Modeling and Optimization of Drug Release From Laminated Polymer Matrix Devices

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The design and modeling of drug delivery devices using laminated layers to produce spatially nonuniform matrix devices leading to desired release rates were investigated with the focus on their optimal laminated hydrogel matrices for the diffusion-controlled release of dissolved drugs. The model consists of polymer layers laminated together through a photopolymerization process to form matrices with a spatially nonuniform initial drug distribution and/or nonuniform drug diffusivities. The model solution establishes that the drug diffusion behavior, especially the early time release behavior, can be manipulated by altering spatially nonuniform initial drug distributions and drug diffusivities in the assembly. Furthermore, optimal control theory and calculus of variation were used to determine a set of initial drug concentrations in the layers to attain a system that exhibits a drug release profile as close to required profile as possible for all time.

Introduction

Constant release rates are desired for drugs possessing a narrow range of therapeutic index. However, in conventional diffusion controlled matrix devices, where the drug to be released is distributed uniformly through a polymer, the release of a dissolved drug from a homogeneous geometry inherently follows first-order diffusion behavior with an initially high release rate followed by a rapidly declining drug release rate, a disadvantage frequently cited in their inability to achieve zero-order release kinetics. Therefore, various approaches employing release mechanisms other than diffusion control have been developed to achieve constant release rates in polymer matrix devices, for example, swelling controlled delivery systems based on hydrogels (Ogata, 1997; Yu and Grainger, 1995), development of surface eroding polymers (Tamada and Langer, 1992), and osmotic pressure pumps (Langer and Peppas, 1992).

However, diffusion controlled matrix devices have been among the most widely used drug delivery systems, mainly due to their low manufacturing cost. Diffusion control is particularly important to transdermal delivery where biodegradation and dissolution are not viable mechanisms controlling the release rate. To obtain near zero-order release behavior in diffusion controlled matrix devices, especially to eliminate the initially high release rate, various methods have been approached to modify release behavior from diffusion controlled matrix devices, such as modification of the geometry of the device (Narasimhan and Langer, 1997; Conte et al., 1993) and the use of rate-controlling barriers (Lee et al., 1980; Bodmeier and Paeratakul, 1990). An alternative approach for regulating drug release in diffusion-controlled monolithic devices is the use of a nonuniform initial concentration profile. In previous work, nonuniform concentration profiles were achieved by utilizing non-Fickian swelling behavior to extract drug from uniformly loaded hydrogel matrices (Lee, 1984) or by preparing multilaminates in which each layer had a different drug concentration by solvent-casting (Bodmeier and Paeratakul, 1990). Limitations of these methods exist with respect to the control over the initial drug distribution, fabrication time, and the use of organic solvent.

While each of the above methods has its advantages and limitations, our laboratory is exploring *in situ* photopolymerization techniques to prepare controlled, nonuniform initial drug concentration profiles in diffusion controlled matrix devices. The detailed experimental procedure is described elsewhere (Lu and Anseth, 1997, 1998). Briefly, a drug is dissolved in liquid prepolymer solutions at different concentrations, and a nonuniform initial drug distribution is then established by photopolymerizing the polymer matrix layer-by-

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layer (each layer containing a different drug concentration). The technique allows great flexibility during the processing of polymer delivery devices to achieve a wide variety of release patterns. For example, any initial concentration profile and/or diffusivity profile can be programmed in the matrix. Furthermore, experimental results (Lu and Anseth, 1997, 1998) have proven the efficacy of this approach by showing that the drug diffusion behavior can be manipulated effectively by altering nonuniform initial drug concentration profiles in multilaminates produced through this layer-by-layer photopolymerization process.

To understand and better interpret the release results from these complex matrices, it was necessary to develop a mathematical model of drug diffusion through these laminated polymer matrices. Extensive advances have been made in modeling diffusion controlled systems containing dispersed drug. For example, Paul (1985) and Narasimhan and Langer (1997) have analyzed the temporal release pattern from different matrix systems containing dispersed drug. However, considerably less effort has been spent on simulating diffusion of drug when the drug concentration is below its saturation solubility in the polymer. To the best of our knowledge, only Lee (1986) has examined the effect of nonuniform initial drug concentration on the release kinetics containing dissolved drug. This lack of interest may be related to the fact that no existing techniques offer control of the initial nonuniform concentration profile of dissolved drug accurately and reproducibly.

As mentioned previously, our laboratory is exploring new approaches to prepare controlled, nonuniform initial drug concentration profiles in polymer delivery devices to achieve a wide variety of release patterns and to allow greater flexibility in processing. The focus of this work was to develop a model to predict quantitatively the release behavior of photopolymerized devices containing nonuniform initial concentration profiles. In addition, another controllable parameter in the laminate device, drug diffusivity (such as variations in the cross-linking density) was incorporated in the model to examine its effects on release kinetics.

