Swelling Controlled Release of Drug from Polymetric Delivery Devices: A Local Similarity Solution

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This paper presents a numerically integrated solution of moving boundary problems involving mass diffusion in polymer-penetrant system with a swelling controlled release of drug. Dividing the diffusion process into a finite number of fixed boundary problems, we have assumed the local similarity assumption to valid during the short period. Unlike the existing parameter expansion methods, the present solution is expected to be valid over a large range of control parameter representing the difference between solvent concentration at interface and the equilibrium value within the polymer. At small times, our numerical result shows that a larger values of the control parameter leads to a shorter interval for zero order drug release providing a higher release rate.

\textbf{KEYWORDS:} moving boundaries, local similarity method, polymer, controlled release

\section{Introduction}

Difficulties involving Stefan problems or moving boundary problems originate mainly from the time-dependent physical domain in which heat or mass diffusions occur. Typical Stefan problems include the growth of crystals, solidification of a melt and drug release in a polymer-penetrant matrix; It is the release of drug that will be studied here.

When a glassy polymer is exposed to a penetrant solvent, which can be gaseous or liquid, the latter diffuses into the former and a glassy-rubbery interface forms and moves through the polymer. Alfrey, Gurnee, and Lloyd\textsuperscript{1} indicated that the motion of the penetrant front proceeds according to time laws, which significantly differs from the classical Fickian relaxation. Different theories or equations of motion are need for well describing diffusion behavior. In polymer-penetrant system, change occurs as a result of the type of polymer, the type of penetrant, and ambient conditions. For some polymer-penetrant systems, however, relatively slow molecular relaxation occurs only at or near the glassy-rubbery interface, while instantaneous Fickian diffusions can be considered both in the glassy and rubbery phases. In this class of problems, a local driving force dominates the motion of the interface. This force arises from the difference between the solvent concentration at the rubbery side of the interface and the threshold concentration for swelling. Experimental observations and data for the phenomenological relation of the local kinetics at the penetrant front have been determined.\textsuperscript{2-8} Astarita and Joshi,\textsuperscript{9} Astarita and Sarti\textsuperscript{10} and Thomas and Windle\textsuperscript{11} considered certain problems involving swelling solvents in sorption and permeation processes in which the surface of the polymer is maintained at a constant concentration of the penetrant. On the other hand, Cohen and Goodhart\textsuperscript{12} studied the problem when the polymer is exposed to a finite amount of penetrant which eventually expires. According to their results, the position of the penetrant front versus time undergoes a long smooth transition from standard Fickian $t^{1/2}$ behavior to exponential time decay, finally reaching equilibrium. Later, Cohen and Erneux\textsuperscript{13} formulated and studied two different problems in the formation and use of pharmaceuticals via controlled drug release systems without volume change.\textsuperscript{14} The problems that Cohen and Erneux considered include the absorption of a constant reservoir of swelling solvent and that of a finite amount of swelling solvent. The main result obtained by Cohen and Erneux\textsuperscript{13} for the former shows a transition from initial $t$ behavior (Case II diffusion) to long time $t^{1/3}$ behavior (Fickian diffusion). Cohen and Erneux\textsuperscript{13} have analytically contributed the asymptotic solution of the interfacial position in the limits of short time behavior, long time behavior, and complete time history for a small parameter which is scaled by the difference between the constant reservoir concentration $C_0$ and the threshold concentration $C^\ast$.

Extending their previous work,\textsuperscript{13} Cohen and Erneux\textsuperscript{15} also formulated and analyzed a mathematical model for the swelling controlled release of drugs, in which the drug is initially immobilized in a glassy polymer matrix. The
drug is then released, which is due to, as a result of its diffusion under the countercurrent diffusion of a solvent into the polymer. While studying more complex system, Cohen and Erneux\textsuperscript{13,15} combine the Hiiguchi model\textsuperscript{16,17} for the transport of drug and the Astarita and Sarti model\textsuperscript{10} for transport of the solvent with volume change.\textsuperscript{18} Their asymptotic results show that the drug release rate is proportional to the difference $C_0 - C^*$ and remains for a short time by the volume expansion of the polymer.

