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Synthesis and Characterization of Biodegradable Thermo- and pH-Sensitive Hydrogels Based on Pluronic F127/Poly(ε-caprolactone) Macromer and Acrylic Acid

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Abstract: Several kinds of biodegradable hydrogels were prepared via *in situ* photopolymerization of Pluronic F127/poly(ε-caprolactone) macromer and acrylic acid (AA) comonomer in aqueous medium. The swelling kinetics measurements showed that the resultant hydrogels exhibited both thermo- and pH-sensitive behaviors, and that this stimuli-responsiveness underwent a fast reversible process. With increasing pH of the local buffer solutions, the pH sensitivity of the hydrogels was increased, while the temperature sensitivity was decreased. *In vitro* hydrolytic degradation in the buffer solution (pH 7.4, 37 °C), the degradation rate of the hydrogels was greatly improved due to the introduction of the AA comonomer. The *in vitro* release profiles of bovine serum albumin (BSA) *in-situ* embedded into the hydrogels were also investigated: the release mechanism of BSA based on the Peppas equation was followed Case II diffusion. Such biodegradable dual-sensitive hydrogel materials may have more advantages as a potentially interesting platform for smart drug delivery carriers and tissue engineering scaffolds.

Keywords: photopolymerization, temperature sensitivity, pH sensitivity, hydrolytic degradation, drug delivery.

Introduction

During the last decades, stimuli-responsive polymer hydrogels have attracted much attention due to their high water content, biocompatibility, especially, the smart response to external stimuli such as temperature,[1] pH,[2] electric field,[3] ionic strength,[4] etc. Among them, thermo- and pH-sensitive hydrogels have been widely investigated as drug delivery carriers because of their adjustable swelling properties, and drug release rate from the hydrogel matrixes could be modulated by changing the temperature and/or the pH of the local medium.[5-9]

Hydrogels derived from poly(*N*-isopropylacrylamide) (PNIPAAm) is one of most extensively studied thermo-sensitive hydrogels and shows phase transition temperature at about 32 °C in response to the variation of the external temperature.[10,11] To modulate the rigid network and phase transition temperature of PNIPAAm hydrogel and endow it pH sensitivity, a approach to copolymerize the NIPAAm monomer with other comonomers containing weakly acidic groups such as acrylic acid has been extensively studied.[12-14] However, to prepare such cross-linked hydrogels, a small crosslinking agent such as *N,N'*-methylenebisacrylamide (BIS) is required,[13,14] and safety concerns remain about the use of PNIPAAm in materials for biomedical applications due to the possible presence of the monomeric acrylamide-based residues, which is a neurotoxin.[15] Moreover, most of these hydrogels have problems in non-biodegradability, which was greatly limited in clinical applications.[16,17]

Pluronic, a synthetic triblock copolymer composed of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO), is a well known FDA approved polymer and has been widely applied in drug delivery systems due to its unique thermo-sensitive gelation property and excellent biocompatibility.[18,19] Above lower critical solution temperature (LCST), it forms physical gel by the hydrophobic interaction between PPO blocks in Pluronic. Many studies employed this thermo-gelation property to control the release of some bioactive molecules in response to temperature modulations.[20,21] While such triblock copolymers exhibit temperature-sensitive properties, they don't show any pH-sensitive property due to the lack of ionizable groups in the structure. Meanwhile, the sol-gel transition of the triblock copolymers is slow and mechanical strength of obtained physical gels is low.

In this study, a photocrosslinkable macromer, Pluronic F127/poly(ε-caprolactone) block copolymer terminated with acryloyl groups, was first synthesized, *in situ* photopoly-

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merization of the as-obtained macromer with acrylic acid (AA) comonomer in aqueous medium was then carried out in the presence of a photoinitiator to produce dual-sensitive hydrogels. PCL, a alphatic polyester with excellent biocompatibility and biodegradability, has been extensively studied as a biomedical material.[22,23] Its degradation product, 6-hydroxyhexanoic acid, is a naturally occurring metabolite in the human body. Incorporation of readily hydrolytic PCL segments into the crosslinks of the hydrogel could provide biodegradability. Acrylic acid (AA), a small comonomer with only one double bond, could be incorporated into the polymeric backbone of the hydrogel as the pH-sensitive component. The introduction of PAA component can be expected to adjust the hydrogel network structure and increase the versatility and efficacy of biodegradable hydrogels in various biomedical applications. The swelling response of the hydrogels to temperature and pH were studied in detail, the hydrolytic degradation of the hydrogels and *in vitro* release kinetics of model protein from the hydrogels were also evaluated.

