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Modifying the release of proxyphylline from PVA hydrogels using surface crosslinking

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Abstract

Drug release profiles were altered to prevent the initial burst effect or introduce a lag phase by creating surface crosslinked layers in poly(vinyl alcohol) (PVA) hydrogels. Confocal laser scanning microscopy (CLSM) confirmed the successful introduction of these surface crosslinked layers. The thickness and crosslinking density of the surface crosslinked layer were highly dependent on the surface crosslinking conditions (i.e., exposure time and glutaraldehyde (GTA) concentration used). By judicious selection of these parameters, the initial burst release could be eliminated and a reproducible delayed release could be achieved. Highly surface crosslinked layers had a tendency to rupture during the swelling process of PVA hydrogels; these raptures were found to coincide with delayed release of proxyphylline from surface crosslinked PVA hydrogels.

Keywords: Initial burst effect; PVA hydrogel; Surface crosslinking; Drug delivery

1. Introduction

PVA hydrogels find extensive applications in tissue engineering and drug delivery because of their low cost, biocompatibility and similarity to natural tissues (Bajpai and Saini, 2006; Brazel and Peppas, 1999; Dai and Barbari, 2000a; Huang and Brazel, 2003; Korsmeyer and Peppas, 1981). Two different strategies have been used to synthesize PVA hydrogels, including chemical crosslinking via irradiation or bifunctional crosslinkers such as GTA and physical crosslinking via freezing/thawing cycles to form crystals (Brazel and Peppas, 1999; Fergg et al., 2001; Hickey and Peppas, 1995; Korsmeyer and Peppas, 1981). PVA hydrogels made from the freezing/thawing process usually have much larger mesh or pore sizes than those synthesized by chemical crosslinking (Fergg et al., 2001; Hickey and Peppas, 1995; Korsmeyer and Peppas, 1981).

Researchers have extensively studied the release of various drugs from PVA hydrogels (Brazel and Peppas, 1999; Huang and Brazel, 2003; Korsmeyer and Peppas, 1981; Lyoo et al., 2006; Mandal et al., 2002; Peppas and Scott, 1992). Drug release from PVA hydrogels can be modulated by controlling the crosslinking ratio or density in hydrogels (Korsmeyer and Peppas, 1981). However, just like many other controlled release systems, an initial burst release has been observed during the course of drug release (Huang and Brazel, 2003; Korsmeyer and Peppas, 1981; Peppas and Scott, 1992). This burst release, while desirable in some formulations, is known to be a cause of patient side effects for many medications and has also been noted as economically wasteful since much of the drug released during the burst phase has no therapeutic effect, while reducing the longevity of the system. Therefore, further improvement on the drug release rate is necessary to eliminate or significantly reduce this initial burst (Huang and Brazel, 2001; Yeo and Park, 2004).

Numerous efforts have been made in the past decades to minimize or prevent the burst effect (Huang and Brazel, 2001; Mandal et al., 2002). For example, surface extraction of hydrogels, double-walled microspheres, coatings placed on drug-loaded microcapsules, and structured composites have been reported in the literature to achieve this purpose. One successful example is that Berkland et al. tuned biphasic release of piroxicam from poly(D,L-lactide-co-glycolide) (PLG) microspheres into zero-order release from double-walled poly(D,L-lactide-co-glycolide)-poly(L-lactide) (PLG-PL) microspheres by reducing the initial burst and leveling the second phase of drug release via

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the introduction of a barrier shell made from PL (Berkland et al., 2004). Mandal et al. claimed that the initial burst release could be significantly reduced by microencapsulating drug-loaded PVA hydrogels into PLG (Mandal et al., 2002). While the introduction of additional barrier layers is naturally an excellent method to tune drug release profiles and reduce burst effect, it is inherently expensive due to the additional materials making it more difficult to control the quality of the barriers.

It has recently been recognized that non-uniform drug release profile might offer more benefits than continuous release profile in some cases because of the nature of therapeutic drugs, and the well-known dependence of diseases and body function on circadian rhythms. For example, delayed release is more desirable in chronotherapeutics (Washington and Wilson, 2006). A lag time or delayed release is necessary for the efficient oral delivery of proteins since oral administration of proteins needs to avoid protein degradation in the stomach and the upper small intestine (Dorkoosh et al., 2001). Various strategies have been used to create a desirable lag time (Lin et al., 2001; Lin et al., 2004; Patel et al., 2006; Washington and Wilson, 2006). Lin et al. used ethylcellulose as an outer coating layer in tablets (Lin et al., 2001; Lin et al., 2004). The lag time could be controlled by adjusting the size of ethylcellulose particles or adding hydrophilic excipients such as spray-dried lactose and hydroxypropyl methylcellulose into this outer coating layer. However, it also requires additional cost due to the introduction of additional materials or reduced efficiency in drug loading.

