Analysis of controlled release of drug from an erodible implantable matrix

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1. Introduction

Diffusional release of a solute from a porous matrix is normally governed by Fick’s first and second laws. Higuchi (1963) first investigated the release of drug from a non-eroding planar surface and from a spherical pellet, assuming a perfect sink condition (c = 0) at the exposed surface of the monolith. The embedded drug is dissolved and is leached out by the penetrating solvent, diffusing outward through the network of capillary channels filled with the extracting solvent (Fig. 1). A pseudo-stationary state was assumed, implying that the inward progressing diffusion front separating the unextracted region ahead of it from the partially extracted region behind it, moves slowly enough that a linear concentration distribution obtains between the diffusion front and the exposed surface of the device. Fick’s first law is applied across this diffusion front, and this serves to determine the velocity and subsequently the position of the front as a function of time. However, this pseudo-stationary approximation is only appropriate when the concentration $c_0$ of drug initially impregnated in the matrix is much greater than its solubility limit $c_s$ in the matrix (high drug loading). The drug concentration is assumed to fall to its solubility limit immediately behind the inward progressing diffusion front, and a perfect sink condition is maintained at the surface of the matrix. No surface or volume erosion of the matrix was considered by Higuchi (1963).

The pseudo-stationary restriction was subsequently removed by Paul and McSpadden (1976) by use of the exact solution for a semi-infinite slab. The full problem of the Stefan moving boundary type was considered by Crank (1975) and has been discussed in considerable detail by Rubenstei n (1975). Lee (1980) has approximated the solution of Paul and McSpadden (1976) in which transcendental expressions appear, and has generalized it to include erodible matrices by
employing the refined version of the heat balance integral method due to Volkov and Li-Orlov (1970). The unsteady Fick's second law (Eq. 1) is integrated twice with respect to the spatial coordinate and the concentration distribution in the partially extracted region is approximated by a polynomial in the spatial coordinate. Lee (1980) used a simple quadratic concentration profile satisfying the boundary conditions to approximate the transcendental expressions of the exact solution on an integral average basis. He found the integral solutions to be much more accurate than the pseudostationary results and much easier to use than the exact solutions. The results are particularly useful for the release of dispersed solute when the solute (drug) loading is not greatly in excess of the drug solubility in the matrix.

2. Analysis

In this work, the controlled release of a drug from within a monolithic eroding matrix is formulated for a one-dimensional, homogeneous, isotropic, planar slab of finite thickness for a wide range of drug loadings, diffusion coefficients and erodibility conditions. The slab geometry is shown below in Fig. 1.

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Fig. 1. Schematic of slab showing front locations and concentration profiles.
We consider here the case for which the polymeric matrix erodes by an entirely heterogeneous process termed "surface erosion". The outer exposed surface of the erodible matrix, initially located at position \( x = s_0 \), is considered to erode inward towards the centerline axis of symmetry located at \( x = 0 \). At the same time a diffusion front, starting at the exposed surface of the matrix, also moves inward towards the axis of symmetry of the slab. In what follows, the general premises of Fischel-Ghodsian et al. (1993) and Abdekhodaei et al. (1996) will be adopted; that is: 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 \( c_s \) until the diffusion front reaches the centerline axis of symmetry at \( x = 0 \). At that point, the maximum drug concentration there begins to drop below the solubility limit for the first time. We denote the drug concentration as \( c(x, t) \), the time-varying thickness of the eroding slab as \( s(t) \), the position of the diffusion front as \( u(t) \), and the initial uniform drug loading concentration within the matrix as \( c_o \).

### 2.1 Mathematical Model

The diffusion of a drug from a high concentration region to one of low concentration in the absence of any pressure gradients in a one-dimensional planar system is governed by the following form of the conservation of mass principle (Fick’s Second Law):

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \tag{1}
\]

In this expression, the diffusion coefficient \( D \) is taken as constant in time and uniform over the width of the slab. The initial concentration throughout the slab at \( t = 0 \) is \( c_o \) and the boundary conditions are:

\[ c(s, t) = 0 \tag{2} \]

\[ c(u, t \leq t_1) = c_s \tag{3} \]

and

\[
\frac{\partial c(0, t > t_1)}{\partial x} = 0 \tag{4}
\]