While these mathematical models were successful in predicting release profiles from known initial parameters, determining suitable initial parameters to obtain desired release behavior requires a trial-and-error process. Thus, optimal control theory and calculus of variation provide a method to calculate rigorously the set of initial parameters to optimize the desired release profile. This study develops, for the first time, an optimization technique to determine the most suitable initial concentration profile to obtain release behavior as close to chosen release behavior as possible in a diffusion-controlled matrix containing dissolved drugs. This technique is widely applicable and can be easily extended to optimize for other matrix parameters such as the diffusivity profile.

Theoretical

Modeling

For the drug delivery devices developed in this research, the system was modeled as one-dimensional transient mass transfer in a laminated disk. A plot for such a polymeric release system containing four layers is shown in Figure 1, where c_1, c_2, c_3, c_4 are drug concentrations in the first, second, third, and fourth layer of the matrix. The disk has a thickness L and an initial drug concentration profile $v(x)$ in contact with a solvent maintained at sink conditions. In this work, we consider the case of a low drug concentration, which was previously shown to not affect the drug diffusivity (Lu and Anseth, 1997, 1998). In addition, drug diffusion is the rate-controlling step rather than swelling or drug dissolution. This assumption is appropriate when the polymer swelling kinetics can be neglected (such as in systems where little swelling occurs), or when the diffusional release occurs from a pre-swollen matrix.

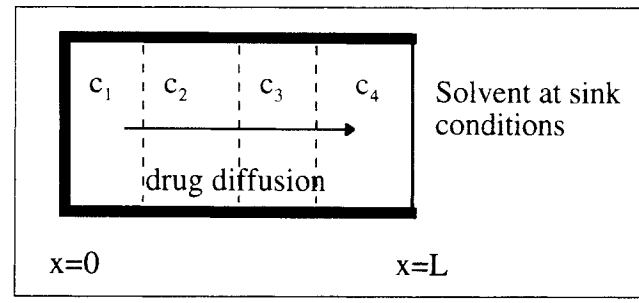

Figure 1. Drug release.

Surface is defined by the wide lines which represent the impermeable surface.

Mathematically, this problem is described using Fick's law as

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right) \tag{1}$$

With the boundary conditions

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = 0 \quad \text{at} \quad x = 0, \quad t > 0 \tag{2}$$

$$c(t, L) = 0 \quad \text{at} \quad x = L, \quad t > 0 \tag{3}$$

and the initial condition

$$c(0, x) = v(x) \quad \text{at} \quad t = 0, \quad 0 < x < L \tag{4}$$

Here, c is the drug concentration, t is the release time, x is the position normal to the effective area of diffusion for one-dimensional diffusional processes, and D is the drug diffusivity.

Solution When D is Constant

When the polymer is homogeneous through the assembly and the drug diffusivity is independent of drug concentration, Eq. 1 simplifies to the following form

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \tag{5}$$

This partial differential equation, with a constant coefficient (D), can be solved analytically with the method of separation of variables. The solution (Sani, 1995) is given by

$$c(x,t) = \sum_{n=0}^{\infty} \frac{2}{L} e^{-D\beta_n^2 t} \cos(\beta_n x) \int_0^L v(x) \sin(\beta_n x) dx \quad (6)$$

where $\beta_n = [(n+0.5)\pi]/L$.

Given the initial drug concentration profile, $v(x)$, the integral term can be evaluated, and the drug concentration as a function of time and space, $c(x,t)$, can then be determined throughout the entire matrix device. Furthermore, the drug flux J may be calculated by differentiation of Eq. 6 and evaluation at the polymer/solvent interface $x = L$.

$$J(t,L) = -D \left.\frac{\partial c}{\partial x}\right|_{x=L} = \frac{2D}{L} \sum_{n=0}^{\infty} (-1)^{n+1} \beta_n e^{-D\beta_n^2 t} \int_0^L v(x) \sin(\beta_n x) dx \quad (7)$$

The cumulative fractional release M_t/M_∞ is then obtained by integrating the flux $J(t,L)$ with respect to time according to Eq. 8

$$\frac{M_t}{M_\infty} = 1 - \frac{\sum_{n=0}^{\infty} \frac{(-1)^{n+1}}{\beta_n} e^{-\beta_n^2 Dt} \int_0^L v(x) \sin(\beta_n x) dx}{\sum_{n=0}^{\infty} \frac{1}{\beta_n} \int_o^L v(x) \sin(\beta_n x) dx} \quad (8)$$

Solution when D is space-dependent

When the drug diffusivity depends on its spatial position in the matrix [such as $D = D(x)$], Eq. 1 is a partial differential equation with a variable coefficient. With no analytical solution available, the Crank-Nicholson numerical method (Press et al., 1992) was used to solve the problem. Then, the time-dependent drug flux and cumulative fractional release can be obtained by solving a set of simultaneous linear algebraic equations at each timestep.

