ELSEVIER

International Journal of Pharmaceutics 248 (2002) 183–192

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Minimization of initial burst in poly(vinyl alcohol) hydrogels by surface extraction and surface-preferential crosslinking

Xiao Huang, Brigitta L. Chestang, Christopher S. Brazel *

Department of Chemical Engineering, The University of Alabama, A127 Bevill Research Center, Tuscaloosa, AL 35487-0203, USA

Received 28 May 2002; received in revised form 5 August 2002; accepted 5 August 2002

Abstract

Surface extraction and surface-preferential crosslinking were investigated as effective methods to reduce the burst effect for proxyphylline release from poly(vinyl alcohol) hydrogels. Both these techniques involved changing the surface characteristics to reduce drug diffusion during the early stages of release, with the goal of subtracting the burst effect from the release profile without altering the long-term release rate. The extraction process was carried out on both relaxed and dry gels. Proxyphylline was extracted from both freshly made and dried hydrogel samples, with the extraction from dried samples providing better control of the burst effect with smaller amounts of drug removed from the gels. The success of extracting from the dried samples was attributed to the lack of drug diffusivity and redistribution after extraction when the majority of the device remained dry. Surface-preferential crosslinking, by dipping preformed proxyphylline-loaded samples in a concentrated crosslinking solution, effectively diminished the burst effect by slowing macromolecular relaxation near the surface. Notably, this technique maintained the same long-term drug release rate as the untreated gels and less than 0.2% of the loaded proxyphylline was removed during the crosslinking step.

Keywords: Hydrogel; Drug delivery; Burst effect

1. Introduction

The burst effect has been well documented in the drug delivery literature, and numerous researchers have sought out methods to have more control of drug delivery rates at the initial dosing. Of the strategies used, it is particularly difficult to eliminate the burst effect without affecting the overall release behavior, as evidenced by the time lags in coated systems and the altered drug release profiles when bulk properties, such as crosslinking ratio, are changed. While the high water content and surface properties of hydrogels make them ideal for biomedical applications, the porous, heterogeneous structure often leads to a burst effect when they are used as drug carriers. Like

* Corresponding author. Tel.: +1-205-348-9738; fax: +1-205-348-7558

E-mail address: cbrazel@coe.eng.ua.edu (C.S. Brazel).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00433-7

other polymer materials, hydrogels can easily be manufactured into different forms for controlled release systems. This ease of processing, coupled with the ability to create systems with various release time scales, makes the use of hydrogels enticing for pharmaceutical formulations.

Of the multitude of drug release strategies, zero-order sustained release is often the objective of drug administration, and researchers have taken many novel approaches in the design of drug delivery vehicles to achieve this sustained release profile (Lee, 1984, 1986; Baveja et al., 1987; Conte et al., 1993; Narasimhan and Langer, 1997; Brazel and Peppas, 1999a). Unfortunately, the achievement of true zero-order release is not an easy task. Hydrogel-based controlled release vehicles tend to have a rapid release upon placement into release media. This initial burst normally ends in a short time, after which the release rate may decrease to a much lower stable level. Although occasionally utilized as part of therapeutic strategies, burst release is often harmful or even dangerous because the extreme release rate may cause an overdose resulting in toxicity to the body. The importance of the burst effect, though realized for a number of years, has been investigated both experimentally and theoretically, though much of the literature (Lee, 1984; Atkins et al., 1993; Ficek and Peppas, 1993; Graiver et al., 1995; Patil et al., 1996; Jameela et al., 1997; Mallapragada et al., 1997a; Coombes et al., 1998; Bibby et al., 1999; Brazel and Peppas, 1999a,b; Huang et al., 1999; Lu and Anseth, 2000; Chung et al., 2001; Park et al., 2001) on this subject focuses on coating methods for microsphere formulations, where the burst effect is especially prominent.

A relatively small number of researchers have offered scientific theories to better understand the burst effect, with the hopes of determining relatively simple methods to reduce this pattern. Desorption or release of the drugs that have been absorbed or trapped on the surface of the device is probably the most frequently suggested reason for initial burst (Cohen et al., 1991; Pekarek et al., 1994; Sah et al., 1994; Uchida et al., 1996; Batycky et al., 1997; Rafati et al., 1997; Coombes et al., 1998; Kishida et al., 1998; Brazel and Peppas, 1999b; Chung et al., 2001). It is commonly surmised that the manufacturing procedure, such as an emulsification process used to prepare microspheres, may result in the condensation or adsorption of the drug on the polymer surface. In microsphere systems, the burst is often amplified due to the large surface area to volume ratio. Another explanation put forth for initial burst is non-uniform drug loading. Higher surface concentrations may be brought about by the migration or redistribution of drug, facilitated by convective forces during water evaporation, as the gels are dried (Sah et al., 1994; Mallapragada et al., 1997a). The porous structure of some polymer networks can also lead to an initial burst as drug diffusion is less hindered in water-filled macropores (Park et al., 1992a, 2001; Atkins et al., 1993; Huang et al., 1999; van de Weert et al., 2000). These large pores are found most often in systems formed by solvent evaporation. A similar theory was given by Patil et al. (1996), with separate diffusion processes occurring in regions of the gel network that were crosslinked at low density relative to the other highly crosslinked domains. The burst effect in hydrogel systems has been reviewed extensively elsewhere (Huang and Brazel, 2001).

