Preparation A Novel pH-Sensitive Blend Hydrogel Based on Polyaspartic Acid and Ethylcellulose for Controlled Release of Naproxen Sodium

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Received 2 August 2008; accepted 29 October 2008
DOI 10.1002/app.29647
Published online 19 March 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Hydrogels based on pH-sensitive polymers are of great interest as potential biomaterials for the controlled delivery of drug molecules. In this study, a novel, pH-sensitive hydrogel was synthesized by poly(aspartic acid) (PASP) crosslinked with 1,6-hexanediamine and reinforced with ethylcellulose (EC). The loading and release characteristics of naproxen sodium (NS) were studied. The PASP–EC blend hydrogels had pH-sensitive characteristics and were strongly dependent on the pH value. The release kinetics for NS from the PASP–EC blend hydrogels and PASP hydrogel were evaluated in simulated gastric fluid (pH = 1.05) and simulated intestinal fluid (pH = 6.8) at 37°C. The results showed that the drug-loaded hydrogels were resistant to simulated gastric fluid, and hence, they could be useful for oral drug delivery. Compared with the PASP hydrogel, the PASP–EC blend hydrogels showed a lower release rate of NS in the same pH conditions. It was evident that the presence of hydrophobic groups (EC) retarded the release of NS and led to sustained release. The kinetics of NS release from the drug-loaded hydrogels conformed to the Korsmeyer–Peppas model. The release exponent of the model was 0.7291, which indicated multiple drug release. The PASP–EC blend hydrogels were biodegradable and pH sensitive; there would be a wide range of applications for them in controlled drug-delivery systems. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 113: 327–336, 2009

Key words: hydrogels; polyaspartic acid; drug delivery systems

INTRODUCTION

Hydrogels are three-dimensional, crosslinked polymers that can retain at least 20% of their own weight in water. They can swell greatly by absorbing water and shrink after deswelling. The swelling capability depends on the characteristics of the polymer and its crosslinking density. For more than 2 decades, considerable attention has been paid to environmentally sensitive, or so-called smart hydrogels. These hydrogels can undergo a reversible and yet discontinuous volume change in response to environmental stimuli, such as changes in pH,[1,2] temperature,[3–5] ionic strength,[6,7] and electric field.[8,9] These smart gels have potential applications in biomedical and pharmaceutical fields. Their capacity to entrap drugs and, successively, to release them in an aqueous medium and the possibility to regulate such release by controlling their swelling in physiological fluids make hydrogels excellent candidates for the controlled release of pharmaceuticals. Numerous drug-loaded hydrogels have been synthesized and investigated. For example, hydrogels composed of acrylamide and methylene bisacrylamide,[10] dextrans grafted with methacrylates,[11] PEG dimethacrylates,[12] and poly(*N*-isopropylacrylamide)[13] have been synthesized and used to encapsulate drugs. However, those hydrogels have the disadvantage of *in vivo* biocompatibility and a low degradation rate.

Poly(aspartic acid) (PASP) hydrogels would seem to have significant advantages over other polymers because of their proteinlike structure. In previous articles,[7] we reported the preparation of a biodegradable PASP hydrogel obtained by chemical crosslinking with 1,6-hexanediamine. 1,6-Hexanediamine was used to synthesize a poly(amino acid) drug carrier to enhance the cellular uptake.[14] PASP and derivatives of PASP appear interesting for biological and pharmaceutical applications because of their biocompatibility and biodegradability.

PASP and its derivatives have also been applied as carriers of macromolecule prodrugs to bond medicines such as dexamethasone,[15] as suitable drug carriers to entrap camptothecin,[16] and to prepare micelles, microparticles, and nanoparticles. So far, studies have mostly been focused on PASP or

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Contract grant sponsor: National Natural Science Foundation of China; contract grant numbers: 20636010, 20876011.

Contract grant sponsor: National High Technology Research and Development Program of China; contract grant number: 2006AA02Z245.

derivatives of PASP as drug carriers. However, few articles have reported on PASP hydrogels for drug control and release.

In this article, pH-sensitive hydrogels with PASP crosslinked with 1,6-hexanediamine and reinforced with ethylcellulose (EC) were prepared. This new hydrogel combined the advantages both hydrophobic polymers and biodegradable hydrogels, therefore, the drug could be released from the composite matrices during a reasonable period of time. This study focused on the examination of the swelling behavior and drug-release kinetics of PASP–EC blend hydrogels.

Naproxen sodium (NS), a phenylacetic acid derivative, was chosen as a model drug. It is a nonsteroidal anti-inflammatory drug that is available commercially for peroral administration. The gastric effects of perorally administered NS may be alleviated, to some extent, by the inhibition of its release in the gastric region. When used in a matrix-type tablet formulation, PASP forms a gel barrier in an acid environment that can modulate or constrain drug release. In this way, NS release in the gastric region may be minimized. Furthermore, at acidic pH values, PASP's amines are protonated and, therefore, can interact with oppositely charged drug ions and, in this manner, serve as excipients for modified-release drug-delivery systems.

EXPERIMENTAL

Materials

L-Aspartic acid was obtained from Changmao Biochemical Engineering Co., Ltd. (Jiangsu Province, China). Polysuccinimide (PSI) with a high molecular weight was prepared in our laboratory.[17] EC was purchased from Tianjing Chemical Reagent Co. (M70, Tianjing, China). 1,6-Hexanediamine was purchased from Shanghai Chemical Reagent Co. (Shanghai, China). NS was purchased from Zhejiang Charioteer Pharmaceutical Co., Ltd. (Zhejiang Province, China). *N*,*N*-Dimethylformamide (DMF), 85% phosphoric acid, methanol, and sodium hydroxide were analytical grade.

