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Surface crosslinking for delayed release of proxyphylline from PHEMA hydrogels

Linfeng Wu, Christopher S. Brazel *

Department of Chemical and Biological Engineering, Box 870203, 201 7th Avenue, The University of Alabama, Tuscaloosa, AL 35487, USA

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Abstract

Delayed release systems find applications in chronotherapeutics and colon-specific delivery. They have also been considered suitable carriers for the oral delivery of peptides and proteins. In prior work, our research group has reported surface crosslinking as an effective technique to modify drug release profiles for poly(vinyl alcohol) (PVA) hydrogels, reducing the early burst effect in particular. Here, we demonstrate the feasibility of delayed release of proxyphylline from poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels via surface crosslinking. Studies on *in vitro* drug release and the morphology changes of PHEMA hydrogels during swelling and drug release showed that the highly surface crosslinked layers and the ruptures occurring in these layers during swelling were likely responsible for the delayed release. In addition, the initial burst was significantly reduced or even eliminated from the drug release profile for PHEMA to achieve near zero-order release by judicious selection of two surface crosslinking parameters: crosslinking reagent concentration and exposure time used for the surface crosslinking treatment.

Keywords: PHEMA hydrogels; Delayed release; Initial burst; Rupture; Surface crosslinking; Lag time

1. Introduction

Great efforts have been made to develop new systems and devices that can release drugs after a predetermined off-release period after administration (Alvarez-fuentes et al., 2004; Cao et al., 2004; Dorkoosh et al., 2001; Franssen et al., 1997; Göpferich, 1997; Kikuchi and Okano, 2002; Kuzuya et al., 2001; Lin et al., 2001, 2004; Narisawa et al., 1995, 1996; Stubbe et al., 2004; Sungthongjeen et al., 2004; Takeuchi et al., 2000). This delayed release has been considered a suitable strategy for the oral delivery of proteins and peptides (Dorkoosh et al., 2001), in addition to the applications in chronotherapeutics and colon-specific delivery (Alvarez-fuentes et al., 2004; Patel et al., 2006; Washington and Wilson, 2006). In the past few decades, many delayed release devices have been designed and used for the delivery of various therapeutic drugs. These devices are based on the principle of barrier-destruction (Lin et al., 2001, 2004; Sungthongjeen et al., 2004), barrier-ejection (Dorkoosh et al., 2001), or barrier-dissolution/erosion (Cao et al., 2004; Franssen et al., 1997; Göpferich, 1997; Kuzuya et al., 2001). The barrier is usually permeable to water, but is impermeable to the drug loaded. Therefore, after the device is administered, water contacts or penetrates into the device, resulting in destruction, ejection, erosion or dissolution of the barrier in the initial period. The loaded drug is released into the surrounding fluid after this barrier is almost completely destroyed, ejected or dissolved/eroded. The off-release period, commonly referred to as the lag time, can be adjusted by varying the barrier thickness, and the composition of the barrier and core in the device. For example, Egalet® (Egalet a/s Denmark) has developed the 3K™ time-release system, which can release drug in a predetermined delayed burst (Washington and Wilson, 2006). The lag time is determined by the length and composition of two lag plugs, which are made from poly(ethylene glycol) monostearate and poly(ethylene oxide) that can be eroded in water. The TIME CLOCK® system proposed by Pozzi and coworkers (Pozzi et al., 1994) could also realize a fast and complete release of therapeutic compounds after a predetermined lag time. In this system, the drugs were loaded in a core tablet, which was coated with a hydrophobic dispersion of carnauba

* Corresponding author. Tel.: +1 205 348 9738; fax: +1 205 348 7558.
E-mail address: CBrazel@eng.ua.edu (C.S. Brazel).

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Table 1
Composition of monomer mixtures, crosslinking agent, initiators and drug loading

Hydrogel	HEMA/water ratio (v/v)	EGDMA (mol% of HEMA)	$Na_2S_2O_5/(NH_4)_2S_2O_8$ (wt% of HEMA)	Drug loading (wt% of HEMA)
PHEMA20	20/80	1.0	0.25/0.25	10.0
PHEMA30	30/70	1.0	0.25/0.25	10.0
PHEMA40	40/60	1.0	0.25/0.25	10.0

wax, bees' wax, poly(oxyethylene) sorbitan monooleate, and hydroxypropylmethyl cellulose in water. The coating thickness could be altered to provide a proportional lag time. However, each of these systems requires precise quality control and/or costly barrier materials. Therefore, a simple, reliable and inexpensive technique or process is always more desirable. Recently, several studies have shown the possibility of using surface crosslinking as a simple technique to achieve time-controlled release from either PVA hydrogels or Eudragit® acrylic polymer tablets (Huang et al., 2002; Kuzuya et al., 2001; Wu and Brazel, 2008). The surface crosslinked layers were introduced by immersing PVA hydrogels in a crosslinking solution or exposing Eudragit® tablets to argon plasma for a short time.

Hydrogels have been recognized as good carriers for the controlled release and delivery of therapeutic compounds because of their biocompatibility and structural similarity to natural tissues (Peppas et al., 2006). PHEMA, the first synthetic hydrogel, has found applications in the medical and pharmaceutical fields for decades. For example, PHEMA or PHEMA-based hydrogels are extensively used in the controlled release of therapeutic molecules, including proteins (Brazel and Peppas, 1999; Lu and Anseth, 1999; Zahedi and Lee, 2007).

In this work, we show the feasibility of delayed release from PHEMA hydrogels via surface crosslinking. Three adjustable processing parameters were investigated to modify the lag times: the surface crosslinking exposure time, the crosslinker concentration used for surface crosslinking solution, and the ratio of HEMA monomers to water used in the synthesis of PHEMA hydrogels. Proxyphylline, a highly hydrophilic low molecular weight drug, was chosen as the model drug (Wu and Brazel, 2008).

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) (≥98.5%) and ethylene glycol dimethacrylate (EGDMA) both purchased from Acros Organics (Fairlawn, NJ), were purified using Dehibit® columns (Aldrich, St. Louis, MO) to remove the inhibitor before use. Glutaraldehyde (GTA) (25 wt%) and sulfuric acid (95–98%) were obtained from Aldrich (Milwaukee, WI). Proxyphylline was obtained from Sigma (St. Louis, MO). Pro-Sil® was obtained from Stephenson Group Limited (U.K.). Ammonium peroxydisulfate (98+%) and sodium metabisulfite (97+%) were purchased from Sigma and used as redox initiators. All chemicals were used as received unless otherwise noted.