The free boundary problem of Cohen and Erneux\textsuperscript{13,15} are extremely difficult or even impossible to be derived, due to the difficulty of time-dependent domain, analytical solutions. However, some mathematical treatment deal with the asymptotic, large or small time solutions, such as the perturbation solution,\textsuperscript{13,15,19} and the Lagrange-Burmann series expansion.\textsuperscript{20,21} However, the application has some limitation since the asymptotic solution provide qualitative estimates. A numerical technique, therefore, may be the only means of quantitatively estimating such problems if no limits are specified.

In this work, a local similarity method is employed to numerically study two cases of Stefan problems. The first case studied here is the diffusion in a glassy polymer with constant reservoir of the solvent on the polymer surface. In this case only one moving glassy-rubbery interface is formed in the polymer and its complete time behavior investigated. In the second case, the swelling controlled release in a polymer matrix, both the dissolved drug and the swelling solvent is diffused simultaneously. Consequently, both a glassy-rubbery interface and moving boundary is formed at two locations, which is due to the volume expansion of the polymer. The method applied in this work is expected to produce quantitatively estimates similar to the Stefan problems of Cohen and Erneux\textsuperscript{13,15}.

\section{Solvent Diffusion in Glassy Polymers}

This study undertakes investigations similar to those of Cohen and Erneux.\textsuperscript{13} The first is a Stefan problem for the penetrating concentration $C(X,T)$ behind a moving glassy-rubbery interface at position $X = S(t)$. The physical configuration diagram of this problem is shown in Fig. 1, which depicts the glassy phase of the polymer, located ahead of the interface, with the diffusivity of the solvent neglected and assumed to be zero. Furthermore, while in the rubbery phase, the diffusivity $D$ of the swollen polymer is taken to be constant. Herein, we also analyze the constant maintenance of an inexhaustible supply of the penetrant solvent at the polymer's surface. The two variables $C(X,T)$ and $S(T)$ to be solved satisfy the equations

\begin{equation}
\frac{\partial C}{\partial T} = D \frac{\partial^2 C}{\partial X^2}, \quad 0 < X < S(T),
\end{equation}

\begin{equation}
C = C_0 \quad \text{at} \quad X = 0,
\end{equation}

\begin{equation}
-D \frac{\partial C}{\partial X} - C \frac{dS}{dT} = k_2(C - C^*)^n \quad \text{at} \quad X = S(T),
\end{equation}

\begin{equation}
\frac{dS}{dT} = k_1(C - C^*)^n \quad \text{at} \quad X = S(T),
\end{equation}

\begin{equation}
S(0) = 0,
\end{equation}

where $k_1$, $k_2$, $D$, $C^*$, and $C_0$ are constant parameters. The former four belong to material parameters and the latter is the system's control parameter. Equation (1) is the Fick's law for a one-dimensional system and eq. (2) is the associated boundary condition at the surface. Equation (3) describes the mass balance at the moving interface. It is seen that the mass flux through the interface is assumed to be proportional to $(C - C^*)^n$. Equation (4) is the mathematical expression of the local kinetics, which drives the interface at a finite rate. The parameter $k_1$, $k_2$ and $n$ in eqs. (3) and (4) are phenomenological quantities, as obtained from experimental observations. The initial position of the interface is given by eq. (5).

A scaling system is introduced to nondimensionalize the model equations (1)–(5), via

\begin{equation}
t = \frac{T}{\alpha}, \quad x = \frac{X}{\beta}, \quad L = \frac{S}{\beta}, \quad u = \frac{C - C^*}{C_0 - C^*},
\end{equation}

where

\begin{equation}
\alpha = \frac{D(C_0 - C^*)^{1-2n}}{Ck_1^2}, \quad \beta = \frac{D(C_0 - C^*)^{1-2n}}{Ck_1},
\end{equation}

and

\begin{equation}
\tilde{C} = C^* + k_2/k_1.
\end{equation}

The reduced dimensionless model equations are

\begin{equation}
\frac{\partial u}{\partial t} = \varepsilon^{-1} \frac{\partial^2 u}{\partial x^2}, \quad 0 < x < L(t),
\end{equation}

\begin{equation}
u = 1 \quad \text{at} \quad x = 0,
\end{equation}

\begin{equation}(1 + \varepsilon u) \frac{dL}{dt} = -\frac{\partial u}{\partial x} \quad \text{at} \quad x = L(t),
\end{equation}