Due to the therapeutic and economic impact of the burst effect, a number of methods have been suggested, designed and tested to reduce or prevent burst. Surface extraction, one of the simplest techniques, has been effectively used in several studies (Lee, 1984; Ficek and Peppas, 1993; Jameela et al., 1997; Mallapragada et al., 1997a). Among these, Lee (1984) conducted an in-depth investigation and found that using the surface extraction technique to modify the initial uniform drug distribution into a sigmoid profile in gels effectively reduced the burst effect. Lu et al. (1998) also studied initial non-uniform drug distributions, using multilaminate structures. Their mathematical model showed a more constant release rate by applying a step-decrease in drug loading profile. Another efficient, though more costly, method of reducing initial burst is surface coating or using multi-layered systems (Park et al., 1992b; Pekarek et al., 1994; Huang et al., 1999; Tongwen and Binglin, 2000; Charalambopoulou et al., 2001). Highly crosslinked gels generally display slower

release profiles due to increased hindrance to diffusion and longer chain relaxation time scales (Brazel and Peppas, 1999a,b). Although they can help prevent initial burst, the devices designed in this way are entirely ineffective because the release rate following the burst is also significantly decreased (Huang and Brazel, in press).

Based on these experimental observations, an experimental design was conceived that if a high degree of crosslinking could be confined to the surface, the initial burst could be diminished while subsequent release rates would not be affected. An important effort was shown by Lee et al. (1980) to achieve zero-order release of progesterone from poly(2-hydroxyethyl methacrylate) (PHEMA), hydrogels and copolymer matrices of HEMA and methoxyethoxyethyl methacrylate. In Lee's study, surface-preferential crosslinking was combined with a drug extraction technique by extracting gels in a crosslinking solution followed by UV exposure to activate the crosslinking reaction at the outer layer of the device. The resulting drug release rates were observed to diminish, as expected, with increased ethylene glycol dimethacrylate crosslinker content. In this well-described study to minimize the burst effect and create zero-order drug release profiles, there were still numerous challenges to overcome: the amount of progesterone removed during extraction was most likely very high (though not reported), and because the surface crosslinking was so concentrated, many of the samples exhibited cracking and crazing. These experiments proved that the burst effect could be minimized in some cases, but the subsequent release rate was also significantly altered, meaning that to achieve a desired release rate, extra drug would have to be loaded and extracted. This creates a definite economic disadvantage, although the release behavior was brought to zero-order. Although no significant burst was reported in this study, the surface extraction–surface crosslinking technology successfully modified the original typical $t^{1/2}$ kinetics of untreated samples to zero-order release of different rates by changing treating time and crosslinked concentration. Other techniques used to reduce burst effect and achieve constant release have been reviewed elsewhere (Huang and Brazel, 2001).

This study addresses techniques to reduce the burst effect in the delivery of small molecular weight solutes from crosslinked poly(vinyl alcohol) (PVA) hydrogels. At present, most of the study on burst release is concerned about delivery of larger molecules such as proteins or peptides due to the applications and potency of these drugs. However, burst release is a significant issue for small molecular weight drugs since the diffusion of these solutes is less hindered by the polymer carrier, and hence burst release is prevalent. In this study, surface extraction and surface-preferential crosslinking are investigated individually to decrease the initial burst of proxyphylline. For the surface extraction method, the release profiles were investigated and tabulated with the quantity of drug lost during the extraction process, which is an important economic factor that has not been examined sufficiently in previous studies. Surface crosslinking was studied as another simple but effective way to minimize burst, with release profiles investigated in combination with the amount of drug removed during the crosslinking step.

2. Experiments

PVA hydrogels were synthesized and loaded with proxyphylline, as described below. PVA was selected for this study as it is a neutral biocompatible material, and proxyphylline was selected as a model small molecular weight solute.

2.1. Materials

Poly(vinyl alcohol) (MW 88,000, 88% hydrolyzed) was purchased from Acros (Fairlawn, NJ). Proxyphylline (Sigma, St. Louis, MO) was used as a model drug. Glutaraldehyde was obtained in a 25 wt.% aqueous solution from Acros (Fairlawn, NJ). Acetic acid, sulfuric acid, and methanol (Aldrich, St. Louis, MO) were used as-received.