where \( t_1 \) is the time at which the diffusion front reaches the axis of symmetry of the slab at \( x = 0 \). The boundary condition at the eroding exposed surface \( s(t) \) of the slab is specified in Eq. (2) above and is maintained over the entire duration of the process. The boundary condition at the diffusion front \( x = u(t) \) takes on one of two values depending on the time. Before the diffusion front reaches the axis of symmetry of the slab at \( x = 0 \), the concentration immediately behind the front remains fixed at the solubility limit \( c_s \) and the boundary condition shown in Eq. (3) applies. However, once the diffusion front reaches \( x = 0 \), that front ceases to exist and the symmetry condition imposed thereafter is expressed by the boundary condition shown in Eq. (4). Thus the calculation proceeds in two distinct phases. Phase I prevails as the diffusion front moves through the slab \( (t \leq t_1) \), and Phase II \( (t > t_1) \) after the front has reached \( x = 0 \), at which time the initial concentration there begins to fall off progressively with the extinction of the unextracted region.
The movement of the diffusion front is determined from a mass balance across it. The rate of mass release out of the unextracted region of the slab equals the mass flux behind the diffusion front on the partially extracted side of the front. Once the concentration profile between the diffusion front and the erosion front has been determined, the concentration gradient immediately behind the diffusion front is known. Applying Fick’s 1st Law then yields the time-dependent position \( u(t) \) of the advancing diffusion front as a function of the yet unknown concentration gradient immediately behind the front as

\[
u(t) = \int_0^t D \frac{dc}{dt} dt \quad \text{(5)}\]

For simplicity and without loss of generality in principle, a constant surface erosion velocity is chosen following Shargel et al. (1993) in the form \( ds/dt = -B \), such that the position of the surface erosion front is given by the linear relation

\[
s(t) = s_0 - Bt \quad \text{(6)}\]

Applying a simple mass balance across the exposed surface of the slab, the total mass \( m(t) \) of drug released per unit area of slab as a function of time may be expressed as

\[
m(t) = c_o (s_0 - u) - \int_u^c dx \quad \text{(7)}\]

Eq. (7) represents the difference between the original mass of drug initially contained in the region \( u < x < s_0 \) extending from the diffusion front \( u \) to the original exposed surface \( s_0 \) before erosion began, and that now remaining in the partially extracted region \( u < x < s \) between the diffusion front and the current position of the erosion front (see Fig. 1). That difference is the mass \( m(t) \) released from the slab up to time \( t \). This cumulative mass release \( m(t) \) is seen to depend critically upon the yet unknown position \( u(t) \) of the diffusion front. This is typical of the so-called Stefan moving boundary problem.

The following non-dimensional quantities are introduced by normalizing the physical variables such that: \( X = \frac{x}{s_0} ; S = \frac{s}{s_0} ; U = \frac{u}{s_0} ; C = \frac{c}{c_s} ; T = \frac{Dt}{s_0^2} \) and \( M = \frac{m}{c_o s_0} \).

two dimensionless parameters: \( \alpha = \frac{1}{C_0 - 1} \) and \( \beta = \frac{BS_0}{D} \). \quad \text{(8)}

The parameter \( \alpha \) is a function of initial drug loading \( C_0 \) only, while the parameter \( \beta \) represents the ratio of the respective contributions of erosion and diffusion processes. From this formulation it can be seen that the normalized mass release is a function of time \( T \) and depends on the two dimensionless parameters, \( \alpha \) and \( \beta \). These two parameters characterize the five material and chemical variables which define the controlled-release device; namely: the slab thickness \( s \), the diffusion coefficient \( D \), the concentration loading \( c_o \), the solubility limit \( c_s \) and the erosion velocity \( B \). The boundary conditions noted in Eqs. (2)-(4) apply behind their respective fronts. The positions of the diffusion and erosion fronts are functions respectively of \( \alpha \), \( \beta \) and \( T \) and of \( \beta \) and \( T \), as shown in Eqs. (5) and (6), while cumulative mass release is a function of \( T \), \( \alpha \) and \( \beta \).
2.2 Approximate Analytical Method - Pseudostationary solution (PSS)

We propose the following relatively simple approach, using the analytical solution (Collins et al. 1997) for the quasi-steady case (in which concentration in the interval situated between the diffusion and erosion fronts was assumed to vary linearly with depth within the matrix). In that work, the mass released has been determined as:

\[ M(T) = (1 - U) - \frac{S - U}{2C_0} = (1 - U) - \frac{1 - \beta T - U}{2C_0} \tag{9} \]

Eliminating \( C_0 \) in favor of \( \alpha \), we substitute \( C_0 = (\alpha + 1) / \alpha \) into relation Eq. (9) to obtain

\[ M(T) = 1 - \frac{\alpha}{2(\alpha + 1)} \left\{ \frac{\alpha + 2}{\alpha} U(T) + 1 - \beta T \right\} \tag{10} \]

It now remains to compute \( M(T) \) for various values of \( T \), evaluating \( U(T) \) from the solution of an implicit algebraic relation for the position \( U(T) \) of the diffusion front. The time \( T_{ss} \) to approach a steady-state output; i.e. corresponding to \( dM(T)/dT \) approaching a constant value, depends on \( \alpha \) and \( \beta \) (Collins et al. 1998), and can be expressed as

\[ T_{ss}(\epsilon) = \frac{\epsilon}{\beta} - \frac{\alpha}{\beta^2} \left[ \ln \left( \frac{\epsilon}{\alpha} \right) - 1 \right] \tag{11} \]

