant} \qquad (23)$$

or when $W(T_{ss}) = -\alpha$. From Eq. (9a), it appears that a singularity exists at $W = -\alpha$. This would indicate that the time to achieve a true steady state is long. However, one can estimate the time required to approach that steady state, within say 95% or 99%. Accordingly, we take $W = -\alpha + \varepsilon$, where $\varepsilon << 1$, which leads to an expression for the time T_{ss} to approach a condition of steady state release of drug from the slab. From Eq. (9a) we can estimate the time $T_{ss}(\varepsilon)$ to approach to within ε this steady state drug release rate as

$$T_{ss}(\varepsilon) = \frac{\alpha}{\beta^2}\left[\left| \ln \frac{\varepsilon}{\alpha} \right| - 1 \right] \cong \frac{\alpha}{\beta^2} \left| \ln \frac{\varepsilon}{\alpha} \right| = \frac{1}{C_0 - 1}\left(\frac{D}{Bs_0}\right)^2 \left| \ln[\varepsilon(C_0 - 1)] \right| \qquad (24)$$

NUMERICAL SOLUTIONS FOR THE EXACT ONE-LAYER SLAB MODEL

The linearized concentration distributions are valid under conditions of pseudo-stationarity (as defined by Higuchi[9,10]); that is, when the velocity of the diffusion front is

not too large as to alter concentration distributions too abruptly. For values of α and β outside the pseudo-stationary range, the diffusion front progresses more rapidly through the matrix medium and the pseudo-stationary approximation upon which the linearized concentration distributions were based may no longer be valid. We have shown that the solutions using linear concentration distributions are accurate to within a few percent of our exact numerically obtained solutions for a wide range of the dimensionless parameters α and β, where α is the ratio between the solubility limit concentration of the drug behind the diffusion front and the initial loading concentration of the drug in the matrix ahead of the diffusion front, and the dimensionless parameter β is the ratio of the erosion front velocity times the initial thickness of the slab divided by diffusion coefficient. The exact numerical results were obtained by a finite-difference computational solution of the governing equations with given initial and boundary conditions.

Thirty-one cases were computed with the following parameter values: Set 1: Three values of β = 0.05; .08; 0.10 with five values of α = 0.08; .10; 0.12; 0.18 and 0.20 (15 possible combinations) and Set 2: Four values of β = 0.1; 0.5; 1.0 and 5.0 combined with four values of α= 0.5; 1.0; 2.0 and 10.0. Those results will be analyzed in detail in a separate paper. Typical results are shown in Fig. 3 below for one such set of computations corresponding to the parameter values: α = 0.5 and β = 0.1. In this range of practical interest, the agreement of the linear approximation with the exact numerical solution for the position and velocity of the diffusion front and the resulting cumulative mass release as a function of time is seen to be very adequate. The cumulative mass curves begin gradually to diverge for $\alpha > 0.5$.

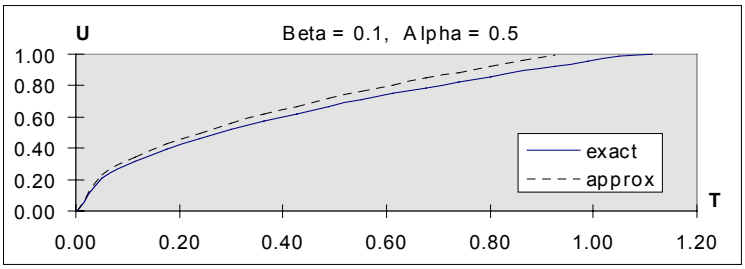


FIGURE 3a. Position U of the moving diffusion front. Comparison of exact numerical solutions with approximate analytical solutions.

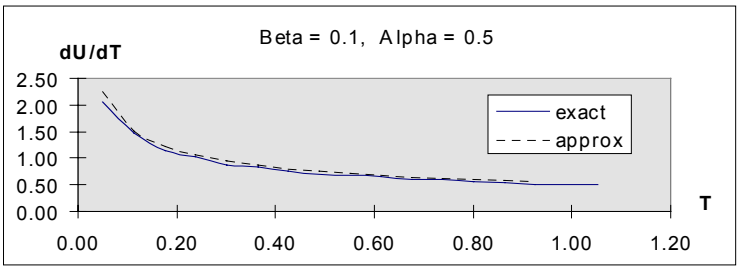


FIGURE 3b. Velocity dU/dT of the moving diffusion front. Comparison of exact numerical solutions with approximate analytical solutions

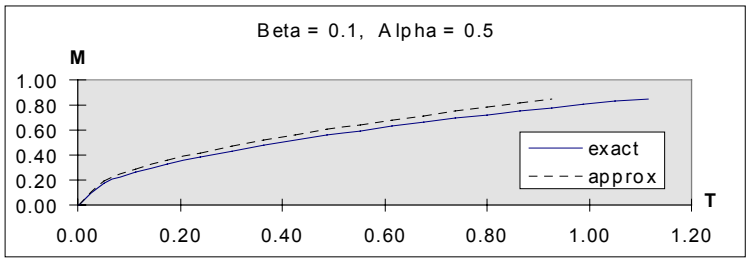


FIGURE 3c. Cumulative mass released. Comparison of exact numerical solutions with approximate analytical solutions.

CONCLUSIONS

By adjusting several design parameters, one may control the cumulative mass release process in a predictable manner. For example, by incorporating the desired macromolecular drug into the casting of a polymeric matrix, "winding tortuous" pores are created which condition the speed of the diffusion process through a corresponding alteration in the effective permeability of the cast drug-impregnated matrix[11]. By coating the matrix with an impermeable film or membrane, one can slow down the rate of drug release until bioerosion occurs. One may also increase the diffusion rate by raising the ratio of drug loading to solubility limit c_o/c_s.

Many of these considerations, including the shape factor and matrix swelling, can be incorporated into further refined versions of the above models which may then serve as a valuable framework for the design of experimental protocols to test and evaluate the sensitivity of such factors on the cumulative mass release of drug into the body as a function of time. Currently, time-consuming trial-and-error methods are employed in the design of such implants. Using the present approach, an efficient computationally aided tool can be created to design the desired implant in order to release the clinically prescribed dose-time program for specific therapeutic applications.

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