2.2. Gel preparation

PVA hydrogels were prepared with proxyphylline present during the crosslinking step, as described elsewhere (Huang and Brazel, in press), to control the drug loading concentration. Briefly, 7 wt.% aqueous PVA solutions were formed by dissolving PVA in DI water at 90 °C for 24 h. The crosslinking reaction was carried out using 25 wt.% glutaraldehyde in aqueous solution, and small amounts of dilute methanol, acetic acid and sulfuric acid solutions. Proxyphylline was added to the aqueous mixture prior to casting and carrying out the crosslinking reaction to ensure that the loading percentage was controlled and that the drug was dispersed evenly in the hydrogel. Proxyphylline was loaded prior to crosslinking at 30 wt.% (g drug/g polymer). For all cases described in this work, the crosslinking agent was added at 1.5 mol% of PVA repeating units. The gelation reaction was carried out between glass plates separated by Teflon® spacers to control the thickness. Disc-shaped samples were cut out, with approximate dimensions of 20 mm diameter × 1 mm thickness. Freshly prepared samples are referred to as in the ''relaxed'' state as they are not fully hydrated, while most samples were dried to constant weight under vacuum. Dry hydrogel samples were disc-shaped, and had thicknesses of 0.06–0.08 cm and 14 mm in diameters.

2.3. Surface extraction

Surface extraction was performed on both relaxed and dried samples by immersing proxyphylline-loaded samples in deionized water at 37 °C for lengths of time ranging from 1 to 10 min. These samples were subsequently dried under vacuum at room temperature.

2.4. Surface-preferential crosslinking

Surface-preferential crosslinking was conducted by dipping dehydrated drug-loaded samples into glutaraldehyde solutions of varying concentration at 37 °C, for only 1 s. Samples were then re-dried. Two different concentrations of crosslinking solution were used, whose compositions were as follows:

1) Crosslinking solution 1 (XS1)—mixture of 25 wt.% glutaraldehyde and 10 vol.% H_2SO_4 (catalyst) at a volume ratio of 2:3;
2) Crosslinking solution 2 (XS2)—mixture of 25 wt.% glutaraldehyde, 10 vol.% H_2SO_4 and DI water at a volume ratio of 2:3:10.

2.5. Dynamic swelling

A hydrogel's ability to control release behavior is dependent on dynamic swelling and polymer chain relaxation processes (Hopfenberg and Hsu, 1978; Colombo, 1993). Therefore kinetic swelling experiments were conducted in DI water at 37 °C. Sample weights were recorded after blotting the surface as a function of time until equilibrium was reached.

2.6. Proxyphylline release

A Type II United States Pharmacopoeia Dissolution System (Model 2100C, Distek, North Brunswick, NJ) was used to conduct release experiments. In each experiment, a drug-loaded sample was placed into a dissolution cell with 700 ml of release medium, which was DI water maintained at 37 °C and stirred at 250 rpm. Release solutions were circulated continuously through flow-through quartz cells to a UV–Vis spectrophotometer (Model 2401PC, Shimadzu, Colombia, MD), where the absorbance of proxyphylline was detected at 273 nm every 0.5 min. Absorbance data were converted to concentrations by applying Beer's law and appropriate calibration experiments.

2.7. Differential scanning calorimetry

PVA has a tendency to crystallize and can be annealed to form additional physical crosslinks. Therefore, differential scanning calorimetry (DSC) (Model 2920 MDSC, TA Instruments, New Castle, DE) experiments were conducted to study the thermal properties and crystallinity of the PVA hydrogels. Approximately 10 mg of dry gel was

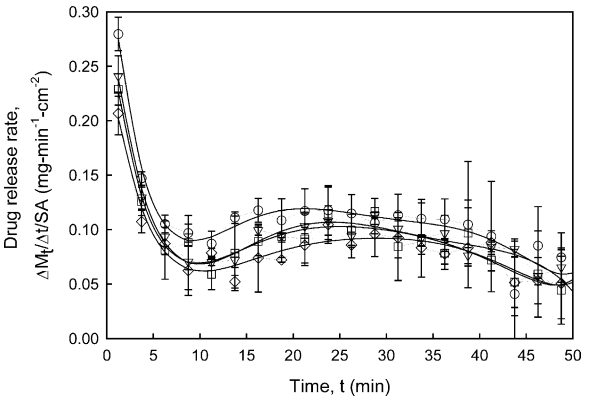

Fig. 1. Effect of surface extraction of proxyphylline from relaxed gels on release in 37 °C DI water. Release rate profiles of samples extracted in their relaxed states for 0 min (○), 1 min (▽), 2 min (□) and 5 min (◇). Samples were made from 7 wt.% PVA aqueous solution, crosslinked at 1.5 mol% and loaded with 30 wt.% proxyphylline. Data are normalized with respect to dry sample surface area. Error bars represent standard deviation for three or four experiments. Lines are guides for the eyes.