PVA has plenty of hydroxyl groups available for chemical crosslinking. Therefore, PVA hydrogel delivery systems can be easily modified to attain desirable release profiles by varying the crosslinking densities, thus affecting the mesh size (Huang et al., 2002). In this study, we created non-uniform crosslinking densities in PVA hydrogels using a simple surface crosslinking technique. By providing surface crosslinked layers, drug release was tuned to prevent the burst effect or introduce reproducible lag release behaviors. CLSM was used to study the structural gradients in surface-crosslinked PVA hydrogels by covalently attaching a fluorophore, 5-(4, 6-dichlorotriazinyl)aminofluorescein (DTAF), to PVA before the synthesis of hydrogels.

2. Materials and methods

2.1. Materials

Methanol and PVA (M_n 88,000, 88% hydrolyzed) were purchased from Acros Organics (Fairlawn, NJ). GTA aqueous solution (25 wt%), Na_2CO_3 (99.5%), acetic acid (99.7%) and sulfuric acid (95–98%) were obtained from Aldrich (Milwaukee, WI). Pro-Sil®, a siliconizing agent, was obtained from Stephenson Group Limited (U.K.). DTAF was bought from Fisher Scientific (Fairlawn, NJ). Proxyphylline were purchased from Sigma (St. Louis, MO) and used as the model drug in this work due to its low molecular weight (238.2 g/mol) and high solubility in water (1 g/g-water), which are suspected to be factors leading to a high initial burst. All of the chemicals were used as received unless otherwise noted.

2.2. Synthesis of PVA hydrogels

PVA hydrogels were synthesized from 7 wt% PVA solutions prepared by dissolving 3.5 g PVA in 46.5 g de-ionized (DI) water at 90 °C for 24 h (Huang et al., 2002; Huang and Brazel, 2003). The PVA solution was stirred with a glass rod and cooled to room temperature (22–25 °C). Proxyphylline (1.05 g) was dissolved in the PVA solution to achieve a proxyphylline/PVA weight ratio of 3:10. The resulting solution was rested at room temperature until no visible trapped bubbles were observed. Solutions of methanol (450 μl, 50 vol%), acetic acid (225 μl, 10 vol%), GTA (450 μl, 25 wt%) and sulfuric acid (675 μl, 10 vol%) were sequentially added into the proxyphylline/PVA solution (Huang et al., 2002; Huang and Brazel, 2003). After thoroughly mixing with a glass rod, the mixture was cast between two glass plates previously treated with Pro-Sil solution. A Teflon® frame with a thickness of 1.58 mm was used to control sample thickness. The glass plates with cast mixture were kept at 37 °C for 24 h to crosslink the PVA polymer chains. After the synthesis, some solution was rejected from the resulting PVA hydrogel membrane as has been reported before (Korsmeyer and Peppas, 1981). Based on the UV–vis analysis of the rejected solution, the actual proxyphylline loading was 19–20 wt% of dry PVA polymer without drug. Disk-shaped samples were cut from the resulting hydrogel film in a diameter of 2.5 cm and dried to constant weights in a desiccator under vacuum at room temperature. A digital caliper was used to measure the thickness and diameter of each dry PVA hydrogel sample at two or three different positions. All dry PVA hydrogel samples were about 1.300–1.400 cm in diameter and 0.60–0.64 mm in thickness.

2.3. Synthesis of DTAF–PVA conjugates

A modified procedure was used to synthesize DTAF–PVA conjugates through the elimination of hydrogen chloride (Fergg et al., 2001; Dai and Barbari, 2000b). PVA (1.3 g) was dissolved in 130 ml DI water at 90 °C for 24 h and the resulting PVA solution was then cooled to room temperature with stirring. DTAF (15 mg) was dissolved in 4 ml Na_2CO_3 solution (3.25 M). The DTAF solution was then added into the PVA solution at room temperature while stirring with a magnetic stir bar. The reaction was carried out in a dark room for 36 h. The polymers were precipitated by adding 400 ml acetone to the reaction mixture. The precipitated polymers were collected and dialyzed against acetone/water solution (1:1) and then DI water to remove unreacted DTAF. The resulting polymers, DTAF–PVA conjugates, were then dried in a desiccator under vacuum in a dark room. To make DTAF-labeled PVA hydrogels, 0.5 g DTAF–PVA conjugates and 3.0 g PVA were dissolved in 46.5 g DI water. The subsequent steps were the same as those used to prepare PVA hydrogels.

2.4. Surface crosslinking

Surface crosslinking was applied to dry PVA hydrogel samples and DTAF-labeled PVA hydrogel samples. Three surface crosslinking solutions (8 ml), namely 3.3, 5 or 10 wt% GTA

Table 1
Compositions of surface crosslinking solutions used

GTA concentration in the surface crosslinking solution	25 wt% GTA (ml)	10 vol% H_2SO_4 (ml)	DI water (ml)
3.3 wt%	1.05	1.05	5.90
5 wt%	1.60	1.60	4.80
10 wt%	3.20	3.20	1.60

crosslinking solution, were prepared using GTA aqueous solution (25 wt%), sulfuric acid solution (10 vol%) and DI water according to Table 1. The crosslinking solution was heated in a 37 °C water bath for 4 min, and then a dry hydrogel sample was completely immersed into the crosslinking solution for a short time. For 5.0 or 10 wt% GTA crosslinking solution, the immersing time was 1.1–1.3 s; however, three immersing times, 1.1–1.3, 10 and 60 s, were used for 3.3 wt% GTA crosslinking solution. The PVA discs were then blotted using absorbent tissue to remove solution adsorbed on the sample surfaces and dried in a desiccator under vacuum to constant weights. It must be noted that due to the dark room, the shortest immersing time for DTAF-labeled PVA samples was 1.4 s.

2.5. CLSM

A Leica CLSM (Model TCS SP2, Exton, PA) was used to observe the surface crosslinked layers in DTAF-labeled PVA hydrogels. Each DTAF-labeled PVA hydrogel sample was swollen in 900 ml DI-water separately for at least 7 days (water was changed once after the first 3 days.). Small slices were cut from the fully hydrated hydrogels to expose the cross-section and mounted on glass slides to expose the whole cross-section to the laser light. An argon laser was used as the light source. Images were taken from the CLSM and analyzed using free software ImageJ from National Institutes of Health (USA) to read the fluorescence emission intensity from the resulting CLSM images. The fluorescence intensities read from the images were used directly without further modulation.

2.6. Kinetic swelling

The release of proxyphylline from PVA hydrogels is highly dependent on the swelling properties of hydrogels. Kinetic swelling experiments were conducted in 37 °C DI water using dry PVA hydrogel samples, either surface crosslinked or untreated. At pre-set time points, each PVA sample soaked in the DI water was removed from the swelling medium to blot off the water adsorbed on the surfaces and then weighed using an electric balance.

2.7. In vitro Release experiments

In vitro release experiments were conducted in a United States Pharmacopoeia type II Dissolution System (Distek Model 2100c, North Brunswick, NJ) coupled with a Shimadzu UV–vis spectrophotometer (Model 2401PC, Columbia, MD). The release medium, 37 ± 0.3 °C DI water, was continuously circulated at 18.5–19.5 ml/min through a quartz flow-through cuvette (0.750 ml) located in the UV–vis spectrophotometer via tubing (internal diameter 2.4 mm; sampling tubing 194 ± 6 cm in length) using a Fisherbrand variable-flow peristaltic pump. The sample solution was continuously returned to the dissolution cell. To begin the experiment, a drug-loaded PVA hydrogel sample was dropped into a dissolution cell containing 700 ml of release medium (37 °C) (Huang et al., 2002), which was stirred at 110 rpm. The UV absorbance of the proxyphylline solution in the flow-through cuvette was measured at 272.6 nm and recorded every 10 s. The release data were adjusted accordingly to account for the sampling lag time, 26 s, which was calculated from the sampling flow rate and the dead volume of the sampling tubing (Pliquett et al., 1995). The proxyphylline concentrations in the release mediums at the end of drug release course (about 0.021 mg/ml) were much lower than the solubility of proxyphylline in water, which ensured that the sink condition was respected in the *in vitro* release experiments.

3. Results and discussion

3.1. Visualization of surface crosslinking

CLSM has recently been used to determine the drug distribution in controlled release systems (Pollauf et al., 2005; Raman et al., 2005) and to characterize the microscopic structure of hydrogels (Chen et al., 2006; Dai and Barbari, 2000b; Fergg et al., 2001). The spatial resolution of CLSM is much larger than the mesh sizes (less than 10 nm) of most non-porous hydrogels such as PVA hydrogels, however the fluorescence intensity distribution is the interest of these studies since the fluorescence intensity is highly related to the local fluorescent molecules. If fluorescent molecules are evenly attached to the polymer chains in hydrogels, after swollen the fluorescence intensity will reflect the polymer density, which is in turn related to the mesh size. Any change in the mesh size in the hydrogel may be reflected by the change in fluorescence intensity if the region is big enough. Since hydrogels usually lack the ability of fluorescence emission, fluorescence dyes were covalently conjugated to the polymers before or after the synthesis of hydrogels (Dai and Barbari, 2000b; Fergg et al., 2001). In this study, DTAF was chosen and conjugated to PVA via the elimination of hydrogen chloride before the synthesis of hydrogels. PVA hydrogels were transparent without color, while DTAF-labeled PVA hydrogels were light yellow.