Preparation of the PASP and PASP–EC blend hydrogels

PASP hydrogels were synthesized by a method described in a previous article.[18]

PSI (15 g) was dissolved in 420 mL of DMF in a 500-mL beaker with a magnetic stirrer, and 7.5 g of EC was added to the beaker. The mixture containing PSI, DMF, and EC was stirred for 5 h at 40°C. After it was uniformly blended, the mixture was trisected into three beakers, and then, either 0.3 g (sample 1), 0.6 g (sample 2), or 1.2 g (sample 3) of 1,6-hexanediamine used as a crosslinking agent was added to the beaker. The crosslinking reaction was carried out for 1 h at 40°C. The reaction scheme of the crosslinked PASP–EC gels is shown in Figure 1. After the crosslinked polymer was formed, the imide ring of the crosslinked polymer was hydrolyzed with 27% NaOH at 40°C until the pH reached 9. Then, the PASP–EC blend hydrogels were purified by exhaustive dialysis in distilled water for 3 days. After dialysis, the hydrogels were concentrated and lyophilized. Thus, pure PASP–EC blend hydrogels was obtained. Figure 2 presents the PASP–EC blend gel framework.

Residue content

After sufficient dialysis for 3 days, the residual 1,6-hexanediamine in rinsing water was determined according to a sensitive colorimetric micromethod.[19] No unreacted 1,6-hexanediamine was detected.

Freeze drying of the PASP–EC blend hydrogels

The crosslinked PASP–EC hydrogel deposition, which was placed in a culture dish, was put into the refrigerator and prefrozen for 48 h before drying. Freeze drying took place in a laboratory freeze dryer (Christ Freeze Dryer, Alpha 1-2/LD-2, Martin Christ, Osterode am Harz, Germany) for 2 h under a vacuum of 0.1 MPa and a condenser temperature of −54°C.

Measurement of the swelling ratio of the PASP–EC blend hydrogels

The measurement of the swelling ratio of the PASP–EC blend hydrogels was conducted at 22°C by a tea-bag method[20,21] with deionized water as the liquid to be absorbed. The tea bags used in the method were made of 300-mesh nylon netting and were 40 cm in diameter. The testing sample of the hydrogel was placed into the tea bag, which was suspended and fully immersed into the liquid at 22°C. After 24 h, the tea bag was hung in the air for 15 min. The swelling ratio of the hydrogel was calculated as follows:

$$\text{Swelling ratio of the hydrogel (g/g)} = (W_t - W_o - W_n)/W_o \quad (1)$$

where W_n and W_o are the weights of the wet nylon net and the dry hydrogel (g), respectively, and W_t is the weight of the tea bag including the swollen hydrogel (g).

pH sensitivity of the PASP–EC blend hydrogels

The pH sensitivity of the hydrogel (sample 1) was investigated in various pH solutions. All of the