Optimization

As illustrated in the results section, nonuniform initial concentration profiles can be employed effectively to manipulate drug release behavior. Hence, optimizing the initial concentration profile $v(x)$ to obtain the desired flux as a function of time, $J^*(t,L)$ provides important insight when designing these systems. This work optimizes the initial concentration profile to achieve desired flux when the drug diffusivity and layer thickness are held constant. However, these and other matrix parameters can also be optimized using this technique to produce any desired release profile, constant or otherwise.

Optimization involves defining an objective functional that represents some features of the process to be maximized or minimized. For controlled drug delivery, the objective functional can be the maximal effect of drug therapy, defined as the difference between the desired drug release rate and the actual release rate; minimal cost of drug; or other parameters according to specific requirements. Specifically, the objective functional N to be minimized in this problem is

$$N = \int_0^L Av^2(x) dx + \int_0^{t_f} [J(t,L) - J^*(t,L)]^2 dt \quad (9)$$

This objective functional keeps the actual release profile $J(t,L)$ close to the desired profile $J^*(t,L)$, while minimizing the amount of initial loaded drug (such as to reduce cost). The initial drug loading contribution to the objective functional is: $F_1 = Av^2(x)$. The boundary contribution to the objective functional is: $F_2 = (J(t,L) - J^*(t,L))^2$. The importance of the two terms can be scaled by the magnitude of the coefficient A. For example, the magnitude of the coefficient A can be adjusted to make $F_1 \ll F_2$, $F_1 = F_2$, or $F_1 \gg F_2$.

In order to determine the necessary conditions for the extreme of N, an augmented objective functional N_A that includes the equality state dynamic constraints of Eq. 2 and has the same extrema of Eq. 9 is formulated (Ramirez, 1994)

$$N_A = N + \int_0^{t_f} \int_0^L \lambda (Dc_{xx} - c_t) dx dt \quad (10)$$

Here, λ represents the costate variable, $c_{xx} = (\partial/\partial x)(\partial c/\partial x)$, and $c_t = \partial c/\partial t$.

The first variation of the augmented functional is

$$\begin{aligned} \delta N_A = & \int_0^{t_f} \int_0^L \left[\left(D \frac{\partial^2 \lambda}{\partial x^2} + \frac{\partial \lambda}{\partial t} \right) \delta c + (Dc_{xx} - c_t) \delta \lambda \right] dx dt \\ & + \int_0^{t_f} \{2D^2 [c_x(t,L) - c_x^*(t,L)] + D\lambda(t,L)\} \delta c_x(t,L) dt \\ & + \int_0^{t_f} D\lambda_x(t,0)\, \delta c(t,0)\, dt - \int_0^L \lambda(t_f,x) \delta c(t_f,x) dx \\ & + \int_0^L [2Av - \lambda(0,x)] \delta v dx \end{aligned} \quad (11)$$

The fundamental theorem of the calculus of variation states that for an extremum of N_A, it is necessary that the first variation $\delta N_A = 0$. Since the variations δc, $\delta\lambda$, $\delta c_x(t,L)$, $\delta c(t,0)$, and $\delta c(t_f,x)$ are not zero, it follows that the necessary conditions for an extremum are:

State equation: Eq. 2 with its boundary conditions (Eqs. 3–4) and initial condition (Eq. 5).

Costate equation:

$$\frac{\partial \lambda}{\partial t} = -D \frac{\partial^2 \lambda}{\partial x^2} \quad (12)$$

Transversality boundary conditions:

$$\frac{\partial \lambda(t,0)}{\partial x} = 0 \qquad \text{at} \quad x = 0 \quad (13)$$

$$\lambda(t,L) = -2D(c_x(t,L) - c_x^*(t,L)) \qquad \text{at} \quad x = L \quad (14)$$

Transversality final condition:

$$\lambda(t_f,x) = 0 \qquad \text{at} \quad t = t_f \quad (15)$$

Optimal control:

With the above necessary conditions satisfied, the first variation becomes

$$\delta N_A = \int_0^L [2A\nu(x) - \lambda(0,x)]\delta\nu(x)dx \qquad (16)$$

To insure that the first variation is always minimized, the control variation $\delta\upsilon(x)$ is chosen in the gradient direction as follows

$$\delta\upsilon(x) = -[2A\,\upsilon(x) - \lambda(0,x)] \qquad (17)$$

The coupled state and costate equation set is a split boundary value problem with the state specified at the initial time and the costate specified at the final time. A control vector iteration method has been used to numerically solve this problem. The control vector iterative method is as follows:

(1) Select an initial concentration profile $\upsilon^0(x)$.

(2) Numerically integrate the state Eq. 2 forward in time with the specified initial and boundary conditions. The Crank-Nicholson finite difference method was used (Press et al., 1992).