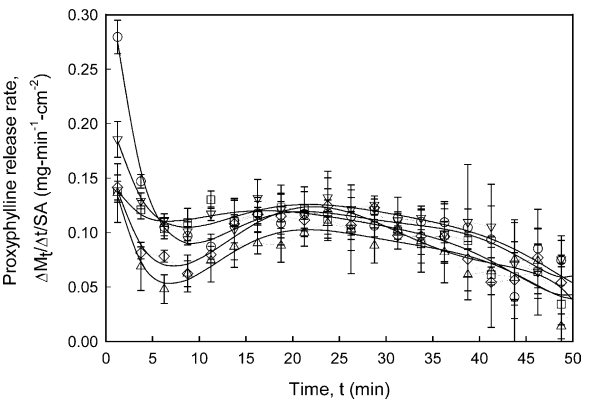

Fig. 2. Effect of surface extraction of proxyphylline from dried gels on release in 37 °C DI water. Release rate profiles of sample extracted in their dry states for 0 min (○), 1 min (▽), 2 min (□), 5 min (◇) and 10 min (△). Data are normalized with respect to dry sample surface area. Error bars represent standard deviation for three or four experiments. Lines are guides for the eyes.

used in each run, and heat flow was recorded as the temperature was ramped from room temperature to 300 °C at 10 °C/min.

3. Results and discussion

3.1. Proxyphylline release from untreated samples

Proxyphylline release from PVA hydrogels loaded uniformly was characterized by an initial burst effect followed by approximately 35–40 min of near-zero-order release rates before beginning to exhaust the sample (Fig. 1, top curve). The average drug release rate was calculated for 2.5 min intervals so that the initial burst can be visualized more clearly. Also, the release data were normalized with respect to dry sample surface areas to account for slight differences in sample size. The release profile for the first 40 min would have been near-zero-order release if not for the burst effect.

3.2. Surface extraction

Surface extraction of proxyphylline from relaxed samples led to only slight reductions in initial burst release compared with the untreated samples (Fig. 1). This lack of burst reduction was attributed to a reduction in polymer crystallinity and drug migration to the surface as the bulk gel was dried.

Surface proxyphylline was also extracted from dried samples, thus reducing the potential for convective drug redistribution to the surface upon re-drying. As shown in Fig. 2, samples that were extracted for as little as 1–2 min exhibited a significant reduction in burst release while the subsequent release profile maintained the same rate as that of the untreated samples. As the extraction time was extended to 5 and 10 min, the initial release rate was lowered even more, and the subsequent release dipped briefly and never reached the same release rate as untreated samples.

Although it is a simple processing technique, one drawback to surface extraction is that some quantity of drug will inevitably be lost during the procedure. For pharmaceutical formulations, this can cause a significant economic impact. Although the effectiveness of the technique has been tested before, there have been limited studies quantita-

Table 1
Quantity of proxyphylline removed by surface extraction of PVA hydrogels

	Extraction time			
	1 min	2 min	5 min	10 min
Extraction of relaxed samples (%)	16.4±0.9	19.4±3.4	29.5±1.9	–
Extraction of dry samples (%)	4.7±0.5	8.1±0.3	14.1±0.9	22.3±1.9

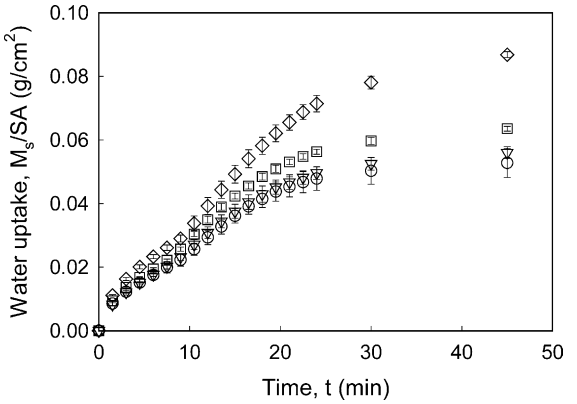

Fig. 3. Dynamic swelling behavior of unloaded PVA samples with simulated extraction in their relaxed states for 0 min (○), 1 min (▽), 2 min (□) and 5 min (◇). Error bars represent the

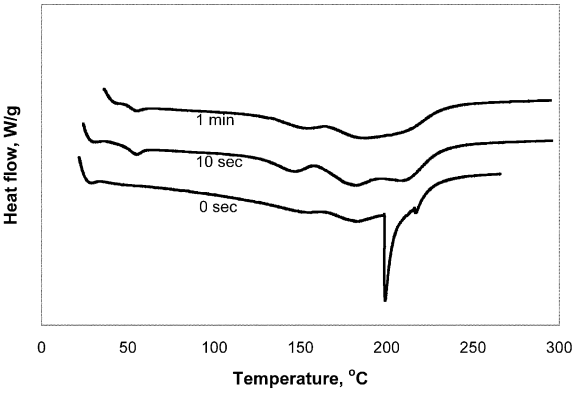

Fig. 4. DSC thermograms of unloaded PVA samples extracted in their relaxed state. Extraction times given in graph.