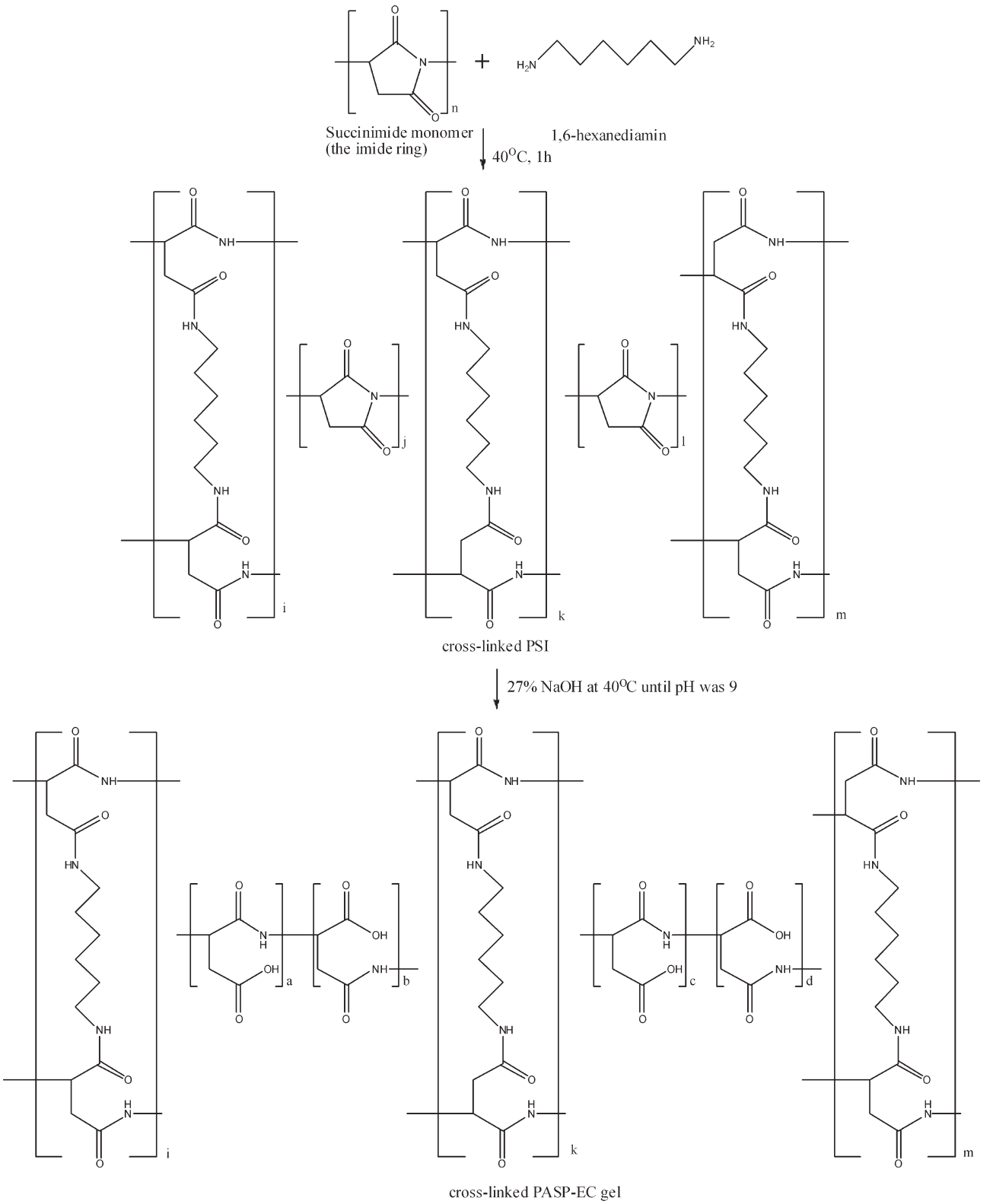

Figure 1 Reaction scheme of the crosslinked PASP–EC gels.

buffer solutions were adjusted to same ionic strength by added sodium chloride to eliminate the influence of the ionic strength. The ionic strength was represented by conductivity, which was measured by a conductometer (DDS-307, Shanghai Precision Scientific Instrument Co., Ltd., Shanghai, China).

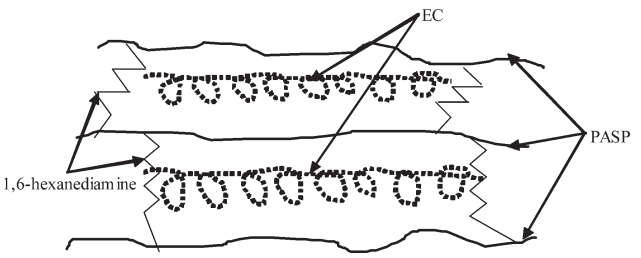

Figure 2 Sketch of the PASP–EC blend gel framework.

Degradation studies

The PASP gel and PASP–EC blend gel (sample 1) were swollen in a phosphate buffer solution (pH 6.8) at 37°C for a desired period. At specified time intervals, the gels were freeze-dried and then weighed. The remaining mass percentage was determined with the dry weight difference before and after the incubation.

Drug-loading procedure

The dried hydrogels (0.2 g; W_0) were immersed into an NS aqueous solution whose volume (V_0) and NS concentration (C_0) were determined and which was left soaking for 24 h at room temperature. After this period, the drug-loaded hydrogels were collected, rapidly washed with water, and freeze-dried for 8 h to a constant weight. The residual volume (V_1) of the solution and the content of NS (C_1) were determined to calculate the ratio of the entrapped drug. The change between the initial concentration of NS aqueous solution and the concentration of residual solution was neglected:

$$\text{Ratio of entrapped drug}\,(\%) = \frac{(V_0 - V_1) \times C_0}{W_0} \times 100\% \tag{2}$$

Drug-release profiles from the hydrogels

Drug release was studied under simulated gastric fluid (pH = 1.05, hydrochloric acid) and intestinal pH conditions (pH = 6.8, potassium dihydrogen phosphate and sodium hydroxide). The spectrophotometric determination of NS was done on a spectrophotometer (Unico2000, Shanghai, China) at 330 nm.

Each sample (400 mg, 20 wt % drug loaded) was introduced into 1000 mL of the medium solution (fresh water, 0.1*N* HCl, or phosphate buffer) in a thermostated glass reactor. The medium was maintained at 37°C and stirred at 150 rpm. Aliquots (5 mL) were withdrawn at appropriate time intervals to measure the absorbance at 330 nm. After the measurements, these aliquots were returned into the glass reactor:

$$\text{Release ratio}\,(\text{wt}\%) = \frac{C_i V_0}{M_0} \tag{3}$$

where C_i is the NS concentration of the released media at the *i*th sample time, V_0 is the initial volume of the solution, and M_0 is the initial weight of the loaded drug.

Infrared spectrum analysis

The dry hydrogel was ground into powder and examined with an infrared spectrum analyzer [Fourier transform infrared (FTIR) spectrum analyzer 250FTIR, Thermo Nicolet Corp., 1 μg/mg KBr].

Elemental analysis

The C, H, and N contents in the gels were detected by Elementar Vario EL (Hessen, Germany).

Scanning electron microscopy (SEM) observations

The surface structure of the dried PASP–EC hydrogel sample 1 was investigated by means of a scanning electron microscope (Hitachi S-570, Tokyo, Japan). The dry PASP–EC hydrogel sample was ground into powder, mounted on a metal stub, and subsequently coated with gold. SEM was used to observe the surface of the PASP–EC hydrogel.

RESULTS AND DISCUSSION

Preparation of the PASP–EC blend hydrogels

The C and N contents in the hydrogel decreased after hydrolysis, whereas the H content increased (Table I). The hydrogel was produced by the hydrolysis of the imide rings of the crosslinked PSI. Because of the ring opening of imide, a water molecule (H_2O) was added to the hydrogel skeletons, which led to an increase in the H content and a decrease in the C and N content.

The FTIR spectra of the hydrolyzed and unhydrolyzed hydrogels are shown in Figure 3. These showed the following principal features: bands at 1100 cm^{-1} (hydroxyl of EC) and 1060 cm^{-1} (ether of EC) were observed in the IR spectra of both hydrogels. This was strong evidence to confirm that EC

TABLE I
Elemental Analysis of the PASP–EC Blend Hydrogels

Hydrogel	C (%)	N (%)	H (%)
Sample 1 (no hydrolysis)	46.04	13.41	4.144
Sample 1 (hydrolysis)	37.09	10.52	4.982

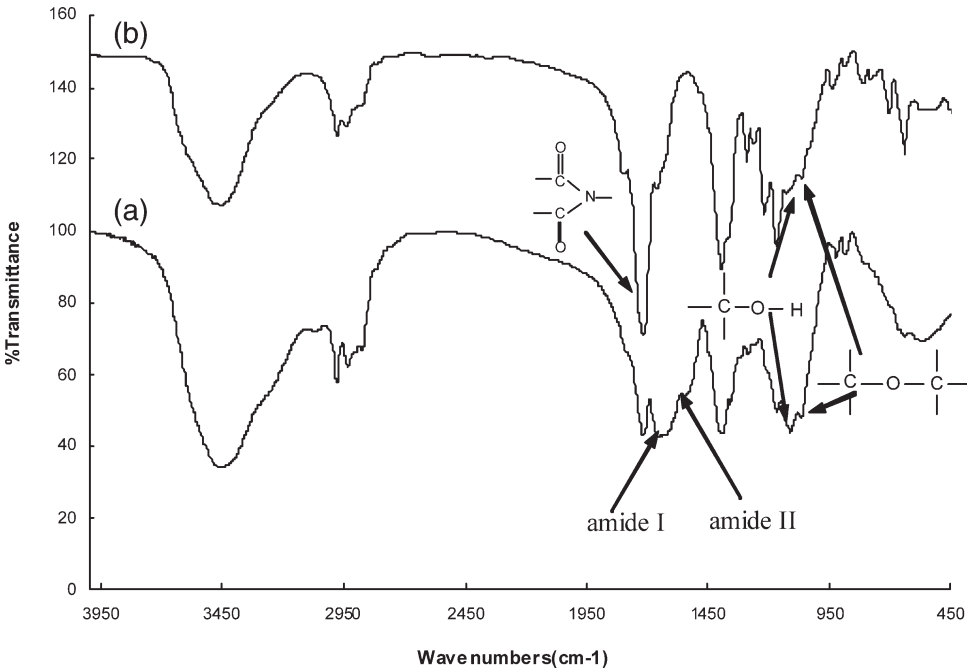

Figure 3 FTIR spectra of the PASP–EC blend hydrogels (sample 1): (a) hydrolyzed and (b) unhydrolyzed hydrogels.

was indeed successfully incorporated into the hydrogel. Compared to the spectrum of the unhydrolyzed hydrogel, the absorption peak of the imide ring (1713 cm^{-1}) became much smaller, whereas new peaks standing for amide (1645 and 1538 cm^{-1}) were observed because of the hydrolysis of the hydrogel.

Effect of the concentration of the crosslinking agent on the swelling ratio of the PASP–EC blend hydrogels

The swelling ratios of these blend gels with different amounts of crosslinking agent were tested in deionized water and NS aqueous solution at 25°C, respectively. The swelling ratios of the hydrogels at room temperature (25°C) varied with the amount of crosslinking agent. As shown in Figure 4, the swelling ratio decreased from 275 to 20 g/g in deionized water with an increase in the 1,6-hexanediamine content from 0.3 to 0.6 g. However, the swelling ratio showed no obvious change with an increasing in the crosslinking agent content from 0.6 to 1.2 g. The hydrogel treated with 0.3 g of crosslinking agent swelled and absorbed water at more than 250 times its own weight. In general, an unduly large concentration of crosslinking agent led to an excessively high crosslinking degree, which resulted in reduced water absorbency when a gel was formed.

NS was selected as a model drug in this study. The drug was loaded into the hydrogel by a swelling–diffusion method. The swelling ratios of the three samples with various crosslinking degrees in

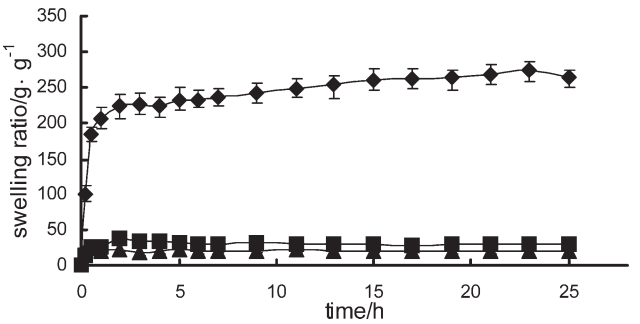

Figure 4 Swelling ratios of the PASP–EC blend gels prepared with various amounts of crosslinking agent [(◆) 0.3 g, sample 1; (■) 0.6 g, sample 2; and (▲) 1.2 g, sample 3, of 1,6-hexanediamine] at room temperature (25°C) in deionized water.