(3) Integrate the costate Eq. 12 backwards in time with the specified final condition of Eq. 15 and the boundary conditions of Eqs. 13 and 14. The boundary condition of Eq. 14 is dependent upon the solution of the state solution (Eq. 2). Again, the second-order Crank-Nicholson implicit finite difference method was used.

(4) Compute a new boundary control, which minimizes the first variation

$$\upsilon^n(x) = \upsilon^{n-1}(x) + \delta\upsilon(x) \qquad (18)$$

with $\delta\upsilon(x)$ given by Eq. 17.

(5) Repeat steps 2 through 4 until the objective functional does not change by more than 0.01%.

During the optimization process, the concentration profile was constrained to values greater than or equal to zero.

Results and Discussion

Modeling

The model developed in the theoretical section can be used to predict the effects of any continuous initial concentration profiles on release patterns. To illustrate this point simply, a four-layer matrix device was analyzed, although complex devices with more layers could be handled by a simple extension of the approach. To simplify the simulation process, the drug diffusivity at the polymer/solvent interface (D), total drug loading, and total matrix thickness (L) were held fixed. In addition, dimensionless time (Dt/L^2), dimensionless distance (normalized by the total matrix thickness x/L), normalized drug concentration (normalized by the sum of the drug concentrations in each layer), and normalized drug flux (normalized by the initial drug loading and the cross-sectional area) were used. Under these conditions, the distribution of the drug loading and the drug diffusivity profile in the polymer are the only two controllable parameters left to consider to simulate the drug release from the proposed laminates. The distribution of drug loading can be achieved by simply changing the initial drug concentration profile in the matrix device, and the diffusivity profile can be achieved by altering the cross-linking density in each layer. To compare simulation results of the various cases, all calculations were performed until 80% of the total drug was released.

Effect of Nonuniform Initial Concentration Profile. To investigate the net effects of a nonuniform initial concentration profile on the resulting release pattern, four-layer devices with constant diffusivity and constant thickness in each layer were considered. Four different normalized initial concentration profiles were studied and are shown in Figure 2a. The corresponding release profiles are plotted in Figure 2b.

The simulation results in Figure 2b illustrate how simple changes in the initial concentration profile dramatically affect the drug release behavior, especially the early time release behavior. For the uniformly distributed drug loading (curve a), the drug release pattern displays an initially high release rate (burst effect). Usually, it is desirable to eliminate the burst effect since it may cause negative side effects or even be toxic to human bodies. From curve b to curve c to curve d, as the distribution of loaded drug is made more nonuniform (such as by increasing the relative loading at the center of the device compared to the surface), the early time release behavior changes significantly. These changes range from a less pronounced burst effect (curve b), to total elimination of the burst effect (curve c), to an initially low release

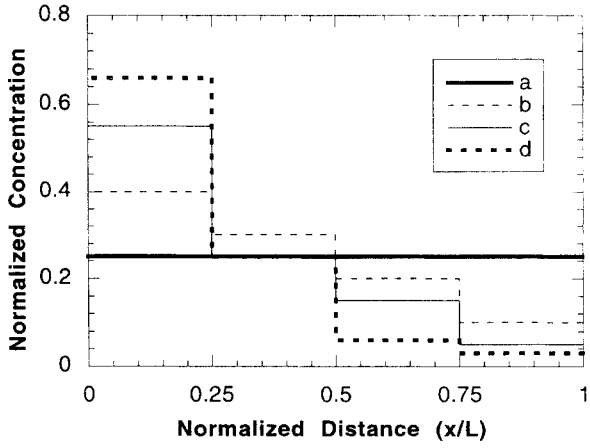

Figure 2a. Normalized initial concentration profiles.

From center outward: (a) 0.25, 0.25, 0.25, 0.25; (b) 0.4, 0.3, 0.2, 0.1; (c) 0.55, 0.25, 0.15, 0.05; and (d) 0.66, 0.25, 0.06, 0.03.

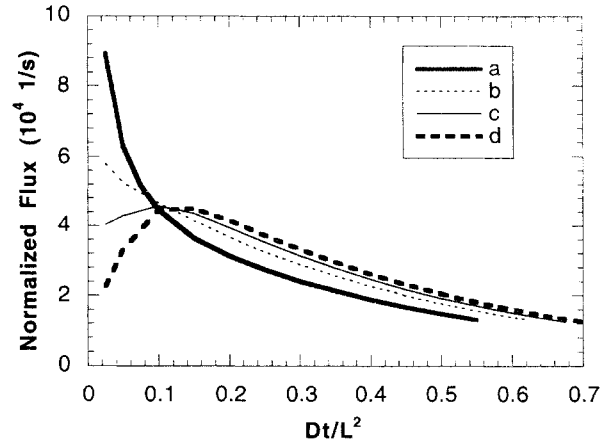

Figure 2b. Effect of nonuniform initial concentration profiles on release pattern.

rate (time lag, curve d). This wide variety of early time release behavior from the burst effect to the time lag can be designed to satisfy specific requirements. For example, the time lag release behavior can be used when tolerance development is very important. Moreover, Figure 2b shows that a steeper concentration gradient gives a prolonged delivery at a higher release rate. This behavior results from the higher concentration of drug diffusing from the center of the device, which increases the release rate at longer time scales compared to matrices with uniform loading.