2.2. Synthesis of PHEMA hydrogels

Three series of drug-loaded PHEMA hydrogels were synthesized, varying in the HEMA/water ratio in the monomer mixtures summarized in Table 1. Typically, 10 ml of monomer mixture with proxyphylline and EGDMA were prepared according to Table 1 in a 25 ml beaker, which was then tightly covered with parafilm. Ultra high purity nitrogen was continuously bubbled through the stirred solution for 30 min to remove dissolved O_2. Then, 100 μl freshly prepared initiator solutions were added into the monomer mixture according to Table 1. The resulting solution was stirred and bubbled with N_2 for another 5 min. It was then transferred into a mold consisting of a Teflon® frame (1.58 mm thick) as the spacer and two glass plates previously treated with Pro-Sil solution to aid mold release. The mold was kept at 37 °C for 2 days. Disk-shaped samples were cut from the resulting hydrogel film using a 2.5 cm cork borer, and dried to constant weights in a desiccator under vacuum at room temperature. The thickness and diameter of the resulting dry PHEMA hydrogel samples varied depending on the composition of the HEMA/water monomer mixture used (Table 2). Larger shrinkage was observed for those synthesized using a lower HEMA/water ratio.

2.3. Surface crosslinking

Surface crosslinking was applied to dry PHEMA hydrogel samples. Six surface crosslinking solutions (40 g) containing 0, 1, 2, 3, 4 or 5 wt% GTA were prepared in beakers by mixing de-ionized (DI) water, GTA solution (25 wt%), and sulfuric acid solution (10 vol%) in beakers. For each crosslinking solution, GTA solution (25 wt%), and sulfuric acid solution (10 vol%) were added in equal volumes. After the beaker was heated in a 37 °C water bath for 5 min, dry PHEMA hydrogel samples were completely immersed into the surface crosslinking solution for a short time: 10, 30 or 60 s. The solution adsorbed on the sample surface was then blotted off. The resulting sample was allowed to react as it was and dried to constant weight in a desiccator without vacuum. Sample codes for various surface crosslinked

Table 2
Dimensions of the dry PHEMA hydrogels (average and standard deviation for six samples)

Hydrogel	Diameter (cm)	Thickness (cm)	Volume (cm^3)
PHEMA20	1.960 ± 0.043	0.077 ± 0.005	0.233 ± 0.025
PHEMA30	2.115 ± 0.066	0.087 ± 0.003	0.305 ± 0.013
PHEMA40	2.278 ± 0.024	0.102 ± 0.003	0.417 ± 0.004

Table 3
Codes for surface crosslinked PHEMA hydrogels

Sample code	Hydrogel used	GTA concentration	Exposure time (s)
SPC20-N	PHEMA20	N/A (untreated)	N/A
SPC20-0G-10	PHEMA20	0 wt% (surface extracted)	10 s
SPC20-2G-10	PHEMA20	2 wt%	10 s
SPC30-N	PHEMA30	N/A (untreated)	N/A
SPC30-3G-10	PHEMA30	3 wt%	10 s
SPC30-4G-10	PHEMA30	4 wt%	10 s
SPC30-5G-10	PHEMA30	5 wt%	10 s
SPC30-4G-30	PHEMA30	4 wt%	30 s
SPC30-4G-60	PHEMA30	4 wt%	60 s
SPC40-N	PHEMA40	N/A (untreated)	N/A
SPC40-2G-10	PHEMA40	2 wt%	10 s
SPC40-3G-10	PHEMA40	3 wt%	10 s
SPC40-4G-10	PHEMA40	4 wt%	10 s
SPC40-5G-10	PHEMA40	5 wt%	10 s
SPC40-4G-60	PHEMA40	4 wt%	60 s

hydrogels synthesized and used in this work are summarized in Table 3.

2.4. 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) as described before (Huang et al., 2002). The release medium, 37 ± 0.3 °C DI water, was continuously circulated (18.5–19.5 ml/min) through a flow-through quartz cuvette (0.750 ml) located in the UV/vis spectrophotometer via tubing (internal diameter 2.4 mm) and a Fisherbrand variable-flow peristaltic pump. To begin the experiment, a drug-loaded PHEMA hydrogel sample was dropped into a dissolution cell containing 950 ml of release medium, which was stirred at 150 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 to account for the sampling lag time, 15 s, which was determined from the sampling flow rate and the dead volume of the sampling tubing (Pliquett et al., 1995; Wu and Brazel, 2008).

2.5. Equilibrium swelling

Since the high drug loading might complicate effects to measure the equilibrium swelling ratio, these measurements in this work were taken after the *in vitro* release experiments. Briefly, after the *in vitro* drug release experiments, each PHEMA hydrogel sample was transferred into a jar containing 100 ml DI water and kept at 37 °C. One week later, the sample was taken out and weighed using an electric balance after the water adsorbed on the surfaces was blotted off. The sample was then put back into the jar. A second measurement of the sample weight, $M_{swollen}$, was performed after another week. In every case, the difference between these two measurements was less than 1%. The swollen hydrogel sample was then re-dried under vacuum to a constant weight and weighed again. Typically, this weight, M_{dry}, is consistent with the calculated PHEMA polymer weight in the dry sample before the *in vitro* release experiment. The equilibrium swelling ratio, q, was calculated using the following equation:

$$q = \frac{M_{swollen}}{M_{dry}}. \quad (1)$$

2.6. Optical microscopy

The morphology of untreated and surface crosslinked PHEMA40 hydrogels was observed before the *in vitro* release experiments and after the swelling experiments using an optical microscope at a 4× magnification and recorded using a charge-coupled device (CCD) camera. In particular, the morphology changes of SPC40-4G-10 samples were also monitored during the swelling and drug release process. In this case, the SPC40-4G-10 samples were dropped into dissolution cells under the same conditions used for *in vitro* release. At preset time points, one hydrogel was taken out and immediately observed using an optical microscope at a 4× magnification.

3. Results and discussion

3.1. Equilibrium swelling ratios

For hydrogels, the equilibrium swelling ratio is not only strongly related to the mechanical strength of the hydrogels, but also related to the rates of water uptake and drug release (Amidon et al., 2000). Typically, this equilibrium swelling ratio is affected by the hydrophilicity of the polymer and the degree of crosslinking in the hydrogel and is measured to better understand the drug release behaviors.

Equilibrium swelling ratios, q, in water at 37 °C were determined gravimetrically for all untreated PHEMA hydrogel samples and those receiving surface crosslinking treatments. For untreated PHEMA samples, the equilibrium swelling ratio decreased from 4.24 ± 0.05 for SPC20-N, to 2.59 ± 0.04 for SPC30-N and 1.86 ± 0.01 for SPC40-N as the HEMA/water ratio increased in the HEMA monomer mixture used for the synthesis of PHEMA hydrogels (Fig. 1). The significant difference in the equilibrium swelling ratios among these three untreated hydrogels is due to the different microstructures which formed during the polymerization (Peppas et al., 1985). It has been reported that the pore or mesh sizes of the resulting PHEMA hydrogels increased with the increase in the water content in the HEMA monomer mixture (Chirila et al., 1993; Peppas et al., 1985). Generally, macroporous and heterogeneous PHEMA hydrogels were formed through phase separation during the polymerization when the water content in the HEMA monomer mixtures was higher than 60 wt% (Peppas et al., 1985) or 43 wt% (Gouda et al., 1970). It has been reported that when ethylene glycol dimethacrylate (2 wt% of HEMA monomers) was used as the crosslinking agent PHEMA hydrogels synthesized from HEMA monomer solutions with a water content of 50 or 60 wt% behaved as homogeneous hydrogels, while those from HEMA monomer

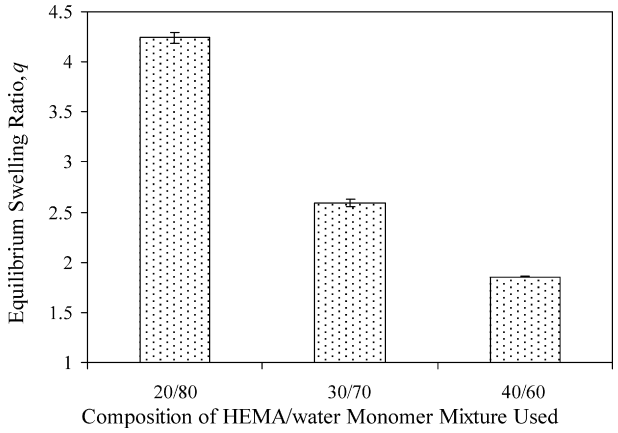

Fig. 1. Effect of HEMA/water ratio in the monomer mixtures on the equilibrium swelling ratios of untreated PHEMA hydrogels. Error bars represent the standard deviations for three samples.

solutions with a water content of 70, 80 or 90 wt% were macroporous and heterogeneous since cells and blood vessels could penetrate into these wet hydrogels (Šprincl et al., 1971). Furthermore, the microstructure of PHEMA hydrogels was also affected by the amounts of crosslinkers and initiators used (Chirila et al., 1993). A more porous or loosely crosslinked structure provides more spaces for water uptake, thus increasing the equilibrium swelling ratio. Therefore, our swelling results for untreated PHEMA hydrogel samples are consistent with the previous observations.

The GTA concentration and exposure time used for surface crosslinking had some effect on the equilibrium swelling behavior of PHEMA hydrogels (Figs. 2 and 3). It has been reported that the equilibrium swelling ratio decreased with the increase of the bulk crosslinking ratio (molar ratio of crosslinking agent to HEMA) for PHEMA hydrogels synthesized through bulk polymerization (Zahedi and Lee, 2007). It was observed in our equilibrium swelling experiments (Fig. 2) that within the investigated ranges increasing the GTA concentration used for the surface crosslinking had a significant impact on PHEMA20 hydrogels, while this was less prominent for the cases of PHEMA30 and PHEMA40. This result is largely due to the formation of new interpolymer crosslinks that were not as prevalent in PHEMA20 hydrogels during their synthesis. An increase in the exposure time to surface crosslinking solution also reduced the equilibrium swelling ratio for PHEMA30 (Fig. 3), although the decrease was nearly insignificant. There are two major contributions to the observed decrease in the equilibrium swelling ratio. First, the surface crosslinked layer had a lower equilibrium swelling ratio than the core layer due to its high crosslinking densities; second, the surface crosslinked layers might create constriction boundaries around the core layer during swelling, thus preventing full relaxation/recovery in the unmodified core region and reducing the water uptake. However, as mentioned earlier the effect of GTA concentration used for surface crosslinking on the equilibrium swelling ratios was more significant for the case of PHEMA20 (Fig. 2). We believe that the porous or loosely crosslinked structures in the freshly synthesized PHEMA20

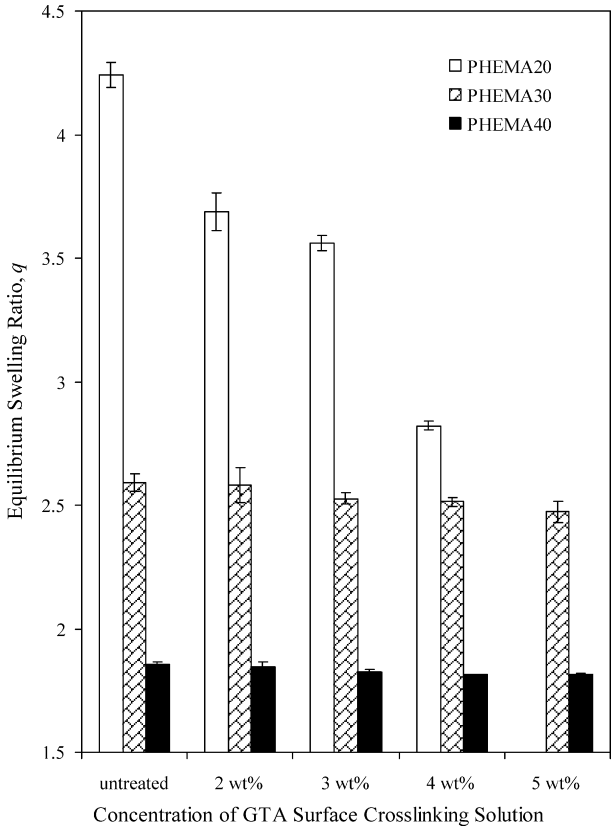

Fig. 2. Effect of surface crosslinking on the equilibrium swelling ratios of PHEMA hydrogels (exposure time 10 s). Error bars represent the standard deviations for three samples.

hydrogels were more prone to collapse during the drying process. Therefore, after chemical crosslinks formed within the collapsed pores near the surfaces during the surface crosslinking, the effect of these chemical crosslinks to prevent the recovery of spaces lost during the drying process after synthesis was more significant when the hydrogel was re-swollen since more spaces were lost for PHEMA20 during the drying process.

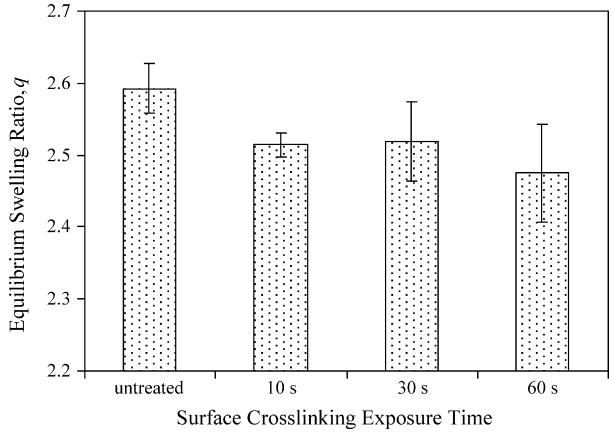

Fig. 3. Effect of surface crosslinking on the equilibrium swelling ratios of PHEMA30 hydrogels (4 wt% GTA crosslinking solution used). Error bars represent the standard deviations for three samples.

3.2. Morphology of PHEMA hydrogels

The morphology of PHEMA hydrogels may change significantly during the swelling and drug release process. No ruptures were observed on any dry PHEMA40 hydrogels under an optical microscope at a 4× magnification before *in vitro* release experiments, whether they received surface crosslinking treatment or not. The surfaces of these hydrogels were not perfect with pits occasionally seen on the surfaces. However, ruptures were observed on both surfaces of the highly surface crosslinked PHEMA40 hydrogels, namely SPC40-3G-10, SPC40-4G-10 and SPC40-5G-10, after the swelling experiments, although no significant morphology change was observed for the SPC40-N and SPC40-2G-10 samples (Fig. 4). The width of the ruptures was found to depend on the surface crosslinking treatment, with the widest stress ruptures occurring in the most highly surface crosslinked samples (i.e., 5 wt% GTA solution for 10 s).

SPC40-4G-10 samples were chosen to investigate the progress of ruptures occurring during the swelling and drug release process. No ruptures were observed on both surfaces during the first 60 min of swelling and drug release (Fig. 5). The first column in Fig. 5 clearly shows ruptures appeared on the surface near the edge at about 70 min. The ruptures progressed towards to the centers of the disc's surfaces as shown in Figs. 5d, f and h. No ruptures were observed near the centers of both surfaces at 80 min, while they were seen at 90 min.

3.3. In vitro drug release

The release of proxyphylline from untreated PHEMA hydrogels was found to be a function of HEMA/water ratio in the monomer mixture used for hydrogel synthesis (Fig. 6). The release profiles from SPC20-N and SPC30-N samples showed two release stages (which is similar to a Super Case II transport mechanism), divided by an inflection point in the release curves, while the release from SPC40-N exhibited one release phase. Less than 30% of the initial proxyphylline loaded was released in the first stage for SPC20-N and SPC30-N. Similar sigmoidal

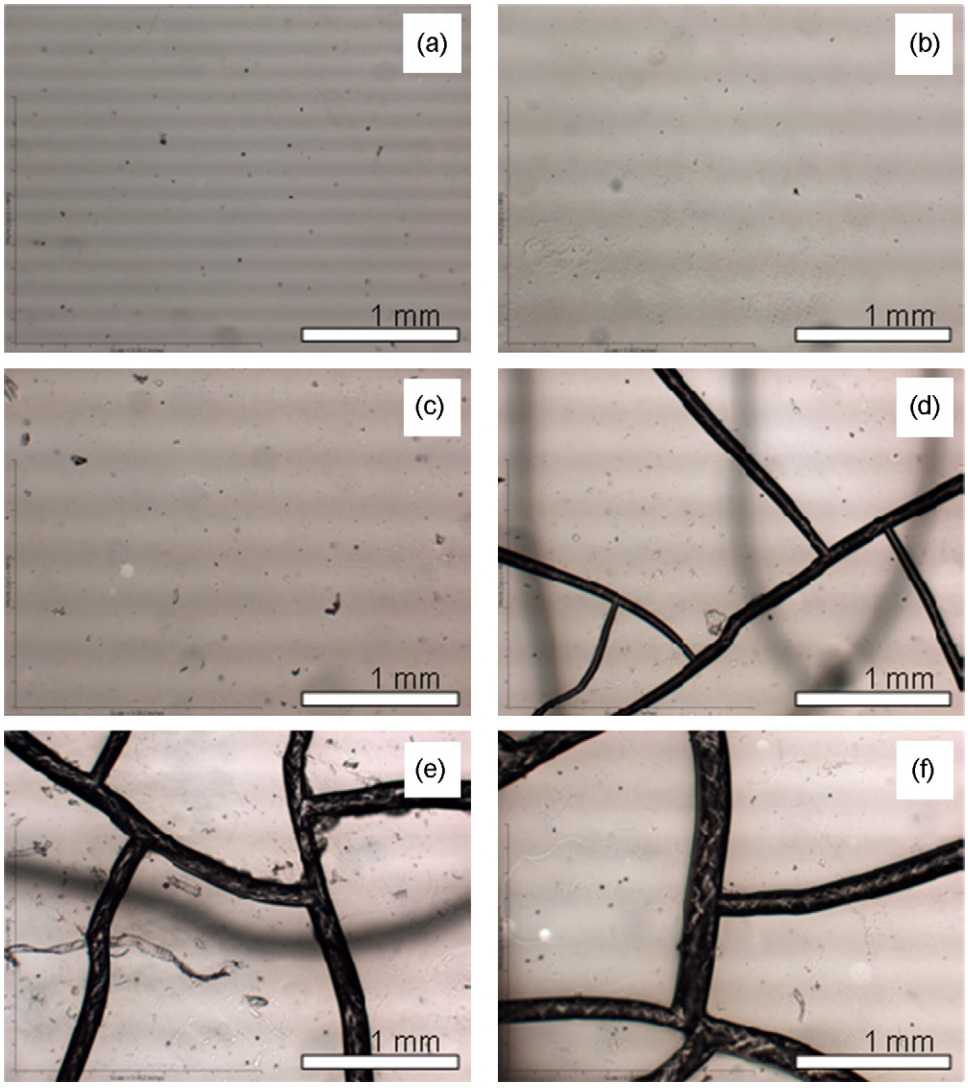

Fig. 4. Optical images of fully hydrated PHEMA40 hydrogels (surface crosslinking exposure time 10 s): (a) untreated; (b) 1 wt% GTA solution; (c) 2 wt% GTA solution; (d) 3 wt% GTA solution; (e) 4 wt% GTA solution; (f) 5 wt% GTA solution.