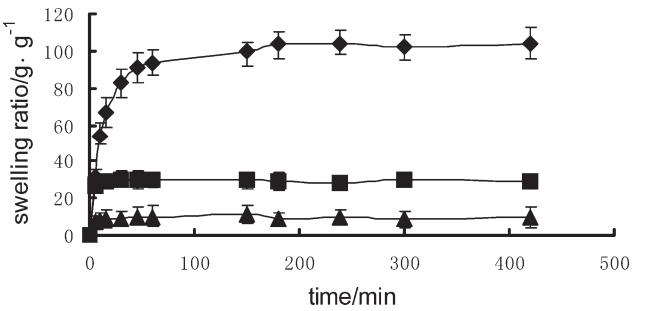

Figure 5 Swelling ratios of the PASP–EC blend gels prepared with various amounts of crosslinking agent [(◆) 0.3 g, sample 1; (■) 0.6 g, sample 2; and (▲) 1.2 g, sample 3, of 1,6-hexanediamine] in a 0.01 mol/L NS aqueous solution (solution conductivity = 595 μs/cm).

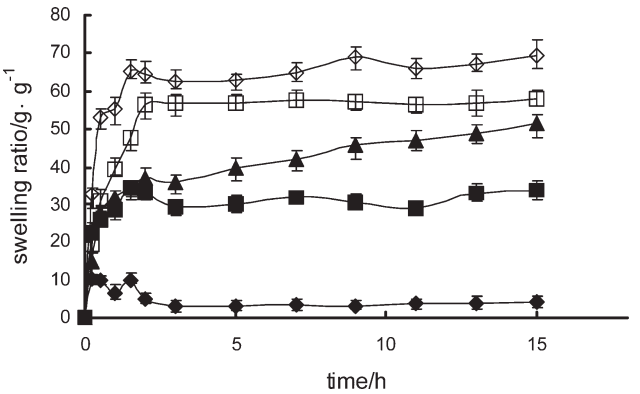

Figure 6 Swelling ratio of sample 1 at various pH values (the solution conductivity was adjusted to approximately 1187 μs/cm): pH = (◆) 2.0, (■) 3.6, (▲) 5.0, (□) 7.0, and (◇) 7.4.

an NS aqueous solution are plotted against time at 25°C in Figure 5. The swelling ratios of the PASP–EC blend hydrogels in an aqueous solution of NS decreased in contrast to those in deionized water.

In according with Flory–Huggins theory, saline solutions have a great influence on ionic gels. The interplay of ionogens in the ionic gel and saline ions in the saline solution resist the swelling of the ionic gel network, so the swelling ratio in saline solution decreases.[22]

pH-sensitive characteristics of the PASP–EC blend hydrogels

Because sample 1, with a higher swelling ratio, could undergo a larger volume change in response to the environmental stimulus, sample 1 was selected for drug release in the following experiment. Sample 1 was immersed in solutions of various pH values to determine the swelling ratio. The swelling behavior of the hydrogels was carried out in buffer solutions in a pH range from 2.0 to 7.4 at conductivity of 1190 μs/cm and 25°C, respectively.

As shown in Figure 6, an increasing pH led to gel swelling. The swelling ratios of the PASP–EC blend hydrogels were strongly dependent on the pH. At low pH, protons in the external medium effectively suppressed the ionization of the carboxylic acid groups of the hydrogels, and consequently, the flexibility of the chain was rather low. As the pH increased, the carboxylic acid groups were ionized and attracted cations into the hydrogel to replace the protons, which raised the concentration of mobile ions inside the hydrogel. This effect was related to the ionization of the PASP–EC blend gel network; with the increase in pH values, the ionized carboxylic acid groups' electrostatic repulsion forced the hydrogel networks to expand and caused its swelling ratio to reach a relatively larger value, than that at low pH values.

The microstructures of the hydrogel swollen in solutions with different pH values were investigated by SEM (Fig. 7). The hydrogel displayed a porous structure. When the pH of the solutions rose, the swelling ratio of the hydrogels increased, which led to a larger and more porous structure.

Ratio of the drug entrapped in various concentrations of NS

Five different NS concentrations in the solutions were prepared as follows: 0.05, 0.1, 0.2, 0.3, and 0.4 mol/L. The dried gel (0.1 g) was placed into the tea bag and was then immersed in 500 mL at each concentration to achieve its equilibrium after 6 h at 25°C. Then, the weight of the swollen gel was measured to calculate the ratio of the entrapped drug for the hydrogel. The swelling ratio of the gel decreased with increasing concentration of NS (data are not shown). With regard to the effect of ionic strength, with a continuously increasing ionic strength, the anionic groups in the hydrogel were screened by Na^+. As a result, the conformation of the hydrogel was changed from an expanded structure to a more compact matrix, so that the swelling ratio dropped with increasing ionic strength. This meant that the volume of solution ($V_0 - V_1$) absorbed by gel matrix decreased with increasing C_0. However, according to eq. (2), when the initial concentration of solution (C_0) absorbed by gel matrix increased, the ratio of the entrapped drug still increased as the multiplied effect of the previous two aspects (Fig. 8).

Hydrogel degradation

Figure 9 shows that the mass erosion of the two hydrogels began to decelerate after day 2; the PASP gel degraded much faster at 37°C than the PASP–EC blend gel. Both of the hydrogels showed excellent degradability. The degradation of PASP-based hydrogels was mainly caused by cleavage of the amide links in the macromonomer. The presence of EC in the hydrogels prevented water from entering its matrix and slowed the degradation of the hydrogel.