The successful conjugation of DTAF to PVA was evidenced by Fig. 1, which shows the UV–vis spectra for DTAF solution, DTAF–PVA conjugate solution, PVA solution and the rejected solution from the synthesis of DTAF-labeled PVA hydrogels. The DTAF solution and DTAF–PVA solution both had an absorbance peak around 492 nm; however, no such peak appeared in the UV–vis spectra for the PVA solution and the rejected solution. The rejected solution had a weak absorption peak at 440 nm. It has been reported that the absorption intensity of fluorescein can be affected by the pH of the solution (lowest at pH 5.3 for DTAF) as does the wavelength of the absorption peak (Guan et al., 2006; Jones and Qian, 1998). However, the ratio of molar absorptivities of DTAF in the pH range of 0.2–11.0 is

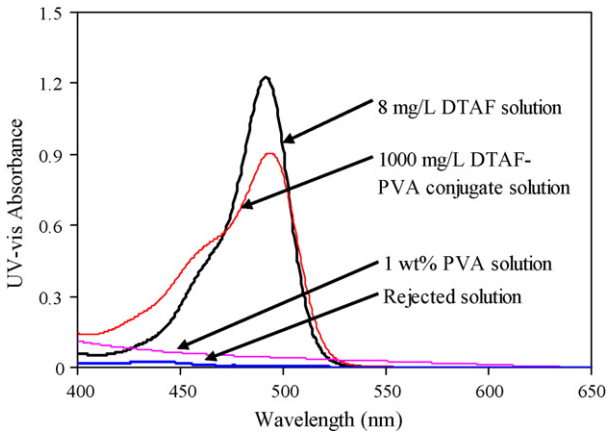

Fig. 1. UV–vis spectra of DTAF solution, DTAF–PVA conjugate solution, PVA solution and rejected solution formed during DTAF-labeled PVA hydrogels.

within the range of 1–3.2 (Jones and Qian, 1998). Therefore, the free DTAF, if any, in the DTAF–PVA conjugate mixture was less than 1% of the total DTAF based on the UV–vis absorbance spectra. The DTAF–PVA label frequency was found to be about 0.00048 mol DTAF per mole of PVA repeat unit. Although this is a low conjugation ratio, the fluorescence was sufficient for CLSM. This also ensured that a majority of the –OH pendent groups remained available, and the bulk crosslinking and further surface crosslinking would not be hindered to synthesize and modify fluorescent hydrogel samples.

Fig. 2a shows a typical CLSM image for the cross-section of a DTAF-labeled PVA hydrogel without the surface crosslinking treatment. The fluorescence intensity for this hydrogel sample was reasonably uniform in the cross-section similar to results reported by Dai and Barbari when working with PVA hydrogel membranes (Dai and Barbari, 2000b). Using the CLSM data, the hydrogel was found to be about 800 μm in thickness using Dai's method (Dai and Barbari, 2000b) which was comparable to the thickness measured using a digital caliper.

The fluorescence intensity distributions for the surface crosslinked DTAF-labeled PVA hydrogels were much different from that for untreated samples. It was observed that the regions near the surface had much higher fluorescence intensities than the bulk section for surface crosslinked DTAF-labeled PVA hydrogels. Some typical CLSM images and the corresponding relative fluorescence intensity distributions are shown in Fig. 2b and c. In the experiments, we did not keep constant microscopic settings for these images since comparisons among images were not our main goal (Chen et al., 2006). The middle section, bulk hydrogel, had uniform fluorescence intensities similar to the untreated DTAF-labeled PVA hydrogel, while the sections near

