

Photopolymerized, Multilaminated Matrix Devices with Optimized Nonuniform Initial Concentration Profiles To Control Drug Release

SANXIU LU, W. FRED RAMIREZ, KRISTI S. ANSETH

Department of Chemical Engineering, University of Colorado, Boulder, Colorado 80309-0424

Received 12 May 1999; accepted 8 November 1999

ABSTRACT: This paper describes a novel approach to obtain desired release profiles from diffusion-controlled matrix devices by employing nonuniform initial concentration profiles theoretically and experimentally. Theoretically, a model was developed to examine the effect of nonuniform initial concentration profiles on matrix release behavior, and an optimization technique was investigated to determine suitable nonuniform initial concentration profiles which provide desired release patterns. Experimentally, release rates of an organic dye from photopolymerized matrix devices were measured to test the application of these mathematical techniques and the efficacy of photolaminated matrices in approximating the optimized release behavior. All system parameters were measured by independent experiments, and the experimental release data agree very well with the computed results. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 89: 45–51, 2000

INTRODUCTION

Diffusion-controlled polymer delivery systems which can release at a constant rate are becoming increasingly important in many pharmaceutical applications. However, in conventional diffusion-controlled matrix devices, in which the drug to be released is dispersed or dissolved uniformly through the polymer, the release rate diminishes with time continuously due to increasing diffusional distance. To circumvent this decreasing release rate and to achieve a constant rate of drug release in diffusion-controlled matrix devices, researchers have investigated several approaches, including rate-controlling membranes^{1,2} and geometry factors.^{3,4}

An alternative approach for regulating drug release in diffusion-controlled monolithic devices is the use of nonuniform initial drug loading. Non-

uniform initial drug loading allows the loading of a higher drug concentration in the center of the device to sustain the release rate at longer times. In previous work, nonuniform initial drug concentration profiles were achieved by utilizing non-Fickian swelling behavior to extract drug from uniformly loaded hydrogel matrices⁵ or by preparing multilaminates in which each layer had a different drug concentration by solvent casting.⁶ In addition, corresponding models also have been developed to investigate the effect of the nonuniform initial drug concentration profiles on matrix release behavior.^{7,8}

Alternatively, we developed a novel approach to immobilize controlled, nonuniform initial drug concentration profiles in diffusion-controlled multilaminated matrix devices utilizing in situ photopolymerization techniques.⁹ In addition, a model was developed to examine the effects of the nonuniform initial concentration profile and/or nonuniform diffusivity profile on the release behavior from the photolaminated matrix device. To further guide the development of diffusion-

Correspondence to: K. S. Anseth

Journal of Pharmaceutical Sciences, Vol. 89, 45–51 (2000)
© 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association

controlled release devices by employing nonuniform initial concentration profiles, an optimization technique was developed which predicts a priori suitable initial concentration profiles to obtain a desired release behavior over an extended release period (e.g., greater than 65% of the total drug released).¹⁰ In this article, achievements in these aspects are presented, and the application of the optimization technique is tested experimentally by synthesizing photolaminated matrix devices with optimized nonuniform initial concentration profiles and comparing experimental release data with theoretical results. Appropriate ancillary experiments were used to determine the model parameters (such as solute diffusivity and matrix thickness) so that in comparing experimental and simulated release data, no adjustable parameters were employed.

THEORETICAL SECTION

For the drug delivery devices developed in this research, the system was modeled as one-dimensional transient mass transfer. A plot for such a polymeric release system is shown in Figure 1, where $f(x)$ is any initial drug concentration profile. The disk has a thickness L in contact with a release medium maintained at sink conditions. In this paper, we consider the case of diffusion-controlled drug release where the drug diffusivity is constant during the release period. However, spatial or time dependent diffusivity can be easily introduced and modeled.