\begin{equation}
\frac{dL}{dt} = u^n \quad \text{at} \quad x = L(t),
\end{equation}

\begin{equation}
L(0) = 0,
\end{equation}

where $\varepsilon$ is a control parameter defined by

\begin{equation}
\varepsilon = \frac{C_0 - C^*}{C}.
\end{equation}

Notably, the parameter $C^*$ is the threshold concentration for swelling and, therefore, parameter $\varepsilon$ must be greater than nonzero to assure movement of the interface.
The exact solution of the free boundary problem (7)–(11) cannot be analytically determined. Rather, the approximate solution of this system is used as the following form

$$u(x, t) = 1 - A(t) \text{erf} \left( \frac{x}{2\sqrt{\varepsilon t}} \right) ,$$  

(12)

which automatically satisfies the boundary condition (8), and while substituted into the diffusion equation (7), it is easily found that

$$A = \text{constant} \quad \forall t > 0 \quad (13)$$

is required for the exact solution. Unfortunately, in the free boundary problem, parameter $A$ normally is not a constant. Consequently, the requirement (13) is surely violated and the analytical expression (12) is never the exact solution of eq. (7). The expression (12), however, works in a numerical treatment in which $A(t)$ is considered to be a piece-wise constant during a time interval $(t_{i-1}, t_i)$ and differs from one interval to another, viz., $A(t)$ can be expressed by

$$A(t) = A(t_{i-1}) , \quad t_{i-1} \leq t < t_i , \quad i = 1, 2, \ldots \quad (14)$$

where $t_{i-1}$ and $t_i$ represent the $(i-1)$-th and $i$-th specified times. Figure 2 schematically interprets this configuration. Errors resulting from the numerical integration in this work can be reduced provided that a small time interval is chosen. Relatively smaller time steps are recommended for larger rates of the penetrant front that occur at the beginning of the diffusion process.

The remaining boundary conditions (9) and (10) then become

$$\left[ 1 + \varepsilon \left( 1 + \text{Aerf} \left( \frac{L}{2\sqrt{\varepsilon t}} \right) \right) \right] \left[ 1 + \text{Aerf} \left( \frac{L}{2\sqrt{\varepsilon t}} \right) \right] = \left( \frac{\varepsilon}{t^n} \text{A exp} \left( - \left( \frac{L}{2\sqrt{\varepsilon t}} \right)^2 \right) \right)^n \quad (15)$$

and

$$\frac{dL}{dt} = \left( 1 + \text{Aerf} \left( \frac{L}{2\sqrt{\varepsilon t}} \right) \right)^n , \quad (16)$$

The strategy of the calculation is to solve the parameter $A$ from eq. (15) and then obtain the interfacial rate $dL/dt$ from eq. (16). However, this can be done only after the position $L$ is located. To determine the history of the interfacial position $L$ is numerically integrated

$$L_i = L_{i-1} + \frac{dL_{i-1}}{dt} (t_i - t_{i-1}) , \quad i = 1, 2, 3, \ldots \quad (17)$$

sequentially from the initial conditions, i.e., $L(0) = 0$ and $dL(0)/dt = 1$. In eq. (16), $L_i = L(t_i), L_{i-1} = L(t_{i-1})$ with $t_0$ corresponding to the initial time, i.e., $t_0 = 0$, and the time interval $(t_i - t_{i-1})$ can be chosen as small as possible depending on the desired accuracy. By using eq. (15) and (16), the numerical scheme used in the calculation is arranged as

$$\begin{align*}
[1 + \varepsilon \left( 1 + A(t) \text{erf} \left( \frac{L_i}{2\sqrt{\varepsilon t_i}} \right) \right)] \\
\times \left[ 1 + A(t) \text{erf} \left( \frac{L_i}{2\sqrt{\varepsilon t_i}} \right) \right]^n \\
= \sqrt{\frac{\varepsilon}{t_i \pi}} A(t_i) \exp \left( - \left( \frac{L_i}{2\sqrt{\varepsilon t_i}} \right)^2 \right) , \\
\frac{dL_i}{dt} = \left( 1 + A(t) \text{erf} \left( \frac{L_{i+1}}{2\sqrt{\varepsilon t_{i+1}}} \right) \right)^n
\end{align*}$$

(18)

In the present numerical simulations, the time step $(t_i - t_{i-1})$ must be appropriately chosen to ensure accuracy. Although a shorter time step is more accurate, required computing time should be a factor. We recommend that smaller time step is required for the short time behavior because of the faster penetrant velocity, while larger time step, in turn, can be used in simulating the long time behavior.