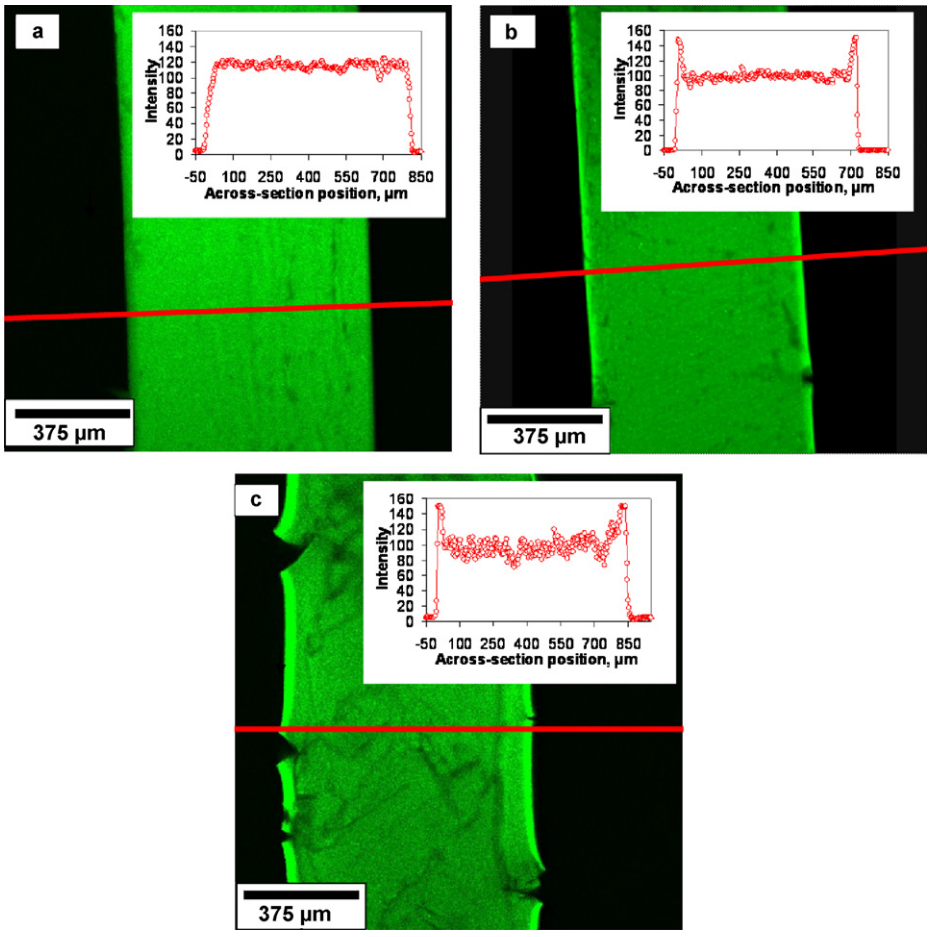

Fig. 2. Fluorescence intensity profiles corresponding to the lines shown in the CLSM images for the cross-sections of DTAF-labeled PVA hydrogels: (a) untreated; (b) surface crosslinked in 5 wt% GTA solution for 1.4 s; (c) surface crosslinked 10 wt% GTA solution for 1.4 s.

the surfaces, namely the surface crosslinked layers, had much higher fluorescence intensities. The significant difference in the fluorescence intensities between the surface crosslinked layer and the bulk should be attributed to the change in the network structure of the hydrogels induced by the surface crosslinking. Although the fluorescence intensity was higher at the surface, a gradient in intensities was found between the surface and the bulk regions of the surface crosslinked hydrogels. This is consistent with what we would expect that the crosslinking density in the surface crosslinked layer gradually decreased from the surface to the bulk since a GTA gradient was needed for the penetration of GTA into hydrogels, thus reacting with PVA. The images yield information about the depth of penetration of the surface crosslinking solution as well as the chain density and mesh space in the surface crosslinked layers relative to the bulk hydrogel. The thickness of the surface crosslinked layer varied for surface crosslinked DTAF-labeled PVA hydrogels depending on the conditions used for the surface crosslinking treatment. Much thicker layers were observed for those receiving surface crosslinking in a higher GTA concentration solution (Fig. 2 b and c) or for a longer exposure time (data not shown). Ruptures were found for those highly surface crosslinked samples (i.e., in 10 wt% GTA crosslinking solution for 1 s (Fig. 2c) or in 3.3 wt% GTA crosslinking solution for 60 s) due to the higher stresses built up in the surface of these hydrogels during the swelling process. Swelling experiments confirmed that these ruptures began to form when the water fronts met at the gel core which marks a transition from anisotropic swelling (increase in thickness) to isotropic relaxation (expansion along the diameter as well for disc-shaped samples) (Brazel and Peppas, 1999) for the highly surface crosslinked hydrogels.