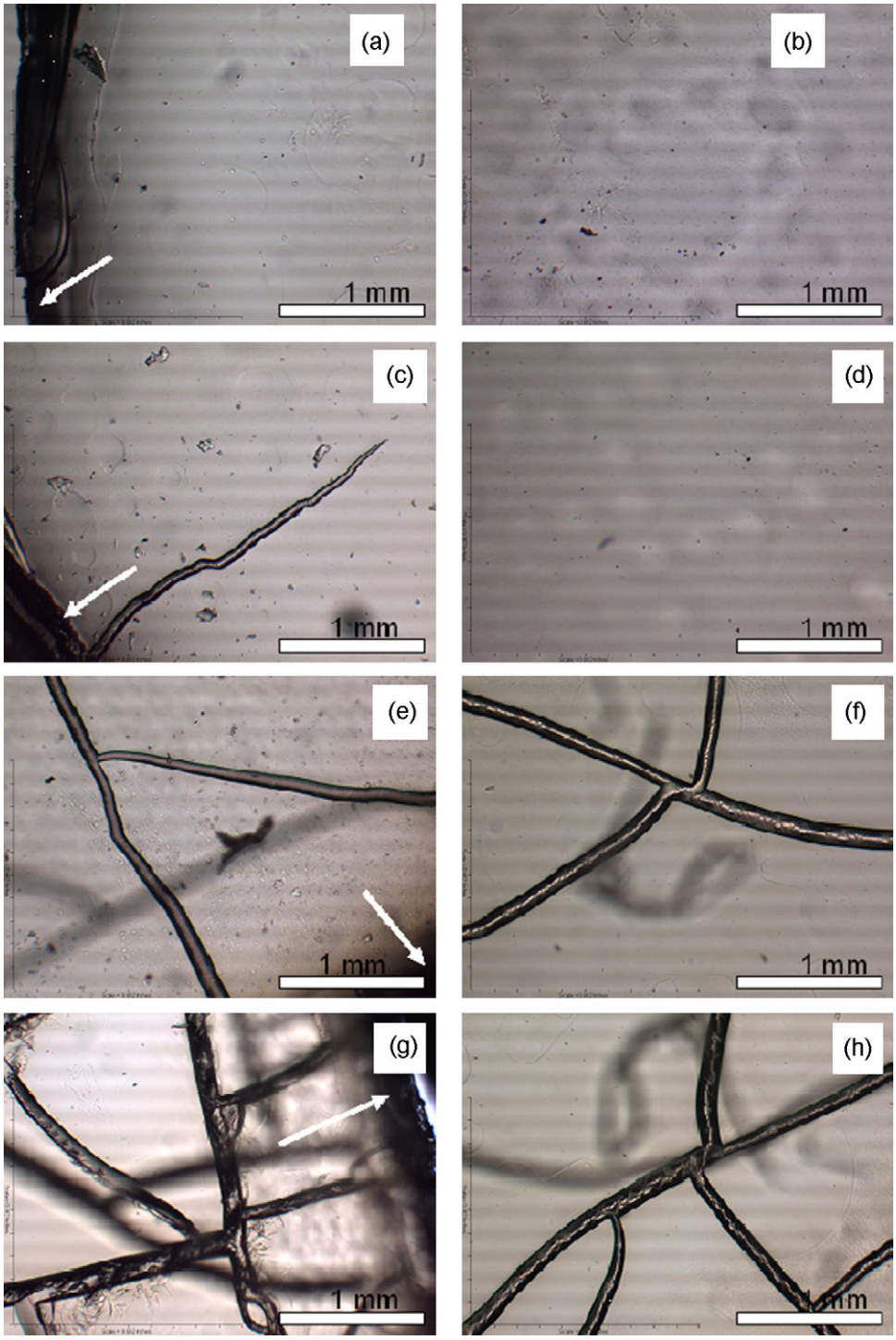

Fig. 5. Optical images of SPC40-4G-10 sample during swelling and drug release (first column shows the surfaces near the sample edge, the second column shows the surfaces near the center): (a) and (b) 70 min; (c) and (d) 80 min; (e) and (f) 90 min; (g) and (h) 25.5 h. The arrows in the images are pointing to the edges of the surfaces.

release profiles have been observed on some controlled release systems such as 43 and 50 μm poly(D,L-lactide-co-glycolide) microspheres (Berkland et al., 2004; Raman et al., 2005). In these studies, the authors attributed the accelerated drug release in the later course to polymer degradation and erosion, which improved drug diffusivity within the dense polymer matrix and might also cause formation of pores in the matrix resulting in higher effective diffusivities. Since PHEMA hydrogels have no ability to degrade or be eroded in water, we hypothesize that the reopening of collapsed pores in SPC20-N and SPC30-N samples are responsible for the sigmoidal proxyphylline release profiles. It is reasonable to suspect that the reopening of collapsed pores was more frequently happening in the late time instead of the initial period (Brazel and Peppas, 1999). The lack of these collapsed

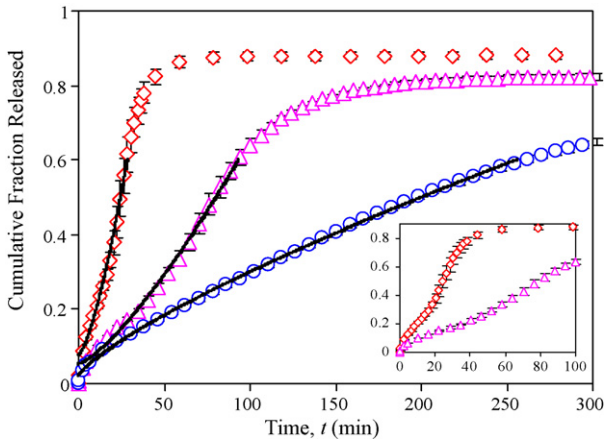

Fig. 6. Proxyphylline release from SPC20-N (◊), SPC30-N (△), and SPC40-N (◯). The inset shows release profiles for SPC20-N (◊) and SPC30-N (△) at short times. Error bars represent standard deviations for three experiments. Solid lines are the corresponding fits using Eq. (3).