Effect of Nonuniform Diffusivity Profile. Polymeric matrix parameters which may affect the diffusion process are of considerable importance in drug release processes through polymers. In particular, the drug diffusivity in the polymer is an important parameter which can be easily controlled by modification of the polymer structure, such as the cross-linking density (Lu and Anseth, 1997, 1998). When the material is not homogeneous in the laminate assembly, the diffusivity is space-dependent, and numerical solutions can be used to model the drug release behavior.

Simulation results showed that the release behavior did not change dramatically with a nonuniform diffusivity profile in the case of a uniform initial drug distribution, so the combined effects of a nonuniform concentration profile and a nonuniform diffusivity profile were examined, as illustrated in Figure 3a. The normalized initial concentration profile, from the center outward, is: 0.55, 0.25, 0.15, 0.05. Three cases were examined when the diffusivity at the outmost layer was held constant: (a) uniform diffusivity, (b) a doubled diffusivity in the inner three layers, and (c) a half diffusivity in the third layer and a five-fold diffusivity in the inner two layers.

Figure 3b shows clearly that the nonuniform diffusivity profile significantly affects the release behavior. Since drug is transported from the center outward by diffusion, higher diffusivity in the inner layers promotes drug diffusion, and, thus, a higher flux as shown in curve b. On the other hand, the magnitude of the smallest drug diffusivity in the assembly is crucial for the total release rate. For example, in curve c the drug diffusivity in the third layer is half of that in curve a, but the drug diffusivities in the inner two layers in curve c are five-fold of those in curve a. However, curve c exhibits a smaller flux compared with curve a due to the smaller drug diffusivity in the third layer. In the limiting case when the drug diffusivity in the outermost layer is much smaller than those in inner layers, the outermost layer functions as a membrane, which controls the matrix release rate.

Optimization

As illustrated in the previous sections, spatially nonuniform initial concentrations and spatially nonuniform diffusivities are controllable parameters that can be altered to manipulate drug release behavior in laminate matrix devices. However, determining the initial conditions that provide the desired release behavior is nontrivial, especially when considering the synergistic effects of several controllable parameters. Therefore, we now focused on optimization techniques to guide in the development of matrix devices that exhibit desired release behavior. In particular, a spatially nonuniform initial concentration profile was found to be one of the most sensitive and versatile parameters, so we chose to optimize the initial concentration profile to obtain as close to a desired release profile as possible for the period of operation.

During the optimization process, an initial concentration profile was chosen and the objective functional was calculated. The initial profile was then perturbed using optimal control theory, and a new objective functional was determined. Theoretically, this process is repeated until the objective functional is minimized, and the resulting initial concentration profile is then taken as the optimum. Practically, this process was continued until the objective functional did not change by more than 0.01%, which means that the release profile did not change significantly with further iterations. For ease of programming, an optimization was performed using a fixed final release time rather than fractional release; however, appropriate final simulation times were chosen that corresponded to required fractional release. Throughout this article, the optimization was performed to obtain desired release behavior until approximately 65% of the total drug was released.

Effect of the Weighting Factor w. To minimize the number of iterations, a positive weighting factor w was incorporated to amplify the control variation δv at each iteration level {such as $\delta v = -[2Av(x) - \lambda(0, x)]^* w$}. Figure 4 shows the ef-

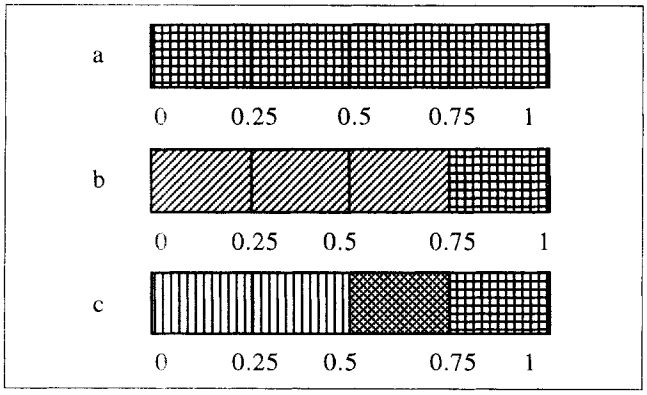

Figure 3a. Nonuniform diffusivity profiles.

Diffusivities are: 20 (▥), 8 (▨), 4 (▦), and 2 (▩), and the unit of the diffusivity is 10^7 mm^2/s. From center outward, the normalized initial concentration profile is: 0.55, 0.25, 0.15, 0.05.