3.2. Swelling

The rate of swelling in hydrogels strongly controls the drug release rate from swellable hydrogels. This swelling provides macroscopic evidence of the glassy-rubbery transition that happens when hydrogels contact a thermodynamically compatible solvent, namely water (Peppas and Khare, 1993). The hydrophilicity of the polymer and the degree of crosslinking in the hydrogel have significant influences on the swelling properties (Amidon et al., 2000). All of the swelling profiles displayed dual sorption pattern (Figs. 3 and 4), where the beginning of the second stage coincided with the disappearance of the glassy core (Brazel and Peppas, 1999). The first swelling phase is associated with the anisotropic swelling of PVA hydrogels, while the second was associated with the isotropic swelling of PVA hydrogels that occurred after the glassy core vanishes in the hydrogels. After the glassy core disappeared, the polymer discs relax in all directions and allow an expansion in the radial direction, causing an increase in the surface area exposed to water accounting for the increased swelling rate in non-surface-crosslinked and lightly surface-crosslinked hydrogels. As mentioned early the simultaneous disappearance of the glassy core with the appearance of surface ruptures causes an increase in the swelling rate for highly surface-crosslinked hydrogels. The swelling profiles for PVA hydrogels differed markedly depending on GTA concentration (Fig. 3) and exposure time (Fig. 4) used in the surface crosslinking. Surface crosslinking slowed the water uptake in both swelling phases, thus postponing the transition time from anisotopic to isotropic swelling. PVA hydrogels receiving surface crosslinking in a higher GTA concentration solution have lower water uptake rates, as did those exposed to the GTA solution for a longer time. We hypothesize that the crosslinking density is much higher for those samples receiving longer exposure time and higher crosslinker concentration, thus reducing the corresponding mesh size and increasing the polymer relaxation constant (Brazel and Peppas, 1999), which can both slow the water uptake.

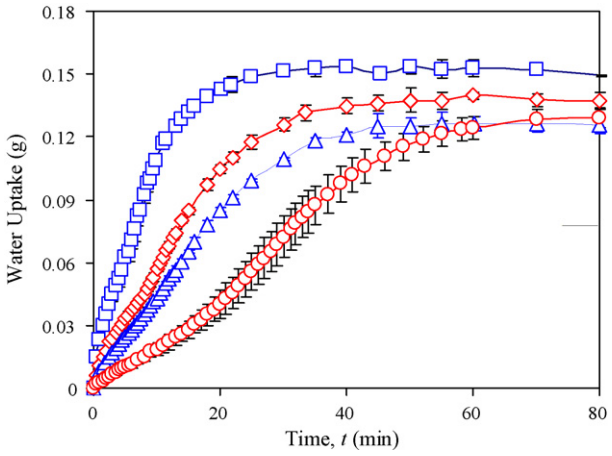

Fig. 3. Effect of surface crosslinking solution on the kinetic swelling for a fixed exposure time of 1.1 s: untreated (□), 3.3 wt% GTA (◊), 5 wt% GTA (Δ), 10 wt% GTA (○). Error bars represent standard deviations for three experiments. Lines are guides for the eyes.

3.3. In vitro release

The crosslinking density has been used as an adjustable parameter to control drug release from hydrogel systems (Korsmeyer and Peppas, 1981; Ren et al., 2006). However,

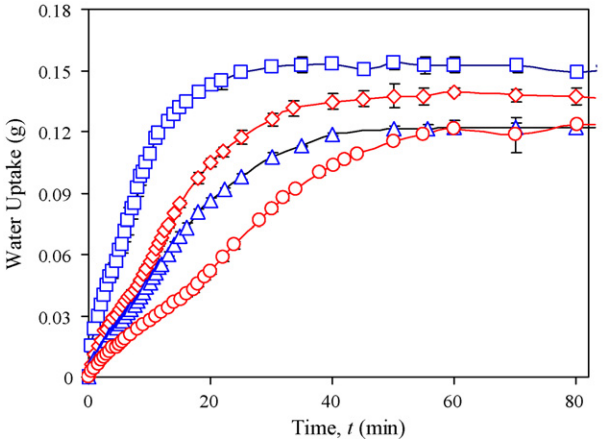

Fig. 4. Effect of exposure time on the kinetic swelling for a fixed 3.3 wt% GTA surface crosslinking solution: untreated (□), 1.1 s (◊), 10 s (Δ), 60 s (○). Error bars represent standard deviations for three experiments. Lines are guides for the eyes.