In Fig. 3, the computational results of the function $A(t)$ for $n = 1$ and $n = 5$, are shown. The time step for the computations is: 0.001 for $t < 0.5$ and 0.01 for $t \geq 0.5$. According to this figure, the advantage of the numerical treatment can be easily found since finite values of $\varepsilon$ can be chosen. This is in contrast to the asymptotic investigation given by Cohen and Erneux,\textsuperscript{13} in which only small $\varepsilon$ is used to describe the complete times history of the interfacial position.

Figure 4 displays the complete time histories of the interfacial position corresponding to $n = 1$ and $n = 5$ respectively, indicating that the short time behaviors are correlate with the results of Cohen and Erneux, i.e., $L = t$. In Fig. 4(c), when the time becomes large, the solutions approach the corresponding asymptotic solutions of longtime behaviors for all $\varepsilon$ derived by Cohen and Erneux. Figures also indicate that when $\varepsilon$ is small, e.g. $\varepsilon = 0.001$, the present result is reduced to that which

![Figure 2](Image330x574 to 529x782)
Cohen and Erneux\textsuperscript{13)} have obtained, as denoted by the empty circles.

Complete time history of the interfacial velocity is also essential to understand the evolution of the diffusion in the polymer-penetrant system. In Fig. 5, the complete time histories of the interfacial velocity for systems corresponding to \( n = 1 \) and \( n = 5 \), respectively, are shown. It is shown in the figure that large \( \varepsilon \) leads to quicker decay of the interfacial velocity, thus corresponding to the results in Fig. 4. Notably, quick decay of the interfacial velocity is an important phenomenon associate with the short time behavior in diffusion.

\section*{3. Swelling-Controlled Release}

Following the study of the first case, the second case investigates the diffusion of a drug in the swollen polymer, when added to the diffusion of the penetrant solvent. The drug is considered to be dissolved within a polymer matrix but not able to diffuse through the ma-
trix. While the penetrant solvent starts to diffuse into the polymer, the drug simultaneously begins to diffuse through the swollen part of the polymer. The release rate of the drug then is determined or controlled by the rate of diffusion of the penetrant solvent. The volume expansion of the swollen polymer is considered to enable movement of both the polymer surface and the penetrant front throughout the matrix. Notably, the scaling system used in the first case is adopted in the simulation. Figure 6 schematically depicts the dimensionless concentration profiles in a semi-infinite matrix for the drug (full line) and solvent (broken line). The new variable \( v \) denotes the dimensionless concentration of the drug, defined by \( v = B_0 \). \( B \) is the dimensional concentration of the drug and \( B_0 \) is the constant concentration of drug which was initially loaded and maintained in the solvent-free matrix. There are two moving fronts: one located at \( x = L_1(t) \), which separates the solvent-free polymer from the swollen polymer and one located at \( x = L_2(t) \), which results from the volume expansion of the polymer due to its gradual swelling. The polymer surface is initially located at \( x = 0 \). The diffusions of the drug and solvent are described in the dimensionless system:

\[
\begin{align*}
L_1(t) < x < L_2(t), \quad & u \approx -u_y \quad (20) \\
& u = 1 \quad \text{at} \quad x = L_2(t), \quad (21) \\
& -u_x = (1 + u_0) \frac{dL_1}{dt} \quad \text{at} \quad x = L_1(t), \quad (22) \\
& \frac{dL_1}{dt} = -v^n \quad \text{at} \quad x = L_1(t), \quad (23) \\
& L_2(t) = \bar{v}C \int_{L_1(t)}^{L_2(T)} \left( \frac{C}{C} + \varepsilon u \right) dx, \quad (24) \\
& v = 0 \quad \text{at} \quad x = L_2(t), \quad (25) \\
& -Dv_x = (v - 1) \frac{dL_1}{dt} \quad \text{at} \quad x = L_1(t), \quad (26) \\
& L_1(t) = L_2(0) = 0 \quad (27) \\
\end{align*}
\]

where \( D \) and \( D_d \) are dimensional diffusion coefficients of the solvent and drug, respectively, and \( \bar{v} \) is the molar volume of the swelling agent. Equations (20)–(23) relate to the solvent transport in the polymer-penetrant system and, in turn, equations (25)–(27) describe the diffusion of the drug in the swollen polymer. The volume change of the polymer due to the gradual swelling is expressed by eq. (24).