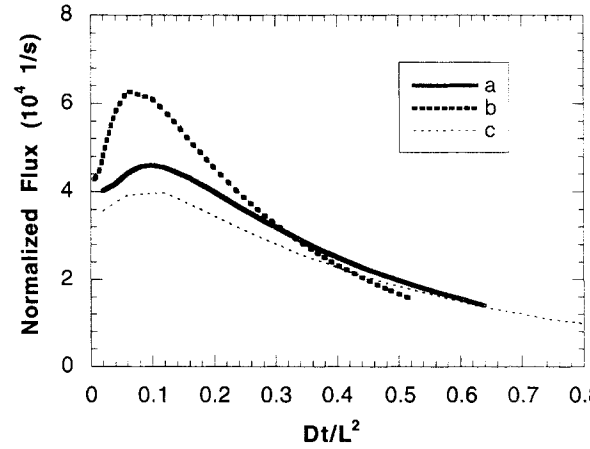

Figure 3b. Effect of nonuniform diffusivity profiles on release pattern.

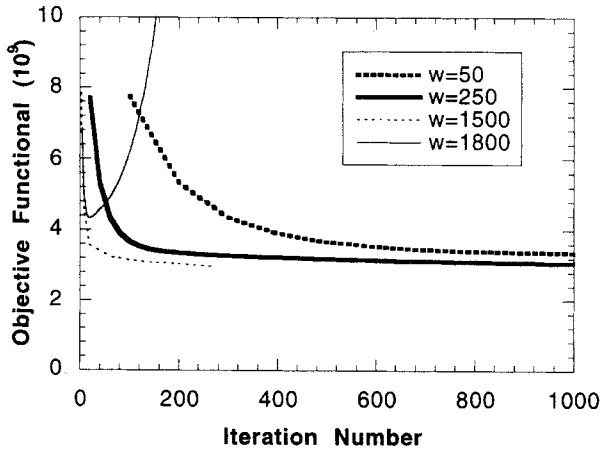

Figure 4. Effect of weighting factor on the iteration number and the objective functional.

fect of the magnitude of the weighting factor on decreasing the number of iterations to minimize the objective functional. In these calculations, the coefficient A was set to zero.

As expected, the magnitude of the weighting factor significantly affects convergence by varying the rate at which the minimum objective functional is approached. For example, when the weighting factor w was increased by a factor of 30 (from 50 to 1,500), the convergence rate increased 30-fold to reach nearly the same optimal result. However, the weighting factor w must be carefully chosen and not too large. For example, when w was 1,800, the objective functional converged erratically. These preliminary results provided guidance in choosing appropriate weighting factors for the following optimizations.

Effect of Initial Concentration Profiles before Optimization. To confirm the property of the optimal policy, that the optimal state is independent of the chosen initial state, three quite different representative initial profiles (curves a, b, and c in Figure 5a) were optimized with the same objective of a constant release rate when the coefficient A was set to zero. From the center outward, the initial concentration spatially increased, did not change, and decreased in curves a, b, and c, respectively. As expected, the convergence rates from these initial profiles were quite different in the three cases: from curve a to curve b to curve c, more and more iteration times were needed to obtain the optimal initial concentration profile; however, after optimization, all three cases reached the same optimal profile (curve d) as shown in Figure 5a. This result illustrates that the optimal concentration profile is independent of the initial concentration profiles chosen to begin the optimization. Furthermore, the optimization process introduced concentration peaks and troughs into the optimal initial concentration profile to achieve constant release behavior. The reason for the oscillating profile is related to the desired constant flux. Once the profile becomes flat, the release rate will inherently decrease with time, so an oscillating profile allows one to delay the time when the concentration profile becomes flat, and hence maintain a constant release rate for longer times. As expected, the magnitude of the peaks increases towards the interior of the device, since the molecules in the center have the longest path to diffuse to the surface.

Figure 5b compares the ideal constant release profile with the optimized release profile. As shown in Figure 5b, the optimized release rate immediately enters the desired release rate regime. For the prescribed release time, the optimized release rate fluctuates around the desired release rate to produce a release pattern with small deviations from the ideal case. This constant release is further illustrated by the nearly linear cumulative release curve. Eventually, the continual loss of drug by diffusion produces a more homogeneous, flat concentration profile, and this results in the final decline of the drug release rate. However, optimization work can examine conditions to provide a release rate as close to zero-order as possible for extended time periods.