Release profiles of NS from the PASP–EC blend and PASP hydrogels

Figure 10 presents the release profiles of NS from the PASP–EC blend hydrogel (sample 1) and the reference PASP hydrogel sample at pH values of 1.05 and 6.8 at 37°C. As shown clearly in Figure 10, the release rate of NS from the PASP–EC blend and PASP hydrogels depended on the pH conditions. The drug release in simulated intestinal fluid (pH

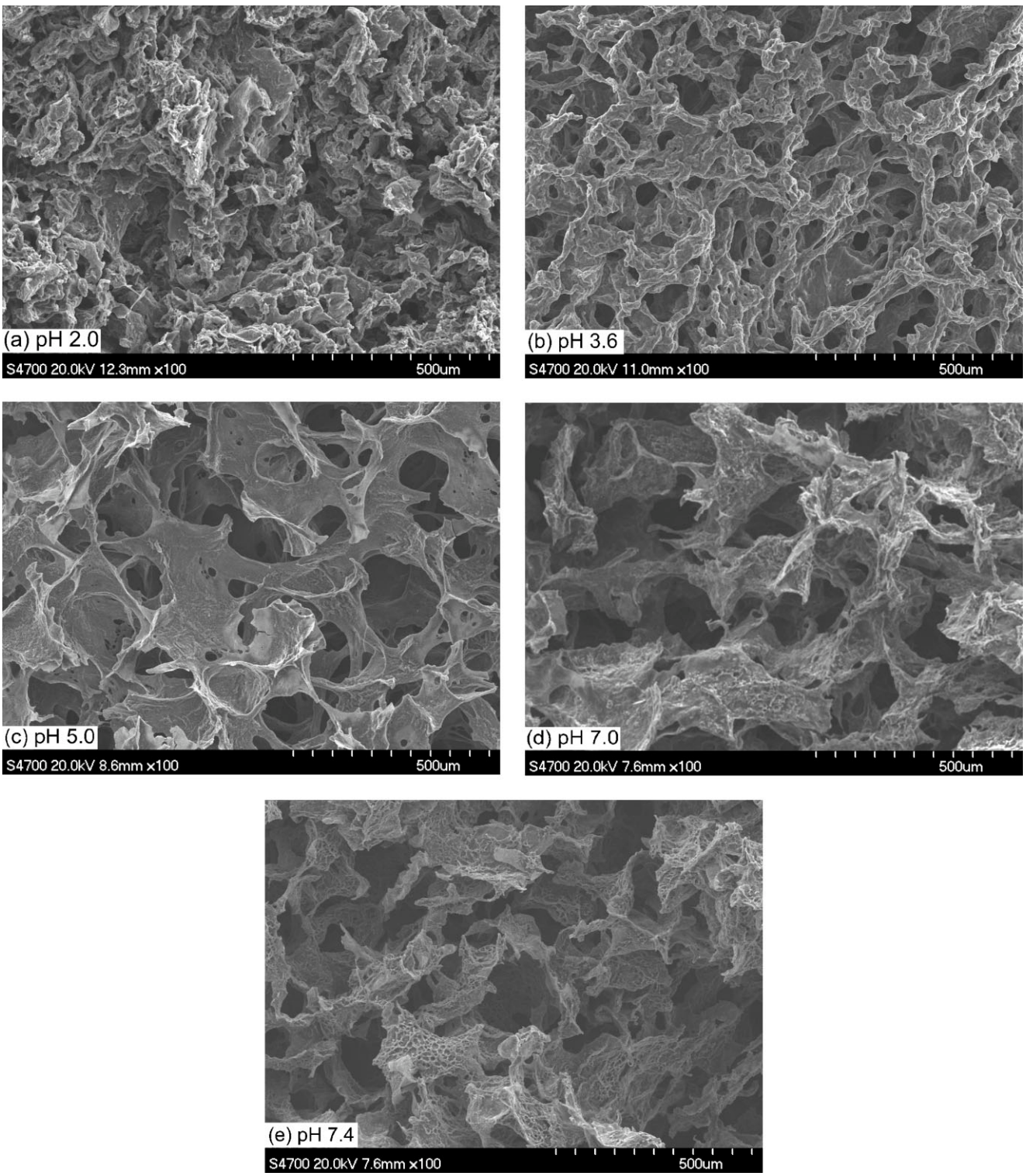

Figure 7 SEM showing the structures of the PASP–EC blend hydrogels swollen in solutions with various pH values: (a) 2.0, (b) 3.6, (c) 5.0, (d) 7.0, and (e) 7.4.

6.8) was faster compared to simulated gastric fluid (pH = 1.05). At 2 h, the neglected NS released from the blend hydrogel in simulated gastric fluid. However, the release ratio in simulated intestinal fluid (pH 6.8) was above 15% at the same time. Gastric emptying time is about 2 h commonly. Therefore, it was evident that the PASP–EC blend hydrogel was adapted to entrap the oral drug.

Compared with the PASP hydrogel, the release of NS from the PASP–EC blend hydrogel showed a

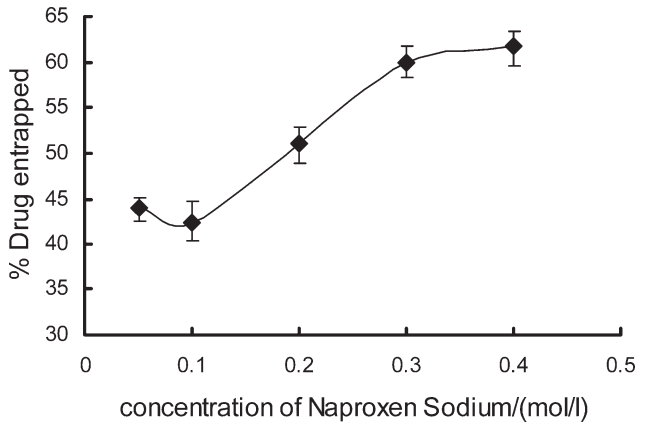

Figure 8 Entrapped drug ratio of sample 1 in various concentration of NS.

lower release rate regardless of the pH value (1.05 or 6.8). At pH 6.8, the cumulative amounts of NS released from the PASP–EC blend and PASP hydrogels were 46.3% and about 93.3% for 10 h, respectively. Therefore, the NS release from the PASP hydrogel was typically a burst effect, whereas the release from the PASP–EC blend hydrogel was a sustained release. At pH 1.05 for 10 h, the corresponding cumulative amounts of NS released from the PASP–EC and PASP hydrogels were 2.8 and 56.0%, respectively. It was evident that the presence of hydrophobic EC retarded the release of NS and led to a sustained release.