Table 4
Fitting release data for untreated PHEMA hydrogels to Eq. (3) (the 95% confidence limits are provided here)

Sample	k ($\times 10^3$ min^{-n})	n	$\alpha \times 10^2$	R^2
SPC20-N	4.0 ± 0.9	1.45 ± 0.06	7.5 ± 0.7	0.988
SPC30-N	0.37 ± 0.04	1.30 ± 0.02	5.8 ± 0.7	0.992
SPC40-N	7.86 ± 0.06	0.776 ± 0.012	1.8 ± 0.4	0.999

Table 5
Fitting release data for PHEMA-20 hydrogels to Eq. (3) (the 95% confidence limits are provided here)

Sample	k ($\times 10^3$ min^{-n})	n	$\alpha \times 10^2$	R^2
SPC20-N	4.0 ± 0.9	1.45 ± 0.06	7.5 ± 0.7	0.988
SPC20-0G-10	8.5 ± 0.1	1.33 ± 0.01	5.2 ± 0.2	0.990
SPC20-2G-10	7.0 ± 0.1	0.96 ± 0.01	0 [a]	0.997

[a] α value for SPC20-2G-10 was found to be −0.01, or essentially 0 since a minus value for α in this case was meaningless.

macropores in SPC40-N samples or reopening of these collapsed pores, if any, should then be responsible for the one-stage proxyphylline release observed. However, an initial burst release was observed to varying extents in the proxyphylline release profiles for all of the untreated PHEMA hydrogels. Modeling studies can give insight into the fundamental processes governing drug release and provide useful guidance for the successful design of release devices. A simple and comprehensive semi-empirical model presented in Eq. (2) has been extensively used to investigate the mechanism of drug transport in swellable hydrogels (Peppas, 1985, 1986; Ritger and Peppas, 1987a,b),

$$\frac{M_t}{M_\infty} = kt^n \quad \text{for} \quad \frac{M_t}{M_\infty} < 0.6 \tag{2}$$

where M_t/M_∞ is the cumulative fraction of drug released at time t, k a 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. k values were used to calculate the drug diffusion coefficients in the hydrogels. Ritger and Peppas (1987a,b) have made the following summarizations for the transport mechanism in gels with a slab geometry (which includes disc-shaped sample as long as the aspect ratio is larger than 10): $n = 0.5$ for Fickian transport; $0.5 < n < 1.0$ for anomalous transport; $n = 1.0$ for Case II transport (zero-order); and $n > 1.0$ for Super-Case II transport.

Recently, much attention has been paid to the initial burst release that occurs in various carriers. To account for this initial burst release, a time-independent term, α, has been incorporated into Eq. (2) to allow the model to be used (Huang and Brazel, 2001; Peppas and Simmons, 2004; Wu and Brazel, 2008):

$$\frac{M_t}{M_\infty} = kt^n + \alpha \quad \text{for} \quad \frac{M_t}{M_\infty} < 0.6 \tag{3}$$

Eq. (3) was used in our work to fit the release data for untreated PHEMA hydrogels as shown in Fig. 6. The α values (Table 4) showed that SPC20-N samples had a much higher burst than SPC30-N and SPC40-N due to their more loosely crosslinked network structure evidenced by their high equilibrium swelling ratio. Drug transport in SPC20-N ($n = 1.45 \pm 0.06$) and SPC30-N ($n = 1.30 \pm 0.02$) showed Super-Case II release patterns, while anomalous drug transport was observed for SPC40-N ($n = 0.776 \pm 0.012$) (Peppas, 1985, 1986; Ritger and Peppas, 1987a,b).

The effectiveness of surface crosslinking to modify the proxyphylline release was investigated by comparing the cumulative release profiles of proxyphylline from SPC20-N, SPC20-0G-10 (surface extracted), and SPC20-2G-10 samples (Table 5 and Fig. 7). Surface extraction did not significantly change the pattern of proxyphylline release profiles although it slightly reduced the initial burst release. However, surface crosslinking PHEMA20 hydrogels in 2 wt% GTA crosslinking solution for 10 s not only reduced the initial burst release observed on SPC20-N samples, but also resulted in a release rate reduction in the second release stage observed on SPC20-N samples, so that a near zero-order release ($n = 0.96 \pm 0.01$) of proxyphylline was

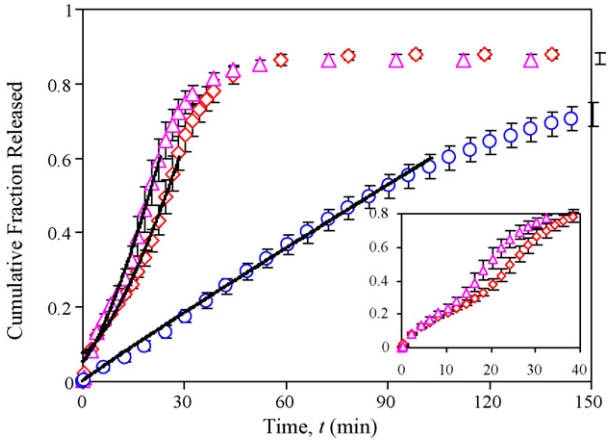

Fig. 7. Effect of surface extraction and surface crosslinking on the proxyphylline release from PHEMA20 hydrogels: SPC20-N (◊); SPC20-0G-10 (△); SPC20-2G-10 (◯). The inset shows the release profiles for SPC20-N (◊) and SPC20-0G-10 (△) at short times. Error bars represent standard deviations for three experiments. Eq. (3) (solid lines) was used to fit the experimental data for all samples except that $\alpha = 0$ was used for SPC20-2G-10.