Effect of the Coefficient A. As stated previously, the objective functional consists of two parts: the initial drug loading contribution $F_1 = Av^2(x)$, and the boundary contribution $F_2 = [J(t, L) - J^*(t, L)]^2$; and the magnitude of the coefficient A can be adjusted to make $F_1 \ll F_2$, $F_1 = F_2$, or $F_1 \gg F_2$. Figure 6 demonstrates the effect of the magnitude of the coefficient A on the optimal initial concentration profile. In

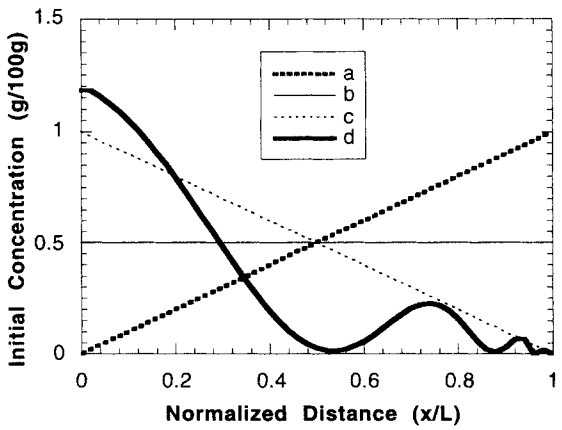

Figure 5a. Effect of initial concentration before optimization on optimal results.

Curves a, b, and c are the chosen initial concentration profiles before optimization; curve d is the optimal initial concentration profile.

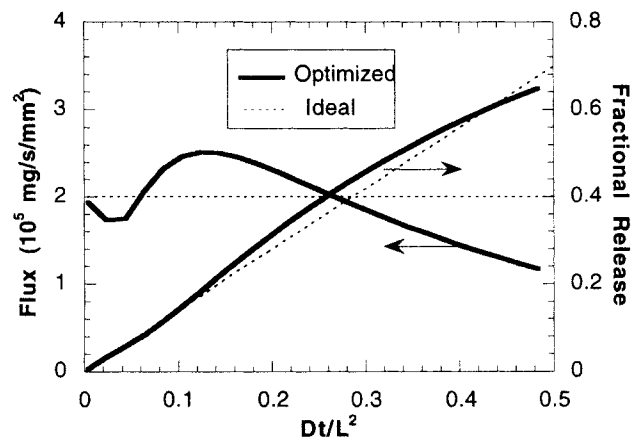

Figure 5b. Ideal and optimized release profiles.

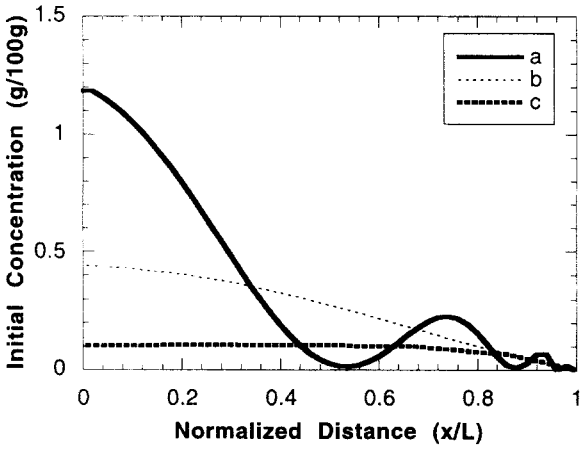

Figure 6. Effect of coefficient A on the optimal initial concentration.

Curves a, b, and c are the optimal initial concentrations at the condition $F_1 = 0$, $F_1 = F_2$, and $F_1 = 10F_2$, respectively.

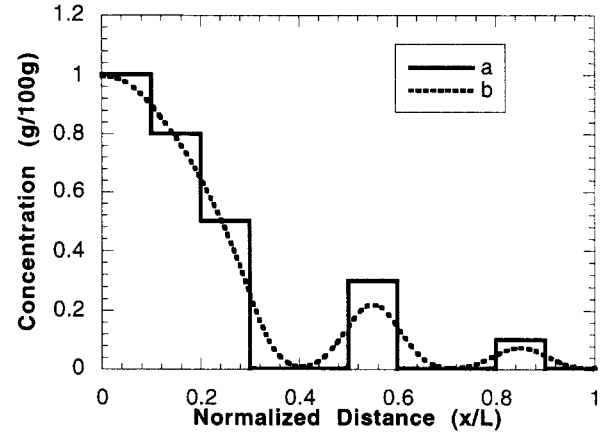

Figure 7. Immobilization of initial concentration.

(a) Initial stepwise concentration profile; (b) initial concentration profile obtained after dimensionless drug redistribution time $Dt/L^2 = 0.001$.

this study, constant release rate was selected as ideal release profile.

When $A = 0$ (curve a, $F_1 = 0$), the contribution of the cost of the initial drug loading to the objective functional is not considered. The optimization process emphasizes minimizing the square of the deviation of the predicted flux from the desired flux, and obtains optimal initial concentration profile (curve a) as demonstrated above. In curve b ($F_1 = F_2$), since the contributions from the cost of the initial drug loading and the desire to maintain a desired flux are of the same importance, the significance of the boundary flux contribution decreases. In this case, the optimization results in a significant decrease in the drug concentration. When A is very large (such as $F_1 = 10F_2$), the drug concentration is further reduced as shown in curve c. In the limiting case when the contribution of the initial drug loading is completely dominating ($F_1 \gg F_2$), the optimal concentration will approach zero to minimize the objective functional. Based on the above analysis and the objective of obtaining a desired release behavior in this article, the coefficient A was set to zero in the following sections.