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

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad (1)$$

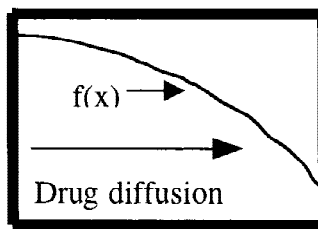


Figure 1. Schematic plot of drug release. The surface defined by the wide lines represents the impermeable surface. $f(x)$ is any nonuniform initial concentration profiles.

with the boundary condition

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

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

and the initial condition

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

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.

Using standard separation-of-variable techniques, the partial differential eq 1 can be solved analytically. Therefore, the flux at the interface of polymer and release medium, $J(t, L)$, may be calculated according to eq 5, and the cumulative fractional release, M_t/M_∞ , is obtained by integrating the flux, $J(t, L)$, with respect to time according to eq 6:

$$J(t, L) = -D \left. \frac{\partial c}{\partial x} \right|_{x=L} = \frac{2D}{L} \sum_{n=0}^{\infty} ((-1)^{n+1} \lambda_n e^{-D \lambda_n^2 t} \int_0^L f(x) \sin(\lambda_n x) dx), \quad (5)$$

$$\frac{M_t}{M_\infty} = 1 - \frac{\sum_{n=0}^{\infty} \frac{(-1)^{n+1}}{\lambda_n} e^{-\lambda_n^2 D t} \left(\int_0^L f(x) \sin(\lambda_n x) dx \right)}{\sum_{n=0}^{\infty} \frac{1}{\lambda_n} \left(\int_0^L f(x) \sin(\lambda_n x) dx \right)}, \quad (6)$$

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

This model was developed to investigate the effects of any given initial concentration profile, $f(x)$ on release patterns theoretically. To guide in the selection of a suitable initial concentration profile to obtain a desired release pattern, an optimization technique was developed to minimize the sum of the square of the difference between the desired release profile and the actual release profile.¹⁰ Briefly, an objective functional N was defined as

$$N = \int_0^L A f^2(x) dx + \int_0^{t_f} (J(t,L) - J^*(t,L))^2 dt. \quad (7)$$

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 (e.g., to reduce cost). An augmented objective functional is then formulated that has the same extrema of eq 7 and includes the equality state dynamic constraints of eq 1. Using the fundamental theorem of the calculus of variation and optimal control theory to obtain necessary conditions for an extremum of the augmented objective functional, one can determine the initial drug concentration profile which exhibits a drug release profile that is as close to the desired profile as possible. Details regarding this technique are provided elsewhere.¹⁰ In this paper, the coefficient A was set to zero, and the concentration profile was constrained to values greater than or equal to zero during the optimization process.

EXPERIMENTAL SECTION

Materials

Monomer, 2-hydroxyethyl methacrylate (HEMA), and cross-linking agent, diethylene glycol dimethacrylate (DEGDMA), were obtained from Aldrich. A hydrophilic dye, acid orange 8 (Polyscience, AO8, MW = 364 g/mol, solubility in water is 3 wt %), was chosen as a model drug to characterize the release of low MW molecules from the designed matrix devices. The photoinitiator was Iracure 651 (1651, Ciba-Geigy). All materials were used as received.

Methods

Hydrogels of poly(HEMA) were prepared by a free-radical photopolymerization at room temperature by using DEGDMA as the cross-linking agent. In these experiments, 40 wt % water based on the prepolymer solution was used to obtain homogeneous hydrogels that maintain their original shape and volume when placed in the release medium (i.e., the resulting gels were equilibrium swollen upon formation). The initiator concentration was 0.1 wt % based on the HEMA weight. The AO8 concentration was less than 1.3 wt % based on the HEMA/water solution, which is well below its solubility in water at room temperature

(3 wt %). The low concentration of AO8 was chosen because AO8 competes for photons of UV radiation at the chosen initiating wavelength 365 nm. However, alternative initiating systems (e.g., visible initiators and 470–490 nm blue light) can be used instead of UV light depending on the absorbance of the drug molecules for practical application.

The solution of HEMA, DEGDMA, deionized water, AO8, and photoinitiator was transferred into a mold consisting of two glass microslides separated by a spacer. The liquid solution was converted to a cross-linked hydrogel by exposure to low-intensity 365-nm UV light (Blak-Ray®, 12 mW/cm²) for several minutes in a nitrogen atmosphere. Upon completion of the polymerization, an additional spacer was introduced into the mold and a new layer was photopolymerized on the top of the first layer. By using this technique, multilaminated matrices with different drug concentration, layer thickness, and polymer composition, or cross-linking density in each layer can be prepared. In this paper, we prepared one-layer and multi-layer samples according to the experimental design.

Uniform disks, 11.5 nm in diameter and 1.0–1.5 mm in thickness, were cut from the previously prepared gels. The disks were coated with an impermeable film on all surfaces except one base to measure one-dimensional diffusion. Each disk was then placed in a vial containing 10 mL of deionized water at room temperature with constant stirring. At predetermined time points the disk was removed and placed into another vial with fresh deionized water to maintain sink conditions. The AO8 quantity released from the disk was followed by monitoring the absorbance using a UV-vis spectrophotometer (Hewlett Packard 8452A diode array spectrophotometer) at 492 nm (the wavelength of maximum absorbance for AO8).

RESULTS AND DISCUSSION

The model described in the theoretical section can be used to examine the effect of any initial concentration profile (continuous or not) on the final release pattern. In this analysis, two initial concentration profiles, stepwise and linear concentration profiles as shown in Figure 2A, were considered for the sake of simplicity, and the case of a uniform initial concentration profile is presented for comparison. In these calculations, all

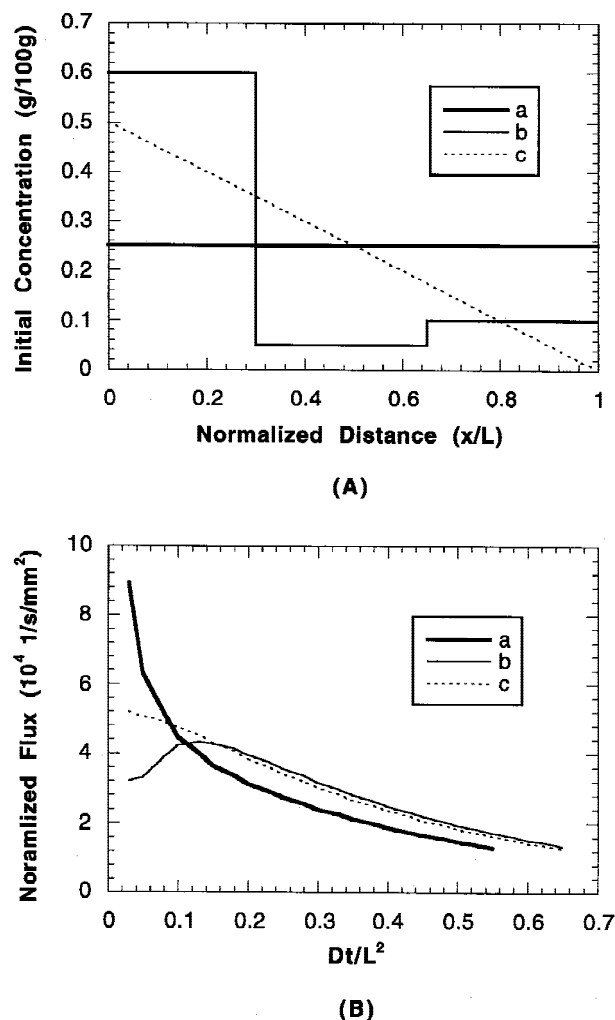


Figure 2. Effect of initial concentration profiles on release pattern. (A) Type of initial concentration profiles as a function of normalized distance: (a) uniform, (b) stepwise, and (c) continuous decrease. (B) Corresponding normalized flux as a function of dimensionless release time.

parameters (e.g., matrix thickness, initial drug loading) are the same except for a different initial drug distribution. Figure 2B presents the corresponding flux and fractional release profiles as a function of dimensionless release time. Compared with the case of uniform drug loading, the initial burst is significantly reduced by using nonuniform initial concentration profile, and the overall release behavior approaches a more constant release profile.

To verify the model, laminated devices were fabricated using photopolymerization to develop disks with nonuniform initial concentration profiles. In the experimental verification, a stepwise

initial solute concentration profile was used even though a continuous concentration profile can be approximated by decreasing the layer thickness (e.g., using spin coating techniques). Specifically, the experimental concentration profile was, from the center outward, 0.75, 0.4, and 0.05 wt %, respectively. In the swollen poly(HEMA) hydrogel matrix device, the AO8 diffusivity was evaluated independently by fitting the first 60% of the experimental release data.⁹ The experimental results demonstrated that the drug release is Fickian diffusion-controlled and the AO8 diffusivity is $\sim 4.0 \times 10^{-7}$ mm²/s, independent of the AO8 concentration to the experimental range. The experimental data are presented in Figure 3 together with the simulated results. It can be seen that the computed release profiles match the experimental results very well, indicating the efficacy of the model in describing the release from these photolaminated devices.

The above model and experimental results illustrate that manipulating nonuniform initial concentration profiles is a very effective approach to controlled drug release. However, selecting an initial concentration profile that provides the desired release rate is not necessarily obvious. Hence, employing modeling to determine a suitable nonuniform initial concentration profile to obtain desired release behavior could be very time-consuming and tedious since it requires a trial-and-error process. Therefore, optimization techniques, which are routinely used in other research areas, appear to be very attractive since they can readily determine initial parameters from known required release profiles. Thus, on

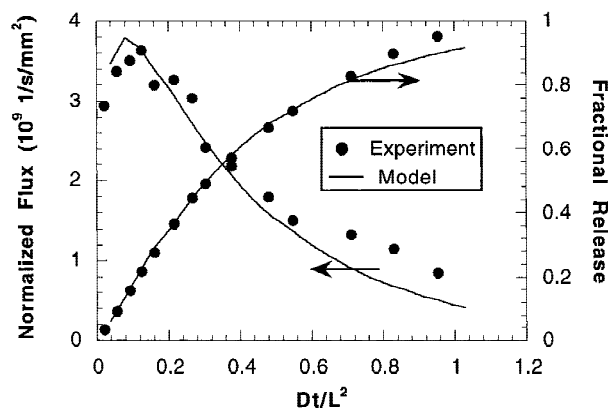


Figure 3. Experimental verification of modeling results. The initial solute concentration profile used, from center outward, is 0.75, 0.4, and 0.05 wt %, respectively.

the basis of the above model, an optimization technique was developed to aid the design of matrix devices with nonuniform initial concentration profiles for controlled drug release, and the following section presents results in this aspect.

With the goal of a constant matrix flux until 65% of the total drug loaded is released, the developed optimization technique calculated the optimal release profile and is presented in Figure 4A. Over the optimization period, the flux behavior remains close to the desired zero-order release with smaller than 50% deviation from the ideal release rate at any instantaneous release time. This approximate constant release is further illustrated by the nearly linear cumulative release curve.

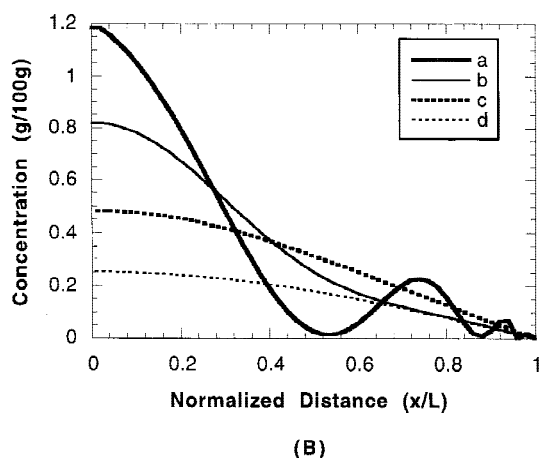
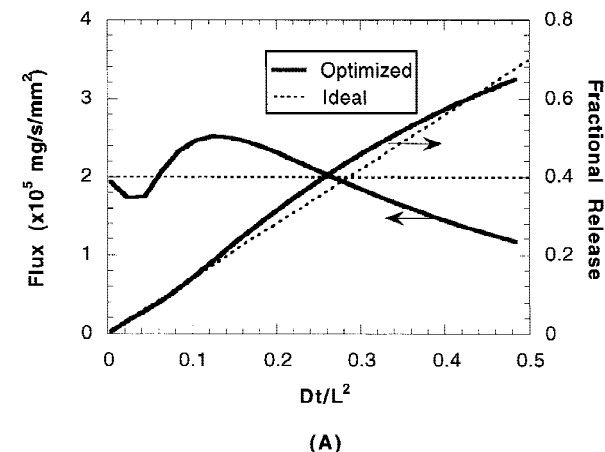


Figure 4. (A) Optimization technique prediction of release profiles versus dimensionless release time as compared to the ideal case. (B) Optimal initial concentration profile (curve a) as a function of normalized distance and the corresponding instantaneous concentration profiles as a function of normalized distance at different dimensionless release times: (b) 0.024, (c) 0.124, and (d) 0.36.

The optimal initial concentration profile (Figure 4B, curve a) shows that the optimization process introduces concentration peaks and troughs into the optimal initial concentration profile with the magnitude of the peaks increasing toward the interior of the device. The instantaneous drug concentration profiles (Figure 4B, curves b–d) in the polymer matrix at different dimensionless release times can help visually explain the oscillating profile. With an oscillating concentration profile, the drug diffuses from concentration peaks to concentration troughs and accumulates in the concentration troughs at the early stages. This drug redistribution in the polymer matrix causes the drug concentration at the outermost peak to decrease, and hence, the release rate decreases with release time. When the inflections in the concentration profiles disappear (Figure 2B, curve b, corresponding to the minimum flux point at the early release region), the drug diffuses continuously outward from the interior. Since a large concentration gradient exists in the matrix device, this continuous diffusion outward results in an increase of drug concentration near the matrix surface. Therefore, the drug flux increases with release time until a maximum flux (corresponding to curve c in Figure 4B) is reached. Finally, the continual loss of drug by diffusion eventually produces a more uniform drug concentration throughout the matrix as demonstrated in curve d (Figure 4B), which causes a smaller diffusion driving force. Consequently, the drug flux decreases monotonically at later release time.

As shown in Figure 4, the optimization technique yields an approximated constant release pattern for diffusion-controlled release from one-dimensional slab geometry by optimizing the nonuniform initial drug concentration profile such that the square of the deviation of the real flux from the desired flux is minimized. However, better zero-order release profiles can be reached by further exploring the optimization technique. For example, one can combine other designing factors (e.g., geometry) with the optimization technique. One also can expand this general optimization technique to optimize several parameters (e.g., concentration, space- and/or time-dependent diffusivity) individually or simultaneously. Detailed analyses regarding this aspect are presently being carried out. In addition, the optimization technique is expected to find applications in other situations by defining other objective functionals.

To demonstrate the versatility of the optimization technique, Figure 5A, and B illustrates how

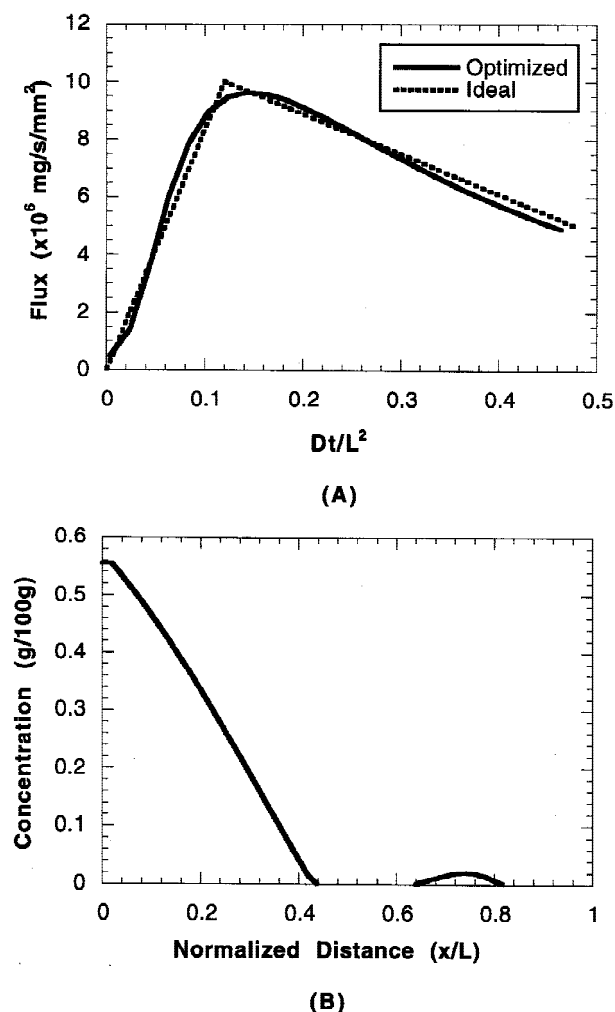


Figure 5. (A) Optimization technique prediction of release profiles versus dimensionless release time as compared to the desired triangular release pattern. (B) Optimal initial concentration profile as a function of normalized distance.

to obtain a more complex release pattern, in particular, a triangular release pattern. This kind of release pattern can be very important for some cancer treatment, where the drug release rate initially increases for patients to develop tolerance until the highest release rate at which the cancer cells are killed. After that, the drug release rate linearly decreases due to the toxicity of the drugs. Again, the optimized release profile follows closely that of the desired case. As mentioned previously, the optimized concentration profile was restricted to concentration values greater than zero. If this restriction is removed, the profile oscillates from positive to negative to sustain the release at the desired rate.

Finally, to illustrate that the developed optimization technique can guide the actual design of controlled release devices, multilayer matrix devices immobilized with the optimal concentration profile for constant release were prepared using the photopolymerization technique. In the experimental matrix, an optimal initial concentration profile was approximated by a stepwise concentration profile immobilized in a nine-layer matrix device as shown in Figure 6A. Specifically, the actual immobilized initial solute concentrations in the nine-layer matrix device, from the center outward, were as follows: 1.1, 0.87, 0.51, 0.18, 0.028, 0.13, 0.18, 0.047, and 0.0 wt %, respectively.

Figure 6B presents both experimental and theoretical release data from the matrix device as

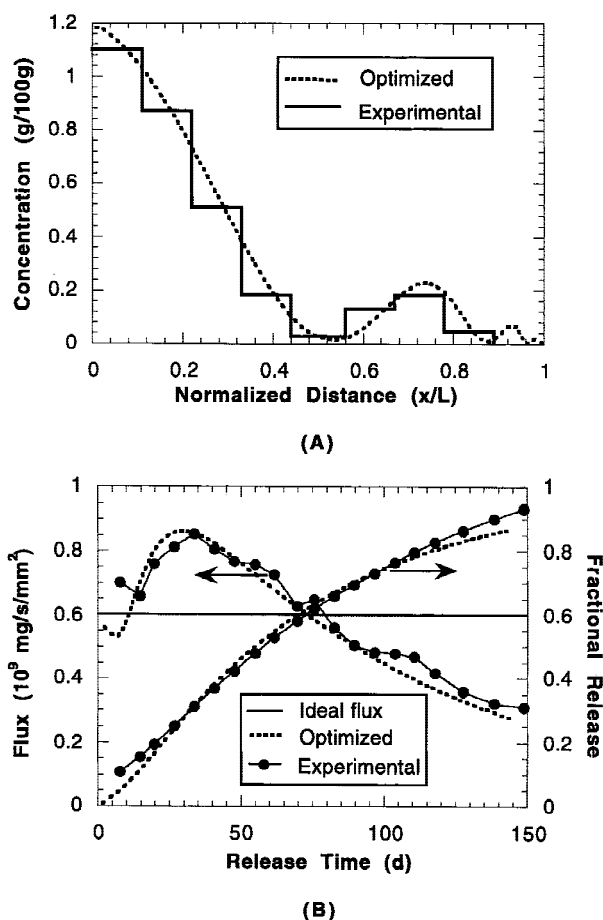


Figure 6. (A) Experimentally immobilized and optimal initial concentration profiles in matrix device as a function of normalized distance. (B) Flux and fractional release of release solute in matrix device as a function of release time. Experimental results as compared to the theoretical prediction.

a function of release time. The theoretical and experimental release curves agree quite well. This result validates the use of the optimization approach to effectively guide the actual design and development of initial concentration profiles in laminated devices to attain systems exhibiting release behavior as close to a desired release profile as possible. This agreement also confirms the efficacy of using photopolymerizations to synthesize multilaminated matrices to approximate the optimized release behavior. Furthermore, the absence of a real burst effect, which is usually seen with matrix type delivery system, is highly significant. Actually, with the experimentally immobilized nonuniform initial concentration profile, the flux ranges from 0.88×10^{-9} to 0.32×10^{-9} mg/s/mm² over the course of 140 days. The actual release varies from the ideal release rate (0.6×10^{-9} mg/s/mm²) less than 50% over the extended time frame, which is extremely important for narrow therapeutic index drugs. It is worth noting that the model used to predict the release contained no adjustable parameters. All parameters used in the computation (e.g., AOS concentration, matrix thickness, AOS diffusivity) were experimentally determined.

CONCLUSIONS

The optimization technique developed provides a technique to determine suitable nonuniform initial concentration profiles to achieve desired release behavior in diffusion-controlled matrix devices, and the photolamination technique provides an effective and easy fabrication method to prepare multilaminates with controlled nonuniform initial concentration profiles in matrix devices. The excellent agreement of the experimental release results with the computed data demonstrates that the optimization technique can effectively guide the actual design and development of initial concentration profile in laminated devices to attain a system exhibiting release as

close to desired release profiles as possible. The agreement also confirms the efficacy of multilaminated matrices in approximating the optimized release behavior. The combination of the developed optimization techniques and the photopolymerization technique provides new directions towards the development of diffusion-controlled release systems.

The authors thank the Packard Foundation for supporting this research.

REFERENCES AND NOTES

1. Lee ES, Kim SW, Kim SH, Cardinal JR, Jacobs H. 1980. Drug release from hydrogel devices with rate-controlling barriers. *J Membr Sci* 7:293–303.
2. Bodmeier R, Paeratakul O. 1980. Drug release from laminated polymeric films prepared from aqueous latexes. *J Pharm Sci* 79:32–36.
3. Narasimhan B, Langer R. 1997. Zero-order release of micro- and macromolecules from polymeric devices: the role of the burst effect. *J Controlled Release* 47:13–20.
4. Conte U, Maggi L, Colombo P, La Manna A. 1993. Multi-layered hydrophilic matrices as constant release devices (Geomatrix™ Systems). *J Controlled Release* 26:39–47.
5. Lee PI. 1984. Novel approach to zero-order drug delivery via immobilized nonuniform drug distribution in glassy hydrogels. *J Pharm Sci* 73:1344–1347.
6. Xu X, Lee PI. 1993. Programmable Drug delivery from an erodible association polymer system. *Pharm Res* 10:1144–1152.
7. Lee PI. 1986. Initial Concentration Distribution as a mechanism for regulating drug release from diffusion controlled and surface erosion controlled matrix systems. *J Controlled Release* 4:1–7.
8. Paul DR. 1985. Modeling of solute release from laminated matrices. *J Membr Sci* 23:221–235.
9. Lu S, Anseth KS. 1999. Photopolymerization of multilaminated poly(HEMA) hydrogels for controlled release. *J Controlled Release* 57:291–300.
10. Lu S, Ramirez FW, Anseth KS. 1998. Modeling and optimization of drug release from laminated polymer matrix devices. *AIChE J* 44:1689–1696.