tively addressing drug loss during surface extraction. The percentage of proxyphylline lost is tabulated for surface extraction of both relaxed and dry samples (Table 1). When proxyphylline

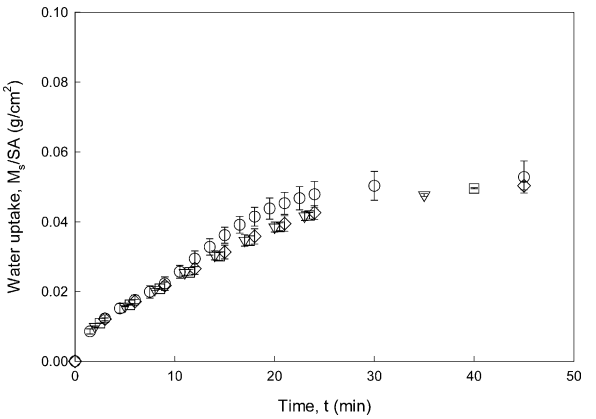

Fig. 5. Dynamic swelling behavior of unloaded samples with simulated extraction in their dry states for 0 min (○), 1 min (▽), 2 min (□) and 5 min (◇). Error bars represent the standard deviation for three experiments.

was extracted from gels in their relaxed states, a large amount of drug was lost. In 5 min, 29.54 wt.% of the proxyphylline loading was extracted; even in only 1 min, 16.41 wt.% was lost. On the other hand, drug loss during the extraction of dry samples was somewhat smaller. When the extraction time was 2 min, the device lost only 8.13 wt.% of the loaded proxyphylline while the initial burst was effectively reduced.

The change in swelling behavior upon rehydration was significant for PVA samples extracted from the relaxed state (Fig. 3). This is theorized to be due to chain disentanglement and loss of crystallinity. Although the low degree of hydration of PVA (88%) and the crosslinked structure both help to prevent crystallinity, DSC experiments were performed on drug-free hydrogel samples to determine if there were any changes in crystalline content after extraction. As Fig. 4 shows, the untreated sample has a sharp endothermic peak

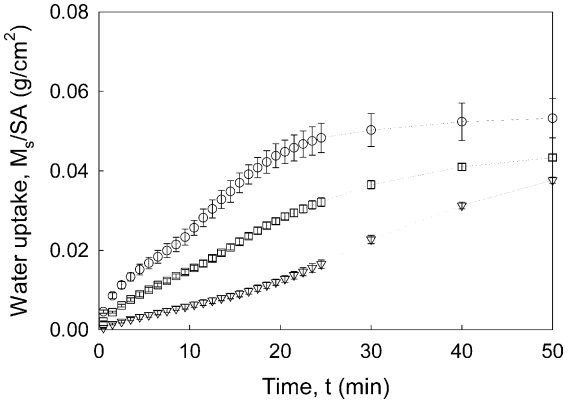

Fig. 6. Swelling profiles of untreated samples (○), samples surface-crosslinked in XS1 solution (▽) and XS2 solution (□). Error bars (too small to see for some data points) represent the standard deviation for three experiments.

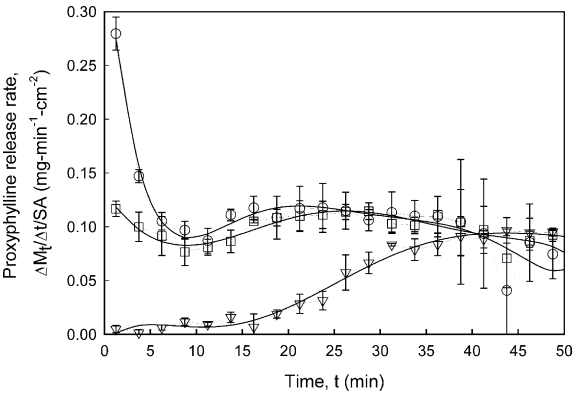

Fig. 7. Effect of surface crosslinking on proxyphylline release from PVA hydrogels in 37 °C DI water. Release rate profiles of untreated samples (○), samples surface-crosslinked in XS1 solution (▽) and XS2 solution (□) at 37 °C. Data are normalized with respect to dry sample surface area. Error bars represent standard deviation for three or four experiments. Lines are guides for the eyes.

near 200 °C, which is the melting point for PVA crystals. After extraction of samples for as little as 10 s, the melting peak was diminished significantly and broadened to lower temperatures, indicating a shift from large to small crystallites and a decrease of total crystallinity. The shift to a more amorphous structure also indicates a decrease in the physical crosslinking caused by the crystalline regions (Mallapragada et al., 1997b). The DSC thermograms show that the bulk structure of the hydrogels was changed when exposed to an extraction medium, even for only a brief time. We theorize this to be due to macromolecular relaxation and disentanglement that reduces the stresses on the hydrogel, breaking up the chain morphology that allows for crystallinity if the samples are dried directly from the relaxed state. By contrast, samples that were subjected to simulated extraction after drying, where only the outer layer of the gel was exposed to water, were much less affected by the extraction as their swelling behavior was basically unchanged after re-drying (Fig. 5). Because of the negligible change in swelling behavior and the fact that proxyphylline molecules away from the surface were kept from diffusing during the surface extraction, the extraction treatment of dry samples allowed better control over the burst effect with less total drug removed.

3.3. Surface-preferential crosslinking

Similar to surface extraction, dynamic swelling experiments were conducted on surface-preferential crosslinked samples to characterize the water imbibition process. Even with the brief surface crosslinking applied to dry PVA samples, the dynamic swelling behavior was altered significantly (Fig. 6). At the early stages of release, from 0 to 15 min, the swelling rate was greatly decreased by surface crosslinking, while during the next 15 min period, the three sets of samples had about the same swelling rate, indicating that the materials had the same inner core structures. The most highly surface-crosslinked system displayed Super Case II diffusion, imbibing water at an increasing rate after initial hydration. Therefore, the surface crosslinking technique successfully decreased the hydrogel swelling rate at early times, and maintained a rate of water imbibition the same as untreated samples beyond the burst stage. With judicious control of the crosslinking step, the diffusional processes can thus be tailored to achieve Fickian, zero-order, or time-lag behavior, each of which can be advantageous for drug delivery applications. Based on the strong correlation between swelling and drug release rates, the

Table 2
Burst and cumulative quantities of proxyphylline released from PVA formulations treated by surface extraction and surface-preferential crosslinking

Sample type	Post-formulation treatment	Total drug released in 10 h (g drug/g polymer) (maximum is 30 wt.%, as initially loaded)	Drug released during first 5 min (burst) (g drug/g polymer)
Untreated samples	None	21.8±0.3	3.6±0.2
Surface extraction of dry samples	1 min extraction	21.2±0.6	2.4±0.1
	2 min extraction	18.2±0.5	2.1±0.1
	5 min extraction	19.8±0.3	2.0±0.2
	10 min extraction	17.7±0.4	1.9±0.4
Surface-preferential crosslinking	Crosslinked by 3.3% solution	20.9±0.4	1.7±0.1
	Crosslinked by 10% solution	23.1±1.4	0.05±0.04

surface-crosslinked systems show promise at preventing the burst effect.

Proxyphylline release rate curves for surface-preferential crosslinked samples are shown in Fig. 7. In the samples that were processed with crosslinking solution XS1, which was relatively concentrated, the initial burst was completely removed and replaced by a delayed release. However, after the lag, the release rate quickly increased to 0.09–0.10 mg/(cm^2 min), which was close to the level of the constant release rate of the untreated gels ($\sim$ 0.11 mg/(cm^2 min)). When diluted crosslinking solution XS2 was applied, neither burst nor delay was observed. In this material, the release was nearly zero-order, with a release rate of 0.10–0.11 mg/(cm^2 min), hardly lower than that of the steady-state release of the untreated samples. Correlating the release results to the swelling behavior, because only the swelling rate of the early stage was decreased, the release profile was changed only in the initial burst part. One important note for these experiments is that the release behavior was reproducible (note error bars in Fig. 7), especially with regard to the initial release rate. Also of note is that the surfaces of the hydrogels crosslinked in XS1 solution cracked during the swelling and release process (as observed by Lee et al. (1980) for a PHEMA-based system) due to the swelling stresses that built up inside the gels. Prior to the presence of the cracks, both release and swelling rates of the gels were low due to the diffusion restriction of highly crosslinked surfaces. Since cracking led to extra surface area, the release rate increased quickly after the delay. Cracks were not observed on hydrogels surface-crosslinked in XS2 solution.

According to the above results, the surface crosslinking process is highly effective. Because the samples were only dipped into crosslinking solution for about 1 s, the economic impact of drug loss could be neglected. Experimental results suggested that dipping the proxyphylline-loaded PVA samples in 37 °C DI water for 1 s only released (0.180±0.029)% of the total drug loading.

4. Analysis of treatment methods

The burst effect was successfully reduced by surface extraction of dry samples and by surface-preferential crosslinking. The percentage of drug released in a burst was reduced significantly, from 3.6 to less than 2 g drug/g polymer by surface extraction, and so much so that only 0.05 g proxyphylline/g polymer was released in the first 5 min when it was heavily surface-crosslinked (Table 2). These values are highly dependent upon the geometry of the devices; if the discs used in our experiments were enlarged, then a much smaller fraction of drug would be released in a burst; however, in the more common formulations using microspheres and small structures, the burst effect is much more prevalent. The trends in decreasing burst effect would be expected by

applying these techniques to other formulations. As the total amount of drug loaded was initially 30 wt.% of the polymer carrier, the fraction of proxyphylline released in 10 h approaches the maximum value, with over two-third of the drug released. The downward trend in cumulative drug released with increasing surface extraction times is reflective of the loss of a significant amount of drug during the extraction, which keeps the total drug released below two-third of that which was originally loaded. This confirms our earlier statement that the surface extraction technique removes a significant quantity of drug. Interestingly, the surface crosslinking done using a 10% glutaraldehyde solution increased the total drug delivered in a 10 h time period. This increase was attributed to surface cracks that increased the surface area for diffusion due to extreme stresses at the highly crosslinked surfaces.