Fabricating Devices with the Optimal Initial Concentration Profile. To immobilize the initial concentration profile obtained in the above optimal matrix devices, one can employ as many thin layers as possible to approximate this. In this case, the photopolymerization technique is especially practical due to its rapid polymerization rate. An alternative method to load exactly the optimal initial concentration profile in matrix is as follows. A stepwise drug concentration profile is first loaded in the matrix device through multilaminates as shown before, but fewer layers are needed compared to the aforementioned process. The hydrogel matrix device is then put at suitable conditions to allow drug diffusion to occur in the matrix while preventing drug release from the device by belting all surfaces. Drug molecules diffuse from high concentration regions to low concentration regions and accumulate in low concentration regions to form a continuous concentration profile. When the drug concentration profile in the assembly reaches the optimal one, the profile is immobilized in the matrix by quenching and storing at low temperatures (such as below the glass transition temperature) until future use. Figure 7 illustrates one simulation result of this process. This approach provides an alternative and novel method to load complex concentration profiles in matrix devices, and the drug distribution can, in many cases, be well approximated by producing an initial stepwise concentration profile, and allowing the drug to redistribute for a prescribed time before quenching.

Optimization for Nonconstant Release Behavior. Theoretically, this optimization technique can be easily extended to other desired release patterns besides constant release behavior. The optimization example shown in Figure 8 demonstrates this idea. In this calculation, the ideal release behavior first linearly increases, then remains constant, and finally linearly decreases. The optimized release profile follows closely that of the ideal case, and, furthermore, the constant release rate and relative release time of the three periods can be easily adjusted to satisfy different requirements. This optimization technique is a useful tool to guide designing various controlled devices with any selected nonconstant release behavior.

Conclusions

A drug delivery device comprising multilaminates with spatial variation in the initial drug loading and in the drug diffusivity in the polymer matrix was simulated. The mathematical analysis quantitatively shows that the burst effect can be intimately controlled by the initial drug distribution in the polymer, and the administration of the spatial variation of drug loading, as well as drug diffusivity, can moderate the variation in time of the release rate.

A dynamic optimization method was developed to search systematically for the set of initial drug concentrations in the layers to attain a system exhibiting release behavior as close to the desired profile as possible. The model structure is expected to extend to optimize other matrix parameters such as the drug diffusivity profile (such as variations in cross-linking density in the laminates) and the layer thickness profile (such as variations in the relative thickness in each layer). It is desirable to optimize the three parameters together instead of individually to determine these synergistic effects.

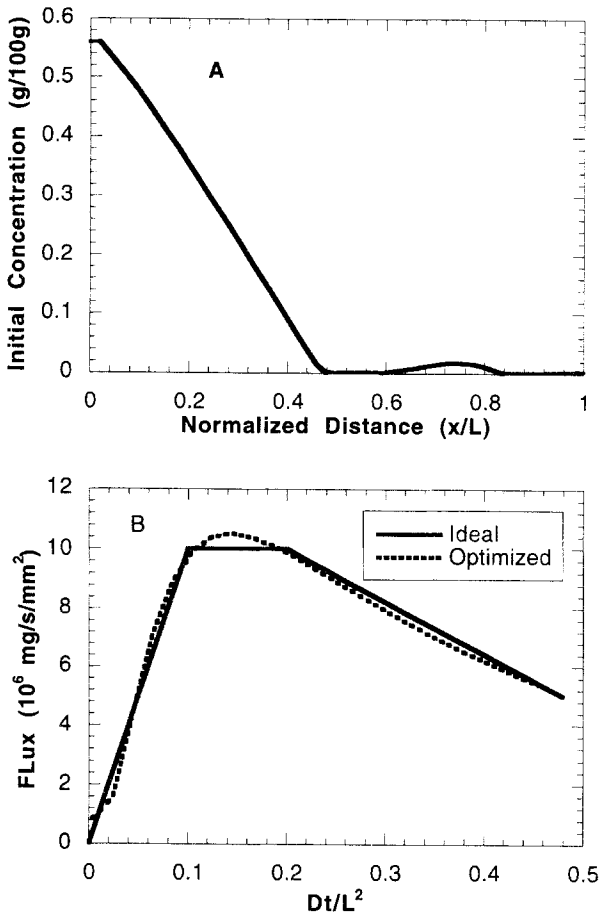

Figure 8. Optimization with desired nonconstant release profile.

(a) Optimal initial concentration profile; (b) optimal release profile.

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