We take the value of \( \epsilon \equiv 0.01 \) so that the resulting value of \( T_{ss}(0.01) \) corresponds to the time required to reach 99% of a steady-state condition. For the range of parameter values investigated here, \( T_{ss}(\epsilon) > 0 \) and mathematical singularities are avoided as long as \( \alpha \leq \epsilon \). It is seen from Eq. (11) that \( T_{ss}(\epsilon) \) varies inversely as \( \beta^2 \) and that a pseudostationary state will be achieved most quickly for larger values \( \beta \) and smaller values of \( \alpha \) (equivalent to larger values of the drug loading \( C_0 \)). In these cases, the diffusion front will move more slowly, allowing for a transition to an equilibrium condition in which the concentration distribution \( C(X) \) will become linear as its gradient stabilizes at a constant value in the region between the two moving fronts.

Exact numerical solutions have been obtained computationally using two distinctly independent methods: a) a finite-volume method and b) a "mass enthalpy"-based approach conducted at our two collaborating universities. They will serve as baseline solutions upon which to assess the validity of the pseudostationary approximations which are presented here. Full details concerning these adapted numerical techniques will appear elsewhere. Suffice it to summarize here that: a) an appealing feature of the finite-volume method is that the discretized equations guarantee that the quantity being studied, for example, the mass concentration of the solute, is conserved in each computational volume element, no matter how coarse the grid scheme used, and b) the mass enthalpy method is based upon an analogy with the enthalpy changes associated with phase changes in classical heat transfer problems. In this method, we compute the "mass enthalpy" instead of the concentration. This approach is particularly attractive since it does not
require a prior knowledge of the position of the advancing diffusion front in order to solve the problem.

3. Results and Discussion

We have developed a series of exact computational solutions by which we may assess the accuracy of the linearized approximation for various combinations of $\alpha$ and $\beta$. These 31 solutions are characterized by the following parameter values:

Set 1:

$\beta = 0.05 \quad \alpha = 0.08 \quad$ Three values of $\beta$ combined with five values of $\alpha$

\[
\begin{array}{lll}
\beta & \alpha & \\
0.08 & 0.10 \\
0.10 & 0.12 \\
0.18 & \\
0.20 & \\
\end{array}
\]

(15 possible combinations)

Set 2:

$\beta = 0.1 \quad \alpha = 0.5 \quad$ Four values of $\beta$ combined with four values of $\alpha$

\[
\begin{array}{ll}
\beta & \alpha \\
0.5 & 1.0 \\
1.0 & 2.0 \\
5.0 & 10.0 \\
\end{array}
\]

(16 possible combinations)

We have obtained tables and plots for: $C(X, T; \alpha, \beta)$, $dU/dT(T; \alpha, \beta)$, $U(T; \alpha, \beta)$ and $M(T; \alpha, \beta)$ for these 31 sets of $\alpha$ and $\beta$. Representative results for the position $U(T)$ of the advancing diffusion front and for the cumulative mass release $M(T)$ are shown below, with one example from each of these two sets; i.e. for set 1: $\beta = 0.10; \alpha = 0.10$, and for set 2: $\beta = 1.0; \alpha = 0.5$

**Fig. 2.** Concentration distribution (linear) at various times $T$ for $\beta = 0.1, \alpha = 0.1$

**Fig. 3.** Concentration distributions (nonlinear) at various times $T$ for $\beta = 1.0, \alpha = 0.5$
The curves in Figs. 2 and 3 display representative concentration distributions $C(X)$ as a function of position within the matrix with dimensionless parameters:

a) $\beta = 0.1$; $\alpha = 0.1$ and b) $\beta = 1.0$; $\alpha = 0.5$ respectively, for various times $T$ during the mass release process. The exact concentration distributions portrayed above are: a) linear (Fig. 2) for low values of $\alpha$ and $\beta$ as assumed in the pseudostationary PSS model and b) increasingly nonlinear (Fig. 3) for larger values of $\alpha$ and $\beta$. Indeed the latter tend to exhibit a curvature which is convex upward, resulting in a slope $dC/dX$ which is less steep than the slope corresponding to the assumed linear pseudostationary distribution of concentration. Consequently, the PSS model overestimates $dC/dX$ behind the diffusion front which, in turn, is proportional to $dU/dT$. Accordingly, the velocity $dU/dT$ of the diffusion front is also overestimated in the PSS model. In other words, the diffusion front moves too quickly in the PSS model, and this leads to the deviation in mass release rate predicted by the PSS model relative to the exact computational solutions. We are currently developing a means for dramatically improving on the accuracy of the PSS model by effectively slowing down the PSS-predicted diffusion front velocity using a finite-zone continuity approximation.