Experimental

Materials. Pluronic F127 (EO_{100}-PO_{65}-EO_{100}, Sigma, USA) was used after drying under vacuum at 90 °C for 24 h. ε-Caprolactone (CL) (99%, Aldrich, USA) was dried over CaH_2 for 48 h and distilled under vacuum just before use. Acrylic acid (AA, analytical grade, Tianjin Chemical Company, China) was distilled under reduced pressure prior to use. Acryloyl chloride (99%, Fluka, Germany) was distilled under N_2 atmosphere prior to use. 1-Vinyl-2-pyrrolidone (NVP, 97%, Fluka, Germany), stannous 2-ethyl hexanoate (95%, Sigma, USA) and the photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA, 99%, Acros, USA), were used as received. Triethylamine and 1,2-dichloromethane (analytical grade, Tianjing Chemical Company, China) were purified by distillation over CaH_2. All other chemicals used were of analytical grade and used without further purification.

Synthesis of Photocrosslinkable F127/PCL Macromer. F127/PCL block copolymer was synthesized by ring-opening polymerization of ε-caprolactone (8 mmol) initiated by Pluronic F127 (M_n=12,600, 1 mmol) using stannous 2-ethyl hexanoate as a catalyst, according to the reported literature.[20] The F127/PCL macromer was prepared by conjugating acryloyl chloride to terminal hydroxyl groups of the above-mentioned block copolymer as described previously.[24] Briefly, dry F127/PCL block copolymer (10 g) was dissolved in 100 mL of dry dichloromethane in a 250-mL round-bottomed flask, triethylamine (1.0 mL) and acryloyl chloride (0.6 mL) were added dropwise to the solution during the period of 1 h under dry argon atmosphere, respectively. The reaction mixture was stirred at 0 °C for 12 h and at room temperature for another 12 h. The product was precipitated in an excess of anhydrous ethyl ether. The product was purified by dissolving it in dry ethyl acetate and removing the precipitate of the byproduct (triethylamine hydrochloride) and ethyl acetate, and dried under vacuum at 40 °C for two days (yield: 92.8%). The degree of acrylation was 94.8%, which was determined by 500 MHz ^{1}H NMR in $CDCl_3$.

Preparation and Purification of Hydrogels. The F127/PCL macromer was dissolved in deionized water to produce a 18 wt% solution, a given amount of AA comonomer with different molar feed ratios of AA to the macromer was mixed with the macromer, and a specified amount of photoinitiator solution of DMPA in NVP (600 mg/mL) was added to the mixture (2 wt% DMPA to the total amount of the macromer and AA comonomer), the resulting solutions were homogeneously mixed and then added to a glass vial. Following this, the mixture was exposed to 365 nm LWUV lamp of 16 W (ZF-7A type, Shanghai Jihui Scientific Instrumental Co. Ltd) for 10 min to ensure the enough copolymerization of the macromer with AA comonomer. The distance between the reaction mixture and the light source is kept 2 cm. As a comparative study of the hydrolytic degradation, the macromer hydrogel without adding AA comonomer was synthesized at the same conditions.

The photocrosslinked hydrogels were cut into discs (10 mm in diameter and 3 mm in thickness). To remove the unreacted monomers and other impurities in the just obtained hydrogel samples, the samples were immersed in distilled water for 7 days at room temperature, and the water was refreshed everyday. Later, the samples were dried at room temperature for 2 days and then dried at 60 °C under reduced pressure for another 2 days. The feed compositions and samples of hydrogels in this study are listed in Table I.

^{1}H NMR Spectroscopy of the Macromer. The ^{1}H NMR spectrum was recorded on a Varian INOVA 500NB spectrometer at 500 MHz at room temperature with $CDCl_3$ as the solvent.

Table I. The Hydrogels Prepared in This Study and Their Diffusional Exponents and Determination Coefficients for the Release of BSA at pH 7.4 (37 °C)

Sample	Macromer (g)	AA (g)	H_2O (g)	Molar Feed Ratio of Macromer to AA	Gel Content (%)	Diffusional Exponent (n)	Determination Coefficient
FA-0	0.5	0	2.28	0	90.7	-	-
FA-1	0.5	0.11	2.28	1:40	94.2	0.76	0.999
FA-2	0.5	0.22	2.28	1:80	93.5	0.78	0.999
FA-3	0.5	0.33	2.28	1:120	92.8	0.81	0.999

Preparation of Buffer Solutions with Different pH. Hydrochloric acid/potassium hydrogen phthalate, sodium hydroxide/potassium hydrogen phthalate and sodium hydroxide/sodium dihydrogen phosphate were used to prepare buffer solutions with different pH ranges from 2.0 to 4.0, 4.0 to 6.0, and 6.0 to 8.0, respectively. In order to eliminate the influence of salt concