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Photopolymerization of multilaminated poly(HEMA) hydrogels for controlled release

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Abstract

A novel approach to immobilize nonuniform initial drug concentration profiles in multilaminated matrix devices utilizing photopolymerization techniques is presented. Solution polymerization of 2-hydroxyethyl methacrylate (HEMA) and diethylene glycol dimethacrylate (DEGDMA) in the presence of a model compound, acid orange 8 (AO8), was conducted using UV light and photoinitiators to construct a laminated matrix device. In this process, each layer was polymerized with a different AO8 concentration to form a nonuniform initial concentration profile in the matrix devices. The AO8 diffusion coefficients measured in this work were used in a concurrently developed model to predict the effects of nonuniform AO8 concentration profiles on AO8 release patterns. The release data predicted by the model agreed well with the experimentally determined data. The results indicate that a zero-order release pattern can be approximated by employing a suitable nonuniform initial drug concentration profile. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Diffusion-controlled release; Nonuniform initial drug loading; Modeling; Photopolymerization

1. Introduction

Diffusion-controlled polymeric matrix devices have been among the most widely used drug delivery systems, mainly due to their low manufacturing cost [1,2]. However, in conventional matrix devices, where the drug to be released is dispersed or dissolved uniformly through the polymer, the diffusional distance increases with time (as drug is released), and hence, the release rate decreases. To circumvent this disadvantage of first-order diffusion behavior, various approaches have been developed to

achieve constant release rates in polymeric matrix devices, including variations in geometry [3,4], development of surface eroding polymers [5,6], and design of devices combining several release mechanisms [7,8].

As an alternative to the above mentioned techniques, nonuniform initial drug loading has also been recently employed to modulate release profiles. For example, Lee [9] immobilized in situ a nonuniform drug concentration profile by utilizing non-Fickian swelling behavior to extract drug from uniformly loaded hydrogel matrices. Controlled drug release behavior was achieved from the diffusion-controlled beads, but the process was limited as to the control over the initial drug concentration distribution. In

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addition, the nonuniform initial concentration approach has also been used in multilayered, degradation-controlled matrix systems, prepared by solvent-casting or compression, to obtain constant or pulsatile drug release behavior [10–12].

The focus of this work is to investigate the use of photopolymerizations to create layered matrix devices with nonuniform concentration profiles with the goal of controlled drug release. One advantage of photopolymerization is that the polymerization conditions are sufficiently mild to be carried out in the presence of biological materials. Photopolymerizations proceed very rapidly at room temperature, and the temperature and pH can be limited to near physiological ranges during the polymerization process. Additionally, since photopolymerizations are initiated with UV or visible light, spatial and temporal control of the polymerization is achieved by controlling the exposure area and the time of light incidence. This control allows easy and rapid production of complex matrix devices (e.g., a multilaminate).

Specifically, in this report we used one-step, *in situ* photopolymerization techniques to prepare drug-hydrogel matrix devices that possess desirable drug release behavior by immobilizing controlled, nonuniform initial drug concentration profiles in the devices. Crosslinked poly(2-hydroxyethyl methacrylate) (poly(HEMA)) hydrogels were chosen as the drug carrier due to its good biocompatibility, ability to release entrapped drug in aqueous medium, and the ease of regulating such drug release by controlling water swelling and crosslinking density [13,14]. The objectives of this research were two-fold: (1) to investigate the transport of solutes through poly(HEMA), specifically, to measure AO8 diffusion coefficient in swollen poly(HEMA) and to quantify the mesh size of the hydrogel, and (2) to explore the effect of nonuniform initial concentration profiles in laminated poly(HEMA) matrix devices on release pattern by modeling and by experiments.

2. Materials and methods

2.1. Materials

Monomer, 2-hydroxyethyl methacrylate (HEMA),

and crosslinking 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 small MW molecules from the designed matrix devices. The photoinitiator was Irgacure 651 (I651, Ciba-Geigy). All materials were used as received.

2.2. Methods

2.2.1. Formation of nonuniform concentration profiles

Poly(HEMA) hydrogels were prepared by a free-radical photopolymerization at room temperature. The choice and concentration of the solvent during the polymerization determine the homogeneous or heterogeneous structure of the gel produced. If water is used as the solvent, the concentration must be below a critical diluent concentration to ensure the production of an optically transparent, homogeneous hydrogel. The critical diluent concentration for water in the monomer mixture has been variously reported, in terms of the mass fraction, from 40% to 60% [14]. The homogeneous poly(HEMA) gels exhibit relatively constant swelling in water regardless of the initial water and crosslinking agent content in monomer mixture. Therefore, in this report, 40 wt% water based on the prepolymer solution was used throughout to obtain homogeneous hydrogels that maintain their original shape and volume in water. 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, for practical application 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.

As shown in Fig. 1(a), a solution of HEMA, crosslinking agent DEGDMA, deionized water, AO8 and I651 was transferred into a mold consisting of two glass microslides separated by a spacer. The

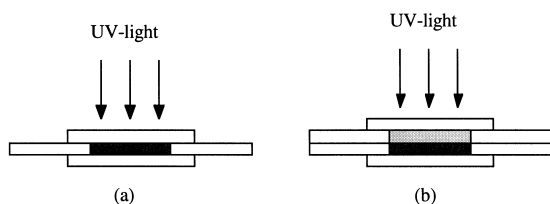


Fig. 1. A schematic plot of the preparation of multilaminated samples. (a) Polymerization of the first layer; (b) polymerization of the second layer.

solution was polymerized to form a crosslinked hydrogel by exposure to low intensity 365 nm UV light (Blak-Ray®, 12 mW/cm²) for several minutes in a nitrogen atmosphere. After polymerization of the film, the space between the two microslides was increased, and a second layer with a different AO8 concentration was photopolymerized between the first layer and the top microslide as shown in Fig. 1(b). In this paper, we prepared one-layer and multi-layer samples according to the experimental design. Multilaminated matrices with variations in the drug concentration, layer thickness, and polymer composition or crosslinking density can be prepared by using this technique.

2.2.2. Solute release experiments

Uniform disks, 11.5 mm 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 placed in a vial containing 10 ml of deionized water at room temperature with constant stirring. At pre-determined 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 over this time increment was followed by monitoring its absorbance using a UV-vis spectrophotometer (Hewlett Packard 8452A Diode Array spectrophotometer) at 492 nm (the wavelength of maximum absorbance for AO8). The amount of AO8 released at time t (M_t) was obtained from an appropriate calibration curve, and the cumulative fractional release at time t , M_t/M_∞ , was then calcu-

lated. M_∞ was defined as the amount of solute initially loaded.

3. Results and discussion

3.1. Effect of nonuniform initial concentration on release behavior

In principle, the proposed nonuniform initial drug loading can overcome the major disadvantage of first-order release associated with conventional diffusion-controlled matrix devices, and furthermore, the proposed photolaminating process provides a method to control intimately the nonuniform initial drug loading. First, experiments were conducted to compare drug release from one-layer, two-layer and three-layer matrix devices with different initial drug concentration profiles. In these experiments, the total drug loading and total matrix thickness were kept constant while the concentration profiles were varied. Specifically, the AO8 concentration profiles in the one-layer, two-layer and three-layer matrix devices were, (a) 0.4 wt%; (b) 0.2 wt%, 0.6 wt %; and (c) 0.05 wt%, 0.4 wt%, 0.75 wt%, respectively. The thickness of each layer corresponding to curves a, b and c were L , $L/2$, and $L/3$, respectively, so the total thickness of each device was a constant L .

The experimental results in Fig. 2 illustrate the effect of a nonuniform initial concentration distribution on the release pattern. As expected, curve a, with a conventional uniform drug loading, shows a typical first-order release behavior: an initially high release rate (burst effect) followed by a rapidly declining drug release rate. Usually, it is desirable to eliminate the burst effect since it may cause negative side effects. Here, the concept of photolamination was used to provide nonuniform initial concentration profiles to control the release pattern. From curve a to curve b to curve c, the number of layers in the matrix increased from one to two to three, and the initial drug loading was made more nonuniform (e.g., by increasing the relative loading at the center of the device compared to the surface). As the gradient in the drug distribution increased, the corresponding release profiles approached more closely the desired zero-order release, especially in the early release

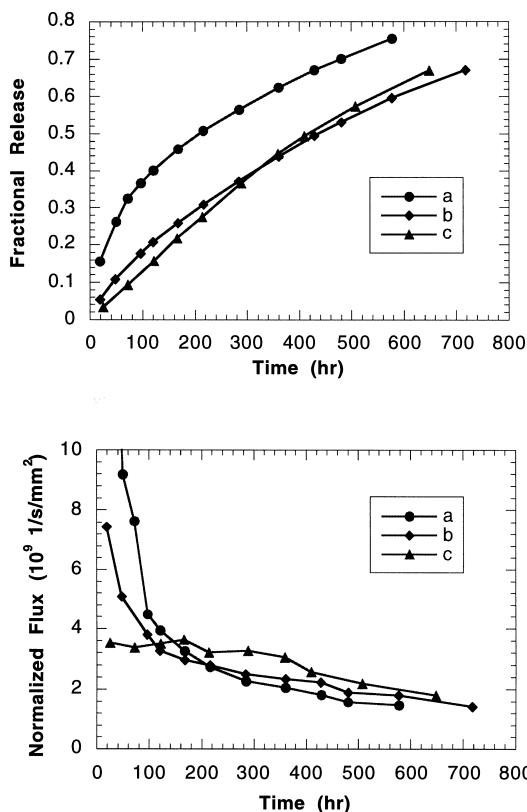


Fig. 2. Effect of initial AO8 concentrations on release behavior. The experimental concentration profiles were, from center outward, (a) 0.4 wt%; (b) 0.6 wt%, 0.2 wt%; and (c) 0.75 wt%, 0.4 wt%, 0.05 wt%.

period. In addition, the burst effect was nearly eliminated.

3.2. Modeling the effect of nonuniform initial concentration on release behavior

As demonstrated by the experimental results above, nonuniform initial drug loadings can be used to manipulate the drug release profile effectively and photopolymerization techniques allow great flexibility in preparing the controlled, nonuniform initial drug distribution. To predict the effects of nonuniform initial concentration profiles on the release pattern, a model, based on Fickian diffusion and the continuity condition for diffusive flux across the layer interfaces in the system, was developed and described elsewhere [15]. Briefly, the system was

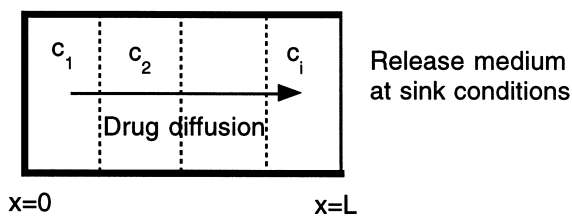


Fig. 3. A schematic plot of drug release from multilaminated matrix devices. The surfaces defined by the wide lines are impermeable.

modeled as one-dimensional transient mass transfer in a laminated disk. A schematic plot for such a polymeric release system is shown in Fig. 3, where c_i is the drug concentrations in the i th layer, from the center outward, of the matrix. The disk has a thickness, L , and an initial drug concentration profile, $v(x)$, in contact with a release medium maintained at sink conditions. In addition, drug diffusion is the rate-controlling step rather than swelling or drug dissolution.

For this diffusion-controlled problem, Crank [16] gave the well-known diffusional release for films at the case of uniform initial concentration profiles. When the initial concentration profile, $v(x)$, is space-dependent, the flux at the interface of polymer and release medium, $J(t, L)$, may be calculated [15].

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

The cumulative fractional release, M_t/M_∞ , is then obtained by integrating the flux, $J(t, L)$, with respect to time according to Eq. (2).

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

This model was used to investigate the effects of any continuous initial concentration profiles on re-

lease patterns theoretically. In this analysis, stepwise drug loading was used because it is easily acquired by photopolymerization as demonstrated above. Fig. 4a shows four initial concentration profiles plotted as a function of dimensionless distance, x/L . The corresponding release profiles from these initial drug distributions are plotted in Fig. 4b, where the solute flux is normalized by the initial drug loading and the matrix cross-sectional area and plotted as a function of dimensionless time, Dt/L^2 .

The simulation results in Fig. 4b confirm theoretically the above experimental conclusion regarding the effect of the nonuniform initial concentration profile on the release behavior. Curves a, b, c, and d are cases corresponding to uniform loading, two-layer loading, three-layer loading and four-layer

loading, respectively. When the drug is uniformly distributed in the matrix device, the drug release pattern displays an undesirable burst effect. With two-layer loading, the initial burst of drug release is reduced significantly. With three-layer loading, the burst is totally eliminated and a more constant release rate is achieved. For the case of four-layer loading, the early release behavior displays a low release rate (time lag). It is seen here that the stepwise drug loading combined with multilayered matrix materials provide a much more constant release rate than obtained by uniform loading, and the wide variety of early time release behavior from the burst effect to a 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.

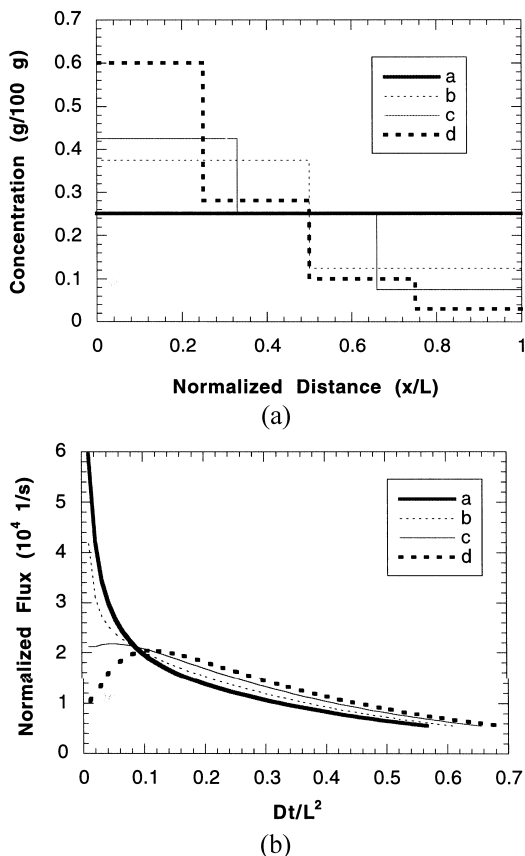


Fig. 4. (a) The initial concentration profiles, from center outward, were: (a) 0.25; (b) 0.375, 0.125; (c) 0.425, 0.25, 0.075; and (d) 0.6, 0.275, 0.1, 0.025. (b) Effect of nonuniform initial drug concentration on release pattern.

3.3. Solute diffusion coefficient

To use the above model to predict the experimental release rates, accurate knowledge of the solute diffusion coefficient is critical. Considering this importance, the drug diffusion coefficient was determined experimentally instead of estimating from semi-empirical approaches reported in the literature [17,18]. A number of techniques have been reported in the literature for the measurement of diffusion coefficients [19,20]. In this work the AO8 diffusion coefficient was evaluated by fitting the first 60% of the release data according to [16].

$$\frac{M_t}{M_\infty} = \frac{4}{\pi^{1/2}} \left(\frac{Dt}{L^2} \right)^n \quad (3)$$

Here, n is an exponent characteristic of the mode of solute transport. For $n=0.5$, the solute release follows the well-known Fickian diffusion mechanism. For non-Fickian diffusion, the exponent n takes values higher than 0.5. The case of anomalous or case II diffusion, when $n=1$, may result when a solvent front penetrates the initially glassy polymer at a constant velocity.

Table 1 presents the experimentally determined AO8 diffusion coefficients in swollen poly(HEMA) hydrogels from fitting of the first 60% of the release data. Samples from experiments 1 to 5 were prepared by in situ photopolymerization of solutions containing AO8 to form a loaded hydrogel matrix. In

Table 1
Fitting of AO8 release data to diffusion Eq. (3)

Experiment number	AO8 conc. (wt%)	Exponent, n^*	Diffusion coefficient ($10^7 \text{ mm}^2/\text{s}$)*
1	0.2	0.46 ± 0.03	3.54 ± 0.32
2	0.4	0.48 ± 0.04	4.36 ± 0.82
3	0.7	0.49 ± 0.03	4.21 ± 0.4
4	0.85	0.49 ± 0.01	4.21 ± 0.5
5	1.25	0.48 ± 0.05	4.24 ± 0.87
6	0.7	0.47	3.99
7	2.5	0.49	3.81

*Mean \pm SD ($n=4$, confidence=0.9).

experiments 6 and 7, the hydrogel disks were first photopolymerized and then equilibrated in an AO8 solution over several months to load the drug. Drug release experiments were subsequently conducted as described previously.

From the data presented in Table 1, AO8 diffusion in the swollen poly(HEMA) hydrogels prepared by in situ photopolymerization occurs by a Fickian mechanism indicated by the exponent values of ~ 0.5 . Additionally, the AO8 diffusion coefficient is almost invariant with AO8 concentration within the range reported. These experimental results provide the basis for subsequent modeling of the AO8 release by Fickian diffusion, and verify the assumption that the AO8 diffusion coefficient is independent of release time and space in the concentration range studied. Vyavahare et al. [21] investigated the release kinetics of a series of small molecular weight molecules (MW (150 g/mol) from swollen poly(HEMA) hydrogel prepared by thermal initiated polymerization without any crosslinking agent. The reported diffusion coefficient, using the double disc method, was about $1.5 \times 10^{-5} \text{ mm}^2/\text{s}$. The diffusion coefficient in this report ($4 \times 10^{-7} \text{ mm}^2/\text{s}$) is nearly 2 orders of magnitude of smaller, which is due to the larger molecular weight of the AO8 (MW=364 g/mol) and the presence of the chemical crosslinks.

For the photopolymerization process, it was necessary to explore the influence of the UV light and polymerization process on the stability of AO8. Experiments were first performed to compare the AO8 amount initially loaded to the total amount of AO8 released after a prolonged time. These experimental results showed that greater than 99% of the AO8 initially loaded was released. Further, the

release of AO8 from gels loaded by in situ photopolymerization (Exp. 1–5) or by sorption method (Exp. 6–7) displayed the same release behavior. Hence, the UV light had no measurable effect on the AO8 loading, and there was no significant degradation or binding of the AO8 to the polymer matrix. Kaetsu et al. [22] claimed that many drugs (e.g., mitomycin C, 5-fluorouracil, bleomycin hydrochloric acid, aspirin) have adequate stability to irradiation exposure. Considering the mild conditions of photopolymerization (e.g., low light intensity, short irradiation time, room temperature, no organic solvent) and alternative initiating systems (e.g., visible initiators and light), photopolymerization may provide a very promising method for preparing controlled drug release systems with no effect on the biological activities of many drugs.

It has been well established that the diffusion coefficient of a solute in a polymer matrix is governed by the free volume in the system. Therefore, the diffusion coefficient of a solute in the hydrogel matrices would be affected by the structure of the polymer, its glass transition temperature, and the degree of swelling. In amorphous, swollen poly(HEMA) networks, we have used the crosslinking density as an effective method to control solute diffusion coefficient. Usually crosslinking agents are incorporated in small amounts, less than 1 wt%, to produce loosely crosslinked, swollen networks for drug delivery. Here, we examined the effect of crosslinking agent concentration on the solute diffusion coefficient in poly(HEMA) network by varying the DEGDMA concentration from 0–5 wt% (about 0–3 mol%) based on the HEMA concentration.

Fig. 5 shows the influence of DEGDMA concentration on AO8 diffusion coefficients, which were experimentally determined by fitting the corresponding release data as per Eq. (3). As expected, the AO8 diffusion coefficient in swollen poly(HEMA) networks decreases significantly with increasing crosslinking agent concentration. The effect of crosslinking agent concentration on solute diffusion coefficient may be interpreted in terms of polymer chain mobility and average mesh size. On a molecular level, solute diffusion through swollen gels depends on the relative size of the solute and the mesh formed by the macromolecular chains. There-

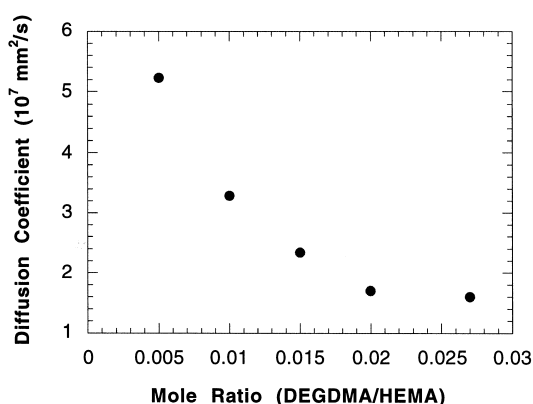


Fig. 5. Effect of crosslinking agent concentration on AO8 diffusion coefficient.

fore, any morphological features associated with reduced macromolecular chain mobility and barriers to solute diffusion are also associated with decreased solute diffusion coefficients. As the crosslinking agent concentration increases, the average molecular weight between crosslinks \bar{M}_c decreases. This decrease may reduce both the polymer chain mobility and the average mesh size between crosslinks, and hence, lead to a greater barrier for solute diffusion. This hypothesis can be checked by measuring the molecular weight between crosslinks of swollen poly(HEMA) network experimentally.

In general, two approaches are commonly used for determining the degree of crosslinking, and hence, the average mesh size in polymeric networks [23]: evaluation of stress-strain data or tensile measurements (rubber elasticity theory) and use of equilibrium swelling experiments (thermodynamical Flory–Huggins theory). The technique using tensile experiments fails to take into account the effect of physical crosslinks, i.e., chain entanglements, as these tends

to disentangle during extension. Therefore, swelling experiments were chosen here to characterize the poly(HEMA) hydrogel. Using a modified Gaussian distribution equation of equilibrium swelling [24], the experimentally determined average molecular weight between crosslinks, \bar{M}_c , and the average mesh size of the swollen poly(HEMA) networks were determined and are listed in Table 2.

In estimating the average molecular weight between crosslinks \bar{M}_c , and thus the mesh size, the Flory–Huggins interaction parameter, χ , is involved, which depends on both temperature and equilibrium polymer volume fraction. In this work, this thermodynamic interaction parameter was calculated as a function of the polymer volume fraction, $\nu_{2,s}$, at 25°C by Eq. (4) [25].

$$\chi = 0.320 + 0.904 \nu_{2,s} \quad (4)$$

These experimental results in Table 2 confirm the hypothesis that the average mesh size is reduced with increasing crosslinking agent concentration. In Table 2, the theoretical average molecular weights between crosslinks are also listed for comparison. These theoretical average molecular weights were calculated by assuming quantitative reaction of the crosslinking agent (both vinyl groups become effective) and the formation of an ideal network without any free chain ends. The experimentally determined average \bar{M}_c compares favorably with the theoretically calculated values, indicating that these poly(HEMA) networks are close to ideal.

3.4. Experimental verification

Critical to the objectives in developing multilaminated delivery devices is the adhesiveness and

Table 2
Average \bar{M}_c and mesh size of swollen poly(HEMA) networks

DEGDMA conc.(mol%)	Equilibrium degree of swelling*	Theoretical \bar{M}_c (10^{-3} g/mol)	Experimental \bar{M}_c (10^{-3} g/mol)*	Average mesh size (\AA)
0.25	2.10 ± 0.06	26.03	16.5 ± 4.9	82 ± 11.2
0.54	2.08 ± 0.32	12.11	9.25 ± 2.85	61 ± 11.8
1.0	1.88 ± 0.04	6.54	9.05 ± 2.17	58 ± 7.7
1.5	1.82 ± 0.04	4.35	5.38 ± 1.35	48 ± 16.2
2.0	1.79 ± 0.05	3.26	3.80 ± 1.78	31 ± 7.0

*Mean \pm SD ($n=5$, confidence=0.9).

resistance to mass transfer, if any, between layers. In the modeling illustrated above, continuity condition for diffusive flux across the material interfaces in the system was assumed. Experiments were conducted to check this assumption by examining the effect of the layer boundaries on the diffusion and release of AO8 molecules in the absence of any nonuniform initial concentration distributing effect. Fig. 6 shows the experimental results. In these experiments, matrices corresponding to curves a and b were identical in composition and drug concentration except that the matrix of curve b was prepared by polymerizing two layers in succession with thickness, $L/2$, and the matrix of curve a was polymerized in one layer with thickness, L . These experimental results indicate that there is little or no diffusion resistance at the interfaces of the layers in the system. Thus, the nature of the fabrication process allows good adhesion and interpenetration of the polymer matrices when photocuring layer upon layer for similar polymer composition in each layer. When the polymer composition in each layer is quite different, it may need further characterization.

Experimental verification of the drug release model presented in the previous section has been attempted. With 1 wt% DEGDMA concentration, the investigated poly(HEMA) matrix was composed of four individual layers of the same thickness, 0.2 mm. In this matrix, the immobilized initial AO8 concentration profile was, from center outward, 1.2 wt%, 0.85 wt%, 0.2 wt%, and 0.0 wt%, respectively. Fig. 7

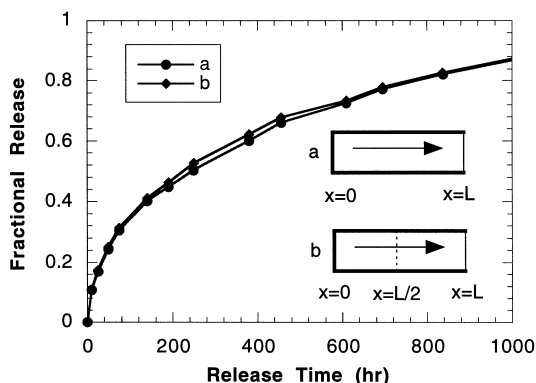


Fig. 6. Comparison of drug release from one-layer and two-layer matrix devices with a uniform drug loading initially.

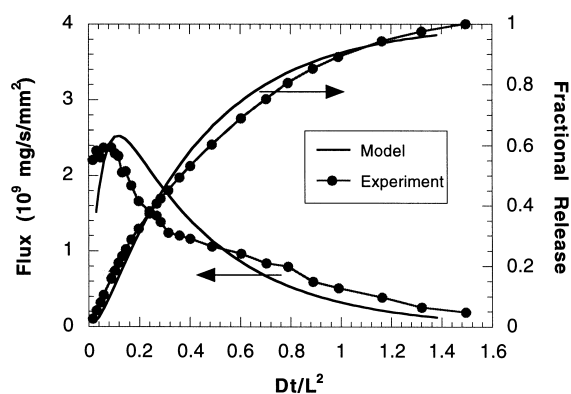


Fig. 7. Comparison of theoretical and experimental solute release. The initial concentration profile used, from center outward, was: 1.2 wt%, 0.55 wt%, 0.2 wt%, and 0 wt%, respectively. Model results (—), experimental results (—●—).

presents experimental data of AO8 released as a function of dimensionless release time.

The AO8 release profiles predicted by the model were also presented in Fig. 7. As shown in Fig. 7, the theoretical release curve and the experimental release curve agree quite well, thus validating the use of the model to analyze the release of drug from such devices. The experimental results also provide support for the theoretical analysis and confirm that diffusion is the dominant release mechanism for water soluble drugs from these polymer matrix tablets. In addition, the absence of a real burst effect, which is usually seen with matrix type delivery system, is highly significant and is shown in Fig. 7. It is worth noting that the model result is an independent prediction and not a fitting, and all parameters used in the model (e.g., AO8 concentration, matrix thickness, AO8 diffusion coefficient) were experimentally determined. Among these parameters, the slight variation in the layer thickness in the matrix is a source of derivation between experimental and model results.

To use the multilayer hydrogel with nonuniform initial drug concentration as a practical drug releasing device, one can quench and store the matrix at low temperature (such as below the glass transition temperature) until future use. Alternatively, the matrix could be quenched and vacuum dried to remove the solvent and produce a glassy poly(HEMA)

network. In the glassy regime, the nonuniform concentration distribution generated by the present process can be preserved in the glassy hydrogel matrix. The release of the entrapped drug does not occur until the hydrogel matrix is swollen (at the time of use). In addition, one will expect almost the same release behavior of the matrix after the proposed storage as that of freshly made matrix since the time to reach swelling equilibrium (about 24 h) is much shorter compared with the releasing time (several months).

As demonstrated above, photopolymerization technique provides an effective and easily implemented method to manipulate the initial drug distribution thereby providing a controllable release behavior and the model is successful in predicting release profiles from known initial parameters. To determine suitable initial parameters to obtain desired release profiles, an optimization technique based on optimal control theory and the calculus of variation has been developed. The optimization focuses on searching systematically for the set of initial solute concentrations in the layers to attain a system exhibiting release as close to zero-order as possible. Details of optimization was presented elsewhere [15].

4. Conclusions

A monolithic delivery device comprising multilaminates with spatial variation of the initial drug concentration was developed. The mathematical analysis quantitatively shows that the solute release behavior can be effectively manipulated by the nonuniform initial solute concentration in the polymer, and experimental results and simulation results agree quite well. These results are indicative of new directions towards the development of diffusion-controlled release systems using photolamination methods.

In the layer-by-layer photopolymerization process, in addition to the drug concentration, the layer thickness via varying the spacer thickness and solute diffusion coefficient via varying crosslinking agent concentration in each layer can be easily changed. Therefore, nonuniform initial concentration, nonuniform layer thickness and nonuniform solute diffusion coefficient are controllable parameters in

the layered assembly. Mathematical analysis and experimental verification of the effect of other two parameters on drug diffusion behavior can be conducted if required.

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