5. Conclusion

Both surface extraction and surface-preferential crosslinking were investigated as techniques to minimize the initial burst release of proxyphylline from crosslinked PVA hydrogels. The surface-crosslinked samples show great promise at reducing the burst effect while requiring only minimal post-formulation treatment. Additionally, the quantity of drug lost from the formulation in the brief contact with the crosslinking solution was less than 0.2 wt.%. The surface-crosslinked samples show reproducible behavior, and the release can be tailored to have reduced burst, no burst, or even a lag release, which may be advantageous for oral drug delivery. Another relatively simple technique, surface extraction, was shown to have some success at minimizing burst when the extraction was carried out on dried samples. However, the success of this technique was at the expense of significant drug loss from the PVA–proxyphylline formulations. Surface extraction from relaxed samples was much less effective, as large amounts of proxyphylline were removed without having any effect on the burst release behavior.

Acknowledgements

The authors wish to acknowledge Dr. David Nikles for his generous help in DSC experiments, financial support from a Graduate Council Fellowship and the Department of Chemical Engineering at The University of Alabama.

References

Atkins, T.W., McCallio, R.L., Tighe, B.J., 1993. Incorporation and release of fluorescein isothiocyanate-linked dextrans from a bead-formed macroporous hydrophilic matrix with potential for sustained release. Biomaterials 14, 16–20.

Batycky, R.P., Hanes, J., Langer, R., Edwards, D.A., 1997. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J. Pharm. Sci. 86, 1464–1477.

Baveja, S.K., Rao, K.V.R., Devi, K.P., 1987. Zero-order release hydrophilic matrix tablets of β-adrenergic blockers. Int. J. Pharm. 39, 39–45.

Bibby, D.C., Davies, N.M., Tucker, I.G., 1999. Poly(acrylic acid) microspheres containing β-cyclodextrin loading and in vitro release of two dyes. Int. J. Pharm. 187, 243–250.

Brazel, C.S., Peppas, N.A., 1999a. Mechanisms of solute and drug transport in relaxing, swellable, hydrophilic glassy polymers. Polymer 40, 3338–3398.

Brazel, C.S., Peppas, N.A., 1999b. Recent studies and molecular analysis of drug release from swelling-controlled devices. STP Pharm. Sci. 9, 473–485.

Charalambopooulou, G.Ch., Kikkinides, E.S., Papadokostaki, K.G., Stubos, A.K., Papaioannou, A.T., 2001. Numerical and experimental investigation of the diffusional release of a dispersed solute from polymeric multilaminate matrices. J. Control. Release 70, 309–319.

Chung, T.W., Huang, Y.Y., Liu, Y.Z., 2001. Effects of the rate of solvent evaporation on the characteristics of drug-loaded PLLA and PDLLA microspheres. Int. J. Pharm. 212, 161–169.

Cohen, S., Yoshioka, T., Lucarelli, M., Huang, L.H., Langer, R., 1991. Controlled delivery systems for proteins based on poly(lactic/glycolic acid) microspheres. Pharm. Res. 8, 713–720.

Colombo, P., 1993. Swelling controlled release in hydrogel matrices for oral route. Adv. Drug Delivery Rev. 11, 37–57.

Conte, U., Maggi, L., Colombo, P., La Manna, A., 1993. Multi-layered hydrophilic matrices as constant release devices (Geomatrix™ systems). J. Control. Release 26, 39–47.

Coombes, A.G.A., Yeh, M.K., Lavelle, E.C., Davis, S.S., 1998. The control of protein release from poly(DL-lactic-co-glycolide) microparticles by variation of the external aqueous phase surfactant in the water-in oil-in water method. J. Control. Release 52, 311–320.

Ficek, B.J., Peppas, N.A., 1993. Novel preparation of poly(vinyl alcohol) microparticles without crosslinking agent for controlled drug delivery of proteins. J. Control. Release 27, 259–264.

Graiver, D., Hyon, S.H., Ikada, Y., 1995. Poly(vinyl alcohol)–poly(sodium acrylate) composite hydrogels. I. Kinetics of swelling and dehydration. J. Appl. Polym. Sci. 57, 1299–1310.

Hopfenberg, H.B., Hsu, K.C., 1978. Swelling-controlled, constant rate delivery systems. Polym. Eng. Sci. 18, 1186–1191.