The presence of hydrophobic aggregation may have been a dominant factor. The density of hydrophobic aggregation depends on the environmental pH. SEM was used to observe the surface of the PASP–EC hydrogel. The size of the micropores in the PASP hydrogel was much larger than in the PASP–EC blend hydrogel. The microstructure of the PASP–EC hydrogel changed on account of the hydrophobic polymer (EC) added (Fig. 11). Ichikawa and Fukumori[23] reported that the presence of EC had a great influence on carbazochrome sodium sulfonate release. This result was same as in our study. At low pH, because the PASP–EC blend gel network possessed a low swelling capacity, a compact hydrophobic aggregation was formed in the gel, which led to much more diffusion resistance in the NS loaded into the hydrophobic moieties and a low release rate of NS. At pH 6.8, because of a higher swelling ratio under an expanding interaction of the ionized PASP network, compact hydrophobic moieties may have weakened or been partly destroyed, which led to the a marked reduction in the diffusion resistance of the NS loaded into the hydrophobic moieties and a higher release rate compared with that at pH 1.05.

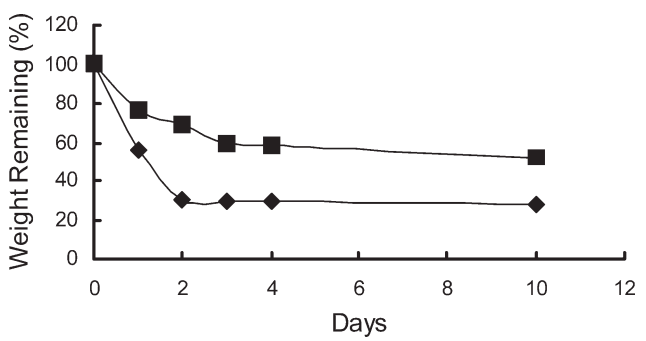

Figure 9 Degradation of the (■) PASP–EC blend gel (sample 1) and (◆) PASP gel in phosphate buffer solution (pH = 6.8) as a function of time.

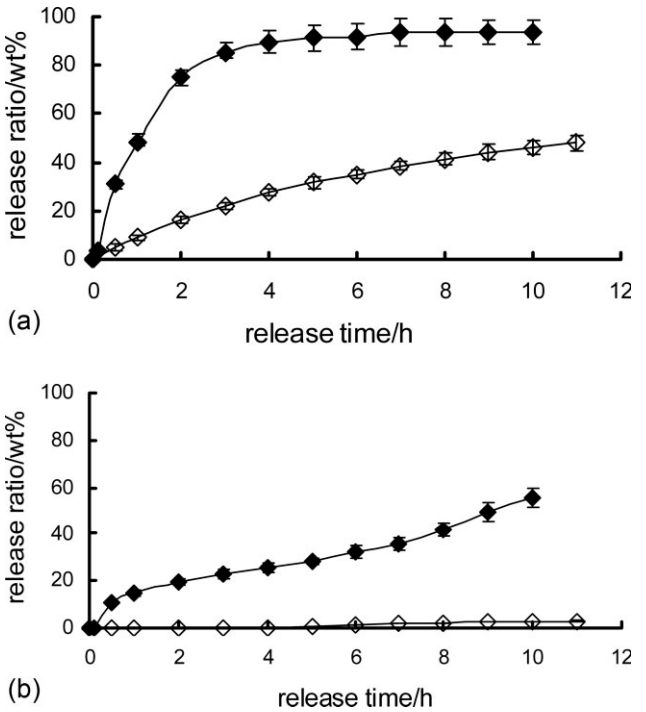

Figure 10 Release profiles of NS from the (◇) PASP–EC blend hydrogel (sample 1) and (◆) PASP hydrogel at pH 1.05 and 6.8 and 37°C. The amount of crosslinking agent for the PASP hydrogel was 0.3 g. (a) pH 6.8 simulated intestinal fluid; the ratio of entrapped drug for both hydrogels was 20%. (b) pH 1.05 simulated gastric fluid; the ratio of entrapped drug for both hydrogels was 20 wt %.

Therefore, we concluded reasonably that the hydrophobic environment formed by the EC network indeed played an important role in the controlled NS release. Actually, the new pH-modulated release was carried out by the control of the density of hydrophobic aggregation related to the environmental pH, which led to the controlled NS release. The experiment indicated clearly that the PASP–EC blend hydrogel used as an NS carrier indeed combined the properties of the pH sensitivity of PASP and the hydrophobicity of EC.