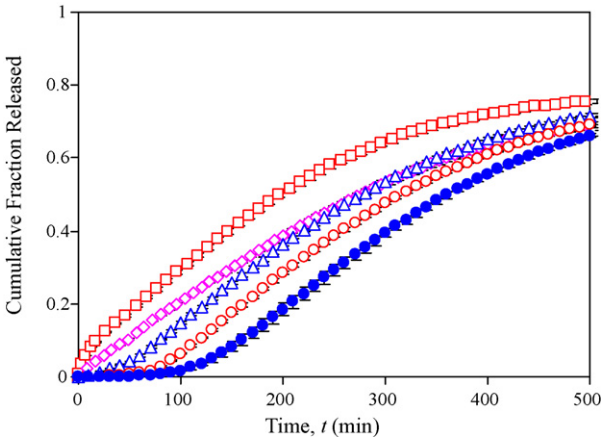

Fig. 8. Effect of surface crosslinker concentration on the proxyphylline release from PHEMA40 hydrogels: SPC40-N (□); SPC40-2G-10 (◊); SPC40-3G-10 (△); SPC40-4G-10 (◯); SPC40-5G-10 (●). Error bars (often smaller than the data symbols) represent standard deviations for three experiments.

observed from time zero to about 102 min. Surface crosslinking layers created in SPC20-2G-10 samples had more chemical crosslinks than the bulk core layers. These layers slowed the polymer chain relaxation during the swelling of the dense polymer matrix and the reopening of the collapsed pores, thus hindering water uptake and drug diffusion in the samples.

The proxyphylline diffusivity in the surface crosslinked layers was reduced to varying degrees, depending on the GTA concentration used for surface crosslinking (Fig. 8). The initial burst release of proxyphylline diminished when surface crosslinking PHEMA40 hydrogels in as little as 2 wt% GTA crosslinking solution for 10 s. For highly surface crosslinked PHEMA40 hydrogels (≥3 wt% GTA for 10 s), the diffusion of drug out of the samples was almost completely hindered by the surface crosslinked layers and little drug, if any, was released in the early time, thus creating a lag phase. After this period, the proxyphylline release rate significantly increased, with release rates comparable to that for SPC40-N (untreated PHEMA40 hydrogels). This drug release rate increase was simultaneous to the surface ruptures occurring from the end of the lag time (Figs. 4 and 5), which were caused by the swelling stresses built up in hydrogels because of the unmatched swelling capacities of the surface crosslinked and the core layers. After ruptures began to appear on the surfaces, proxyphylline imbedded in the core layer could be released into the release medium by bypassing the highly surface crosslinked layers, which almost completely hindered the transport of proxyphylline through them. Because proxyphylline is a small hydrophilic molecule, the ability to create a lag time makes this simple technique potentially useful for tailoring the release of numerous drugs.

Lag time is an important parameter in the design and evaluation of delayed release systems. In a recent study for release of buflomedil HCl, Sungthongjeen et al. (2004) determined lag times by visually examining when the outer coatings began to rupture in a dissolution apparatus. Strübing et al. (2007) calculated the lag time by extrapolating the linear part of release profile to the abscissa. A lag time, t_{lag}, has been cooperated into Eq. (2) to model the delayed release (Ford et al., 1991; Kim and

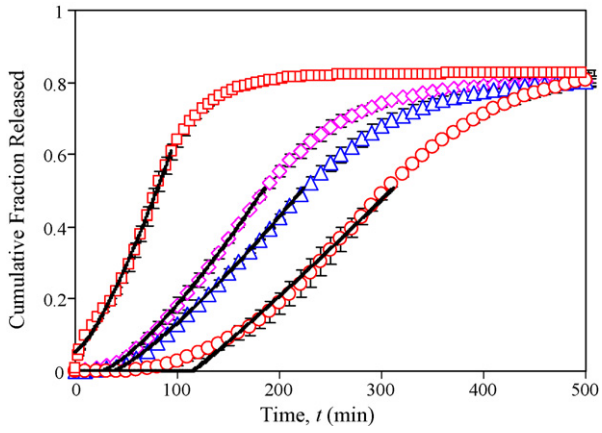

Fig. 9. Effect of surface crosslinker concentration on the delayed release of proxyphylline from highly surface crosslinked PHEMA30 hydrogels (exposure time 10 s): untreated (□); 3 wt% GTA (◊); 4 wt% GTA (△); and 5 wt% GTA (◯). Error bars represent standard deviations for three experiments. Solid lines are the corresponding modeling fits using Eq. (4) (Eq. (3) was used for untreated samples).

Fassihi, 1997), yielding:

$$\frac{M_t}{M_\infty} = k(t - t_{lag})^n \quad \text{for } t > t_{lag} \quad \text{and} \quad \frac{M_t}{M_\infty} < 0.50 \qquad (4)$$

By fitting the release data to Eq. (4), the lag time can be determined in addition to k and n.

Eq. (4) was used to fit the experimental release data for SPC30-3G-10, SPC30-4G-10, SPC30-5G-10 (Fig. 9), SPC40-3G-10, SPC40-4G-10, SPC40-5G-10 (Fig. 10), SPC30-4G-30, SPC30-4G-60 (Fig. 11) and SPC40-4G-60 samples. The lag times, t_{lag}, exponent terms, n, and k were determined by regression (Table 6). It must be noted here that the parameters k and n in Eq. (4) should have different meanings from those in Eqs. (2) and (3), since the proxyphylline release from these highly surface crosslinked PHEMA hydrogels was directly related to the rupture progress on the surfaces. Therefore, the relationship

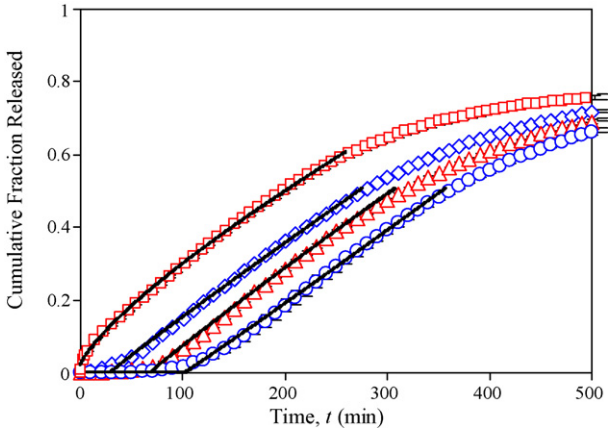

Fig. 10. Effect of surface crosslinker concentration on the delayed release of proxyphylline from highly surface crosslinked PHEMA40 hydrogels (exposure time 10 s): untreated (□); 3 wt% GTA (◊); 4 wt% GTA (△); and 5 wt% GTA (◯). Error bars represent standard deviations for three experiments where not shown error bars are smaller than the data symbols. Solid lines are the corresponding modeling fits using Eq. (4) (Eq. (3) was used for untreated samples).