To derive the solution of the drug release system we first adopt a coordinate transformation, \( y = L_2 - x \), and reformulate equations (20)–(28) in terms of \( y \) and \( t \):

\[
\begin{align*}
& u \varepsilon^{-1} u_y \quad 0 < y < L^*(t), \quad (29) \\
& u = 1 \quad \text{at} \quad y = 0, \quad (30) \\
& u_y = (1 + u_0) \frac{dL_1}{dt} \quad \text{at} \quad y = L^*(t), \quad (31) \\
& \frac{dL_1}{dt} = -u^n \quad \text{at} \quad y = L^*(t), \quad (32) \\
& L_2(t) = \bar{v}C \int_0^{L^*(T)} \left( \frac{C}{C} + \varepsilon u \right) dy, \quad (33)
\end{align*}
\]
\[ \frac{D_d v}{D} = \varepsilon (v - 1) \frac{dL_v}{dt} \text{ at } y = L^*(t), \]

where \( L^*(t) = L_2(t) - L_1(t) \), represent the distance between the moving polymer surface and the penetrant front. Notably, if the volume expansion of the polymer is neglected, i.e., \( \bar{v} = 0 \), then equations (29)–(32) and (37) are identical to the diffusion system (7)–(11) of the first case. The local similarity solutions of variables \( u \) and \( v \) used herein are in the forms

\[ u(y, t) = 1 + A(t) \text{erf} \left( \frac{y}{2(e^{-1}t)^{1/2}} \right), \]

and

\[ v(y, t)A^*(t) \text{erf} \left( \frac{y}{2(D_d \varepsilon^{-1} t)^{1/2}} \right), \]

This automatically satisfies the boundary conditions (30) and (35), respectively, and would \( A \) and \( A^* \) be constants, they would be the exact solutions of the diffusion equations (29) and (34). However, the parameters \( A \) and \( A^* \) are not constants for satisfying the moving boundary conditions at \( y = L^*(t) \). The expressions (38) and (39), however, like (12) of the first case, can also be numerically treated in which \( A(t) \) and \( A^*(t) \) are considered to be constants during a time interval \( (t_{i-1}, t_i) \) and to differ from one interval to the next.

The procedure of the calculation is

(a) Set the initial penetrant front and volume expansion front at \( L_1 = (0) = L_2(0) = 0 \) and then \( L^* = 0 \) with \( dL_v/dt = -1 \).

(b) Substitute (38) and (32) into (31) to obtain a nonlinear algebra equation of \( A \), where \( A \) is solved by Newton-Rafsen iteration.

(c) Integrate the penetrant front position \( L_1 \) from eq. (32) with Runge-Kutta integration after \( A \) is determined.

(d) Determine \( A^* \) and the volume expansion front by eqs. (36) and (33).

(e) Obtain the diffusion region between the penetrant front and volume expansion boundaries at next time step as \( L^* = L_2 - L_1 \).

Repeat step (b) to (e), to determine the history of the penetrant and expansion fronts. Moreover, the drug release rate, as defined by Cohen and Erneux,\(^{15}\) can be presented as the nondimensional form

\[ m = \left[ -v_2 \right]_{y=L_2}. \]