Four models (zero-order, Higuchi, Hixon–Crowell, and Korsmeyer–Peppas models) were applied to fit the release data. A curve-fitting analysis (Table II)

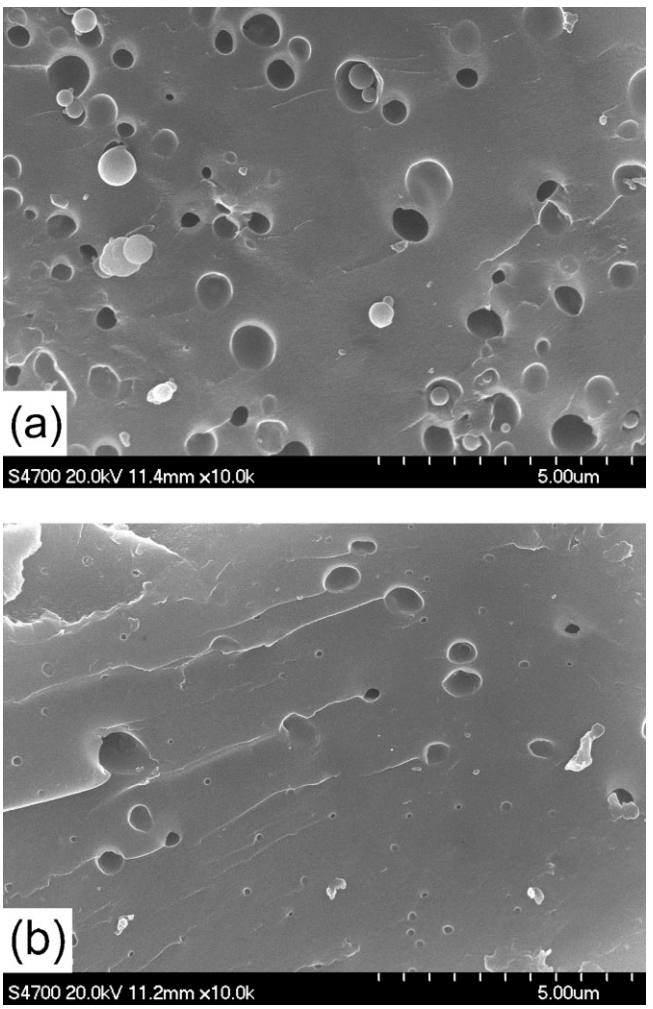

Figure 11 SEM showing the structures of the hydrogels (drug free): (a) PASP and (b) PASP–EC blend hydrogels.

conducted on the data suggested that the kinetics of NS release from the drug-loaded hydrogel conformed to the Korsmeyer–Peppas model. Korsmeyer et al.[24] used a simple empirical equation to describe the general solute release behavior from controlled release polymer matrices:

$$\frac{Mt}{M_\infty} = kt^n \tag{4}$$

where Mt/M_∞ is the fraction of drug released, k is the kinetic constant incorporating the properties of the polymeric system and drug, t is the release time, and n is the release exponent. This equation is used to analyze the first 60% of a release curve, where the release is linearly related to t^n, regardless of the geometric shape. The value of n gives an indication of the release mechanism: when $n = 1$, zero order is suggested; $n = 0.5$ stands for Fickian diffusion (Higuchi model); and when n is between 0.5 and 1 non-Fickian (anomalous) kinetics are indicated.

The log fraction of drug release versus the log time curve showed high linearity and proved that the kinetics of NS release followed the Korsmeyer–Peppas model well. The correlation coefficient of the Korsmeyer–Peppas plot of PASP–EC for drug release at pH 6.8 was 0.9916. n is the slope value of log Mt/M_∞ versus the log time curve. The exponent of release profile (slope) had a value of 0.7291 and showed a combination of diffusional and dissolutional mechanisms, which indicated that the drug release from the hydrogel was controlled by more than one process.

From the viewpoint of the architecture forms of amphiphilic polymers, the PASP–EC blend hydrogel was novel because it was based on the physically interlocked interaction of two networks without covalent bonding. This may be useful in the design and development of novel controlled delivery systems.

CONCLUSIONS

A novel pH-sensitive hydrogel was prepared with PASP crosslinked with 1,6-hexanediamine and reinforced with EC. Because of carboxylic acid groups, the PASP–EC blend hydrogel had predominantly pH-sensitive swelling properties. NS, a nonsteroidal anti-inflammatory drug, was successfully encapsulated into the gel matrix with the percentage of drug entrapped ranging between 40 and 60. The controlled drug release behaviors of the PASP–EC blend hydrogels were investigated. The presence of the hydrophobic polymer EC overcame disadvantageous burst effect of the hydrophilic network, and therefore, the PASP–EC blend hydrogels showed a sustained NS release. The kinetics of NS release from the drug-loaded hydrogel could be explained by the Korsmeyer–Peppas model. The study will be very

TABLE II
Various Mathematical Models and Statistics Obtained from the Drug-Release Profiles

Model[a]	Statistic	PASP–EC
Zero-order model	R^2	0.9542
	k	0.0428
Higuchi model	R^2	0.9891
	k	0.1587
Hixon–Crowell model	R^2	0.9753
	k	0.0177
Korsmeyer–Peppas model	R^2	0.9916
	k	0.0920
	n	0.7291

R^2 = correlation coefficient.

[a] Zero-order model: $Mt/M_\infty = kt + C$. Higuchi model: $Mt/M_\infty = kt^{0.5} + C$. Hixon–Crowell model: $Mt/M_\infty = 1 - (1 - kt)^3$. Korsmeyer–Peppas model: $Mt/M_\infty = kt^n + C$. k: the kinetic constant. For comparison, only the points with $Mt/M_\infty < 0.6$ were used.

useful in the design and development of novel controlled delivery systems.

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