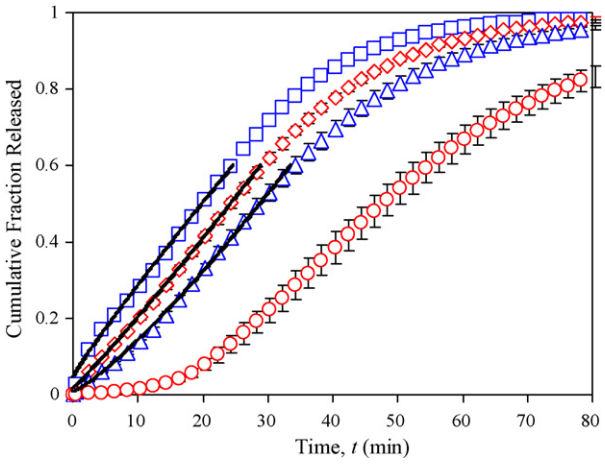

Fig. 5. Effect of surface crosslinking solution on proxyphylline release from PVA hydrogels (exposure time 1.1 s): untreated (□), 3.3 wt% GTA (◊), 5 wt% GTA (Δ), 10 wt% GTA (○). Error bars represent standard deviations for three experiments. Solid lines are the corresponding modeling fits using Eq. (1).

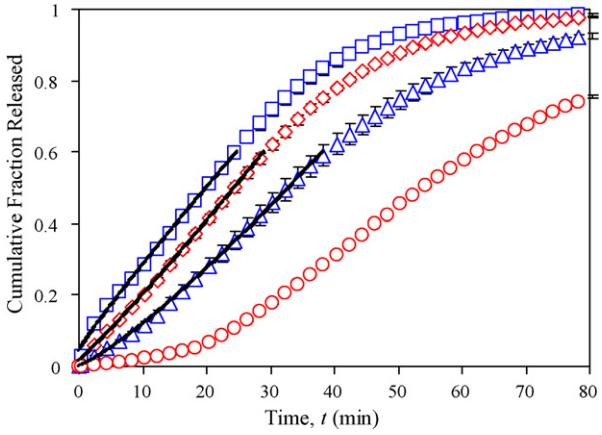

Fig. 6. Effect of exposure time on proxyphylline release from PVA hydrogels (3.3 wt% GTA solution): untreated (□), 1.1 s (◊), 10 s (Δ), 60 s (○).Error bars represent standard deviations for three experiments. Solid lines are the corresponding modeling fits using Eq. (1).

in most cases, the crosslinking density was homogeneous throughout the release device. Few investigations have been reported using spatial-variable crosslinking densities in a device for controlled drug release (Huang et al., 2002), although novel asymmetric PVA hydrogel membranes have been created for other purposes by varying the crosslinking density along the cross-section, thus varying mesh size (Dai and Barbari, 2000a,b).

In vitro release of proxyphylline was studied for untreated PVA hydrogels and PVA hydrogels receiving surface crosslinking under different GTA concentrations (Fig. 5) and exposure times (Fig. 6). The release of proxyphylline from untreated PVA hydrogels showed an initial burst in the early several minutes which comprised up to 15% of the total drug released as has been reported (Huang and Brazel, 2003), but was significantly reduced by immersing dry PVA hydrogels in 3.3 wt% GTA solution for only 1.1 s (Fig. 5). Recently, a modified power law equation has been proposed and used to account for the initial burst encountered in many controlled release systems (Huang and Brazel, 2001; Peppas and Simmons, 2004):

$$\frac{M_t}{M_\infty} = \alpha + kt^n \quad \text{for} \quad \frac{M_t}{M_\infty} < 0.6 \tag{1}$$

where M_t/M_∞ is the cumulative fraction of drug released at time t, α the initial burst factor, k the constant incorporating characteristics of the macromolecular network/drug system and the release medium, and n is a value indicative the drug transport mechanism in the macromolecular network. Eq. (1) was used to fit the drug release data from untreated and lightly surface crosslinked PVA hydrogels here. The initial burst factor α decreased from 0.0441 for untreated PVA hydrogels to almost negligible for three lightly surface crosslinked PVA hydrogels (Table 2). In this case, surface extraction could not possibly account for this reduction as shown by Huang et al. (Huang et al., 2002). Therefore, the surface crosslinked layers, which hindered the diffusion of proxyphylline within the hydrogels as evidenced by the decrease in k values, were largely responsible for reducing the burst effect. Surface crosslinking also modified the drug release mechanism from anomalous to Case II transport and even Super Case II transport (Table 2). Therefore, by carefully choosing the surface crosslinking conditions, zero-order release with significantly reduced burst effect could be achieved.

For highly surface crosslinked PVA samples (i.e., in 10 wt% GTA crosslinking solution for 1 s or in 3.3 wt% GTA crosslinking solution for 60 s), the release of proxyphylline was significantly reduced in the first 16–18 min, during which less than 8 wt% of drug was released into the DI water. However, the release rate significantly increased after the first 16–18 min, following a zero-order release pattern. Therefore, the first 16–18 min can be viewed as a lag phase due to the fact that a small fraction of drug was released during this period. It must be noted that the later zero-order release should be attributed to the ruptures, which progressed during the swelling process for these highly surface crosslinked hydrogels, instead of a Super Case II transport mechanism for drug transport within the hydrogels.