Huang, X., Brazel, C.S., 2001. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J. Control. Release 73, 121–136.

Huang, X., Brazel, C.S., in press. Analysis of burst release in PVA hydrogels. Chem. Eng. Commun.

Huang, Y.Y., Chung, T.W., Tzeng, T.W., 1999. A method using biodegradable polylactides/polyethylene glycol for drug release with reduced initial burst. Int. J. Pharm. 182, 93–100.

Jameela, S.R., Suma, N., Jayakrishnan, A., 1997. Protein release from poly(ε-caprolactone) microspheres prepared by melt encapsulation and solvent evaporation techniques: a comparative study. J. Biomater. Sci. Polym. Ed. 8, 457–466.

Kishida, A., Murakami, K., Goto, H., Akashi, M., Kubota, H., Endo, T., 1998. Polymer drug and polymeric drugs. X. Slow release of 5-fluorouricil from biodegradable poly(γ-glutamic acid) and its benzyl ester matrices. J. Bioactive Compatible Polym. 13, 271–278.

Lee, P.I., 1984. Effect of non-uniform initial drug concentration distribution on the kinetics of drug release from glassy hydrogel matrices. Polymer 25, 973–978.

Lee, P.I., 1986. Initial concentration distribution as a mechanism for regulating drug release from diffusion controlled and surface erosion controlled matrix systems. J. Control. Release 4, 1–7.

Lee, E.S., Kim, S.W., Kim, S.H., Cardinal, J.R., Jacobs, H., 1980. Drug release from hydrogel devices with rate-controlling barriers. J. Membr. Sci. 7, 293–303.

Lu, S., Anseth, K.S., 2000. Release behavior of high molecular weight solutes from poly(ethylene glycol)-based degradable networks. Macromolecules 33, 2509–2515.

Lu, S., Ramirez, W.F., Anseth, K.S., 1998. Modeling and optimization of drug release from laminated polymer matrix devices. AIChE J. 44, 1689–1696.

Mallapragada, S.K., Peppas, N.A., Colombo, P., 1997a. Crystal dissolution-controlled release systems. J. Biomed. Mater. Res. 36, 125–130.

Mallapragada, S.K., Peppas, N.A., Colombo, P., 1997b. Crystal dissolution-controlled release systems. II. Metronidazole release from semicrystalline poly(vinyl alcohol) systems. J. Biomed. Mater. Res. 36, 125–130.

Narasimhan, B., Langer, R., 1997. Zero-order release of micro- and macromolecules from polymeric devices: the role of the burst effect. J. Control. Release 47, 13–20.

Park, T.G., Cohen, S., Langer, R., 1992a. Poly(L-lactic acid)/pluronic blends: characterization of phase separation behavior, degradation, and morphology and use as protein-releasing matrices. Macromolecules 25, 116–122.

Park, T.G., Cohen, S., Langer, R., 1992b. Controlled protein release from polyethyleneimine-coated poly(L-lactic acid)/pluronic blend matrices. Pharm. Res. 9, 37–39.

Park, Y.J., Liang, J., Yang, Z., Yang, V.C., 2001. Controlled release of clot-dissolving tissue-type plasminogen activator from a poly(L-glutamic acid) semi-interpenetrating polymer network hydrogel. J. Control. Release 75, 37–44.

Patil, N.S., Dordick, J.S., Rethwisch, D.G., 1996. Macroporous poly(sucrose acrylate) hydrogel for controlled release of macromolecules. Biomaterials 17, 2343–2350.

Pekarek, K.J., Jacob, J.S., Mathiowitz, E., 1994. Double-walled microspheres for drug delivery. Mater. Res. Soc. Symp. Proc. 331, 97–101.

Rafati, H., Coombes, A.G.A., Adler, A., Holland, J., Davis, S.S., 1997. Protein-loaded poly(DL-lactide-co-glycolide) microparticles for oral administration: formulation, structural and release characteristics. J. Control. Release 43, 89–102.

Sah, H.K., Toddywala, R., Chien, Y.W., 1994. The influence of biodegradable microcapsule formulations on the controlled release of a protein. J. Control. Release 30, 201–211.

Tongwen, X., Binglin, H., 2000. A mechanism on the drug release into a prefect sink from a coated planar matrix with a super-saturation loading in the core. Int. J. Pharm. 197, 23–34.

Uchida, T., Yagi, A., Oda, Y., Goto, S., 1996. Microencapsulation of ovalbumin in poly(lactide-co-glycolide) by and oil-in-oil (o/o) solvent evaporation method. J. Microencapsul. 13, 509–518.

van de Weert, M., van't Hof, R., van der Weerd, J., Heeren, R.M.A., Posthuma, G., Hennink, W.E., Crommelin, D.J.A., 2000. Lysozyme distribution and conformation in a biodegradable polymer matrix as determined by FTIR techniques. J. Control. Release 68, 31–40.