In the numerical simulation, the diffusion coefficients \( D_d \) and \( D \) are assumed equal with specified conditions of \( C^* = 0.08 \) and \( k_2/k_1 = 1 \). The numerical results of the two way diffusion system are first compared with the results for the small-\( \varepsilon \) behavior derived by Cohen and Erneux.\(^{15}\) Figure 7 display the complete time histories of the penetrant front and volume expansion front for \( n = 1 \) and \( \bar{v} = 0.1 \) under \( \varepsilon = 0.1, 1.0 \), and 10.0, re-

\[ \text{Fig. 7. The complete time histories of the positions of the penetrant front } L_1 \text{ and the volume expansion front } L_2 \text{ with different } \varepsilon. \text{ Positive values correspond to } L_2 \text{ and negative values are } L_1. \text{ The empty circles stand for the results obtained by ref. 15 with small } \varepsilon. (n = 1, \bar{v} = 0.1) \]

\[ \text{Fig. 8. The complete time histories of the positions of the penetrant front (negative } L_1 \text{) and volume expansion front (positive } L_2 \text{) with different } \bar{v}. \text{ (a) } n = 1, \varepsilon = 1; \text{ (b) } n = 5, \varepsilon = 1. \]
spectively. According to this figure, the time history of the swollen domain \( L^* \) with small parameter \( \varepsilon \) are correlate with the conclusions of Cohen and Erneux. This is, \( \varepsilon = 0.01 \) is reduced to that which Cohen and Erneux have obtained as noted by the empty circles in Fig. 7. Also, Fig. 7 indicates that increasing the control parameter of \( \varepsilon \) decreases the velocity of the penetrant front. Consequently, the speed of the volume expansion front increases, and the swelling domain \( L^* \) for relatively small \( \tilde{v} \) will become less. Figure 8 proves that the molar volume of the swelling agent, \( \tilde{v} \), increases the moving distance of the expansion front, but decreases that of the penetrant front. Thus totally increasing the swollen domain, as compared with the results of the exclusion of the polymer’s volume change. Notably, if the volume expansion effect is neglected, the system reduces to the one-way diffusion problem previously.

If the time histories of the moving boundaries are affected by the parameters \( \varepsilon \) and \( \tilde{v} \), then the drug release rates will be influenced by the same parameters. The variations of the drug release rate combined with time and influenced by the parameters \( \varepsilon \) and \( \tilde{v} \) are shown in Fig. 9. According to this figure, the drug release rate becomes larger but decays more quickly with larger \( \varepsilon \). For each specific \( \varepsilon \), the release rate decays more slowly in the short time regime than in the long. It is the most interested to be observed in the short time interval that variation of the drug release rate is of zero order of time because it is desirable in design of a drug carrier. Figure 9 shows that the release rate remains constant during the use of shorter time span. Although larger \( \varepsilon \) results in higher release rate, the time interval for zero order release rate becomes shorter. In line with the conclusion of Cohen and Erneux, our results indicate that the release rate varies as \( t^{-1/2} \) (broken lines in Fig. 9) in the long time regime when \( \varepsilon \) is small.

§4. Conclusion

This work provides a local similarity method to numerically simulate two free boundary problems in controlled release pharmaceuticals, which have also been studied by Cohen and Erneux.\(^\text{13, 15}\) In the first case, a swelling solvent diffusion in glassy polymers is studied without considering volume change due to the swelling. This problem, when coupled with both the drug diffusion in the swollen part and the volume expansion of the polymer, becomes our second case. Therefore, the first case is in fact a special case of the second one. For both, the asymptotic solutions for small \( \varepsilon \) have been successfully derived analytically.\(^\text{13, 15}\) To date, the solutions for large \( \varepsilon \), however, can only be numerically ascertained. Within the concept of local similarity, we first divided the complete time histories of the diffusion systems into finite numbers. Which made them fixed boundary problems to be analytically solved. The complete time histories of the systems then were numerically integrated.

For small parameter \( \varepsilon \), results obtained in this work can be successfully compared to those obtained by Cohen and Erneux.\(^\text{13, 15}\) The main advantage of this numerical treatment is that the result for all values of \( \varepsilon \) can be precisely achieved, provided that the divided time steps are as small as needed. A constant drug release rate is desired, however, this can only be observed during the short time frame. The asymptotic result of Cohen and Erneux on small \( \varepsilon \) can lead to a precise estimate of the maximum time interval for zero order release. Whereas, for large \( \varepsilon \), they determined a qualitative trend that small parameter \( \varepsilon \) corresponds to a larger time interval for zero order release but yields smaller rate. Our results, on the other hand, can quantitatively estimate of the time interval for the zero order release and the corresponding release rate, as illustrated in Fig. 9. Finally, the numerical evidence of this work also shows the volume expansion of the polymer only slightly affects the drug release for finitely large \( \varepsilon \).