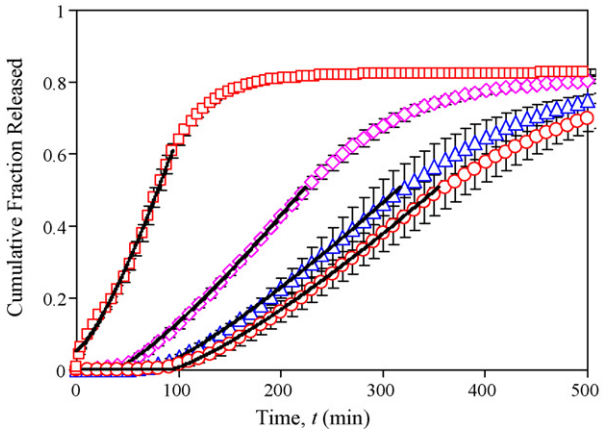

Fig. 11. Effect of surface crosslinking exposure time on the delayed release of proxyphylline from highly surface crosslinked PHEMA30 hydrogels (GTA concentration 4 wt%): untreated (□); 10 s (◊); 30 s (△); 60 s (◯). Error bars represent standard deviations for three experiments. Solid lines are the corresponding modeling fits using Eq. (4) (Eq. (3) was used for untreated PHEMA30).

between the k values in Table 6 and the proxyphylline molecular diffusion within hydrogels is more complicated and these k values cannot be directly used to calculate the drug diffusion coefficient in the hydrogels. However, evaluating the n values does give some guidance to achieve zero-order release or other release patterns after the lag time.

Surface crosslinked layers created using a higher GTA concentration solution led to a greater hindrance to water uptake by the hydrogels. Because water uptake is connected to drug release in swellable hydrogels, proxyphylline released from surface crosslinked hydrogels (Figs. 9 and 10) followed the trend of increased lag time with an increase in GTA concentration used for surface crosslinking. The lag time determined using Eq. (4) is 69.4 ± 2.4 min for SPC40-4G-10 samples, which is consistent with the observation in Fig. 5 that ruptures appeared on surfaces near the edge before 70 min. Within the investigated range, a lag time as high as 102.3 min has been obtained for SPC40-5G-10 samples, while a lag time of only 28.4 ± 0.3 min was obtained for SPC30-3G-10 samples. Super-Case II release profiles were observed for highly surface crosslinked PHEMA30 hydrogels (Fig. 9) although the proxyphylline release was attributed to the ruptures occurring on the surfaces after the lag time, while the PHEMA40 hydrogels which shared anomalous transport with no surface crosslinking have near zero-order release profiles with each of the surface crosslinking treatments ($0.95 < n < 1.03$) (Fig. 10).

The effect of surface crosslinking exposure time on the delayed release was investigated using PHEMA30 (Fig. 11) and PHEMA40 hydrogels surface crosslinked in a 4 wt% GTA solution for various times (Table 6). Again, the surface crosslinking exposure time had a significant influence on the lag time built into these highly surface crosslinked PHEMA30 and PHEMA40 hydrogels. A longer exposure time created surface layers with higher crosslinking densities and a larger thickness, thus reducing the ability of chains to relax in the network. Therefore, the diffusivity in these layers decreased and the ability of these hydrogels to resist the rupture stress increased, causing an increase in the lag time for drug release, from 38.3 ± 1.1 min for SPC30-4G-10 to 93.3 ± 0.8 min for SPC30-4G-60 and from 69.4 ± 2.4 min for SPC40-4G-10 to 115.7 ± 0.1 min for SPC40-4G-60. However, increasing the exposure time within the investigated range did not significantly change the pseudo drug transport mechanisms in the hydrogels (Table 6).

Table 6
Fitting release data for highly surface crosslinked PHEMA hydrogels to Eq. (4) (the 95% confidence limits are provided here)

Sample	k ($\times 10^3$ min^{-n})	n	t_{lag} (min)	R^2
SPC30-3G-10	0.74 ± 0.01	1.29 ± 0.01	28.4 ± 0.3	0.999
SPC30-4G-10	0.82 ± 0.01	1.23 ± 0.02	38.3 ± 1.1	0.999
SPC30-5G-10	3.54 ± 0.01	1.74 ± 0.01	60.4 ± 1.6	0.999
SPC30-4G-30	0.66 ± 0.01	1.21 ± 0.02	75.6 ± 1.8	0.999
SPC30-4G-60	0.48 ± 0.01	1.25 ± 0.01	93.3 ± ± 0.8	0.999
SPC40-3G-10	2.56 ± 0.01	0.96 ± 0.01	29.9 ± 0.1	0.998
SPC40-4G-10	2.79 ± 0.20	0.95 ± 0.01	69.4 ± 2.4	0.998
SPC40-5G-10	1.68 ± 0.01	1.03 ± 0.01	102.3 ± 1.1	0.998
SPC40-4G-60	0.94 ± 0.01	1.09 ± 0.01	115.7 ± 0.1	0.998

4. Conclusion

Proxyphylline release from PHEMA hydrogels was found to depend on the HEMA/water ratio used in the polymerization, with an initial burst up to 7.5% of proxyphylline loaded. Using the relatively simple process of surface crosslinking, the release profiles were altered to eliminate the burst effect or instill delayed release profiles, depending on the conditions selected for the surface treatment. Importantly, the surface crosslinking method allowed reproducible results. The lag times were adjusted by varying the exposure time and the GTA concentration used for surface crosslinking. A morphology study of various PHEMA40 hydrogels during swelling and drug release confirmed that the ruptures occurring during the swelling were largely responsible for the drug release after the lag time and the highly surface crosslinked layers inhibited the initial drug diffusion in these surface crosslinked layers. The technique investigated here offers a relatively simple method to reproducibly alter drug release profiles in hydrogel systems, while requiring only minimal treatment compared to coating methods.

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