Representative plots of the corresponding position of the advancing diffusion front as a function of time are displayed for the two selected cases in Figs. 4 and 5.

![Cumulative Mass Release](image1)

**Fig. 4.** Position of diffusion front as computed by 3 methods for $\beta = 0.1$, $\alpha = 0.1$

![Diffusion Front Position](image2)

**Fig. 5.** Position of diffusion front as computed by 3 methods for $\beta = 1$, $\alpha = 0.5$

From Fig. 4 it is clear that the PSS pseudostationary solution (set 1) agrees well with the two independently computed exact solutions. Similarly, excellent agreement with the exact solution was obtained for all parameter ranges in set 1. However, that degree of agreement deteriorates slightly in Fig. 5 for higher values of the parameter $\alpha$ (set 2) corresponding to a lower drug loading and hence 10-fold higher diffusion front velocities.
Fig. 6. Cumulative mass release (exact vs. approximate) for $\beta = 1$, $\alpha = 0.5$

A representative comparison for the cumulative mass release as a function of time for the selected case in set 2 is shown in Fig. 6. Superposed on this plot are the computed results of Lee (1980) using an integral method for the same set of parameters ($\beta = 1$, $\alpha = 0.5$). Lee applied his analysis only to the early phase of the release, stopping in phase 1 before the diffusion front reached $X = 0$. His phase 1 solution appears to be marginally better than the simpler PSS but still exhibits a significant deviation from the exact computed solutions shown on Fig. 6. These differences will be assessed in more detail in the following subsection.

3.1 Error analysis of PSS

The error in mass release $M$ has been normalized with respect to $M_0 = C_0S_0$, which is the non-dimensionalized mass of drug originally contained within the matrix. It can be readily seen from Fig. 7 that the pseudostationary PSS is accurate to within a maximum error of 0.05% for the drug loading parameter range of $0.065 < \alpha < 1$ for all values of $\beta$ within the rather broad range of $0.05 < \beta < 5$. 
Fig. 7. Percentage deviations in the PSS-predicted mass release relative to exact solution

4. Conclusions

In this work, we have evaluated the domains of validity of the non-erodible pseudostationary solution first proposed by Higuchi (1963) and which we have adapted to the case of a finite-thickness eroding slab with uniform drug loading and diffusion coefficient. We have shown that this solution, which is relatively simple mathematically and is based upon an assumed linearity of the concentration distribution in the interval lying between the moving diffusion and erosion fronts, will be accurate within a limited pre-determined $\alpha$ - $\beta$ domain.

We note from the two independently derived exact numerical solutions of this moving boundary Stefan problem which have served as a baseline in this investigation that: a) the overestimation of the concentration gradient immediately behind the penetrating diffusion front as a result of an assumed linear vs. the actual convex upward distribution of concentration with distance from the exposed surface leads to b) an overestimation of the velocity of the diffusion front which in turn results in c) an underestimation of the mass release rate of the drug into the body.

These considerations explain the restriction of an accurate pseudostationary solution to the parameter range of low $\alpha$ and high $\beta$. In physical terms, this means that pseudostationarity can only obtain when the relative distance between the two moving fronts changes slowly on a time-scale compared to the time for propagation of the diffusion front toward the axis of symmetry of the slab. This is the case for: (i) a high drug loading (low $\alpha$) which slows the advance of the diffusion front into the unextracted region by requiring it to dissolve a higher mass concentration of drug as it progresses into the monolith, or (ii) a faster moving erosion front (high $\beta$) which
allows the latter to match rapidly the velocity of the diffusion front and hence to narrow the rate of change of the distance between the two fronts.

The PSS pseudostationary solution is useful here principally to predict the mass release from the drug delivery device. Its parameter domain of accuracy can be dramatically improved by, in effect, slowing down the velocity of the diffusion front. This is equivalent to reducing the original PSS overestimation of the concentration gradient behind the diffusion front. This will cause the resulting mass release to approach more closely the exact release rate predicted from the full baseline numerical solutions. This improvement will be described in full mathematical detail elsewhere.

It appears that we may now have a firm grasp of the ranges of validity of these simpler analytical approximations. This enhanced understanding and extension of the validity of the analytical pseudostationary approximation to encompass higher drug loadings, for example, up to a factor of 3 and beyond, can be helpful in the preliminary phases of design of controlled-release drug delivery devices. Such a computational design tool is required to solve the inverse problem of specifying the release-dependent design parameters of drug concentration loading, drug solubility limit, drug diffusion coefficient within the porous monolith, initial slab thickness and the degree of erodibility of the monolithic exposed surfaces in order to effect a prescribed diffusion-controlled mass release as a function of time over pre-determined periods. Further applications in these areas are presently under investigation.

REFERENCES