Table 2
Fitting release data for untreated and lightly surface crosslinked PVA hydrogels to Eq. (1) (The 95% confidence limits are provided here)

Sample (surface crosslinking conditions)		$\alpha \times 10^2$	$k \times 10^2$ (min^{-n})	n	R^2
GTA, (wt%)	exposure time (s)				
N/A	N/A	4.41 ± 0.01	2.84 ± 0.01	0.926 ± 0.001	.996
3.3	1.1	1.60 ± 0.12	1.54 ± 0.02	1.079 ± 0.004	.999
3.3	10	0.17 ± 0.38	0.72 ± 0.02	1.215 ± 0.006	.999
5.0	1.1	0.61 ± 0.12	0.81 ± 0.01	1.222 ± 0.002	.999

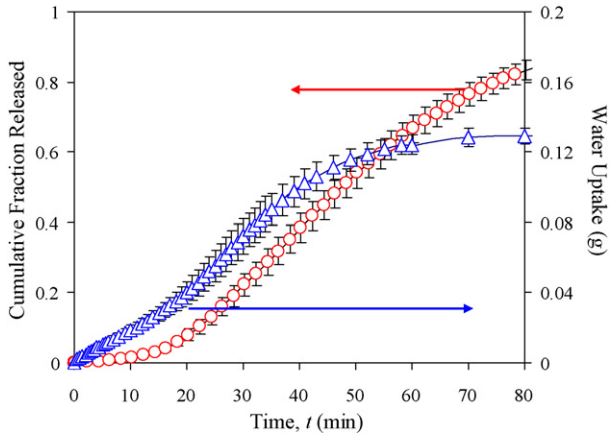

Fig. 7. Delayed release of proxyphylline from highly surface crosslinked PVA hydrogels (10 wt% GTA solution for 1.1 s). Error bars represent standard deviations for three experiments. Lines are guides for the eyes.

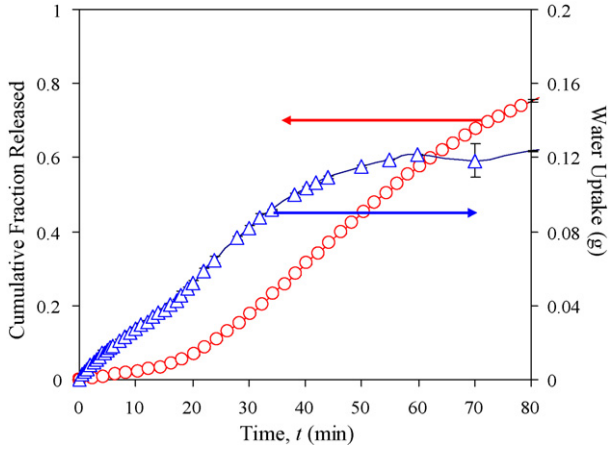

Fig. 8. Delayed release of proxyphylline from highly surface crosslinked PVA hydrogels (3.3 wt% GTA solution for 60 s). Error bars represent standard deviations for three experiments. Lines are guides for the eyes.

The connection between drug release and swelling is addressed in Figs. 7 and 8 for these highly surface crosslinked PVA samples. The isotropic expansion in the second swelling phase led to ruptures (Fig. 2c), which penetrated through the surface crosslinked layers, thus leaving less hindrance to drug release and water uptake, which was clearly evidenced in Figs. 7 and 8 that a significantly increase in drug release rate was immediately following the increase in the rate of water uptake, if not at the same time. As a result, fast release of proxyphylline from these PVA samples and fast water uptake occurred in the second swelling phase, while much slower drug release and water uptake happened in the first swelling phase due to the highly surface crosslinked layers.

4. Conclusion

A surface crosslinking technique was used on PVA hydrogels to adjust the proxyphylline release profiles by varying the exposure time and crosslinker concentration. The successful introduction of those surface crosslinked layers was confirmed by CLSM. The significant initial burst release of proxyphylline observed for untreated PVA hydrogels with a burst factor of 4.41% was almost entirely eliminated from the release profile by slightly surface crosslinking the PVA hydrogels in GTA solution. A delay of about 18 min (less than 8 wt% of drug released in this period) was obtained for those highly surface crosslinked PVA hydrogels. The procedure developed has provided a relatively simple, potentially inexpensive method to reproducibly modify the release behavior to reduce the burst effect or introduce a lag time. Although it may be difficult to significantly increase the lag time to several hours for PVA hydrogels, this technique should be useful to achieve variable lag times for other hydrogels systems such as poly(2-hydroxyethyl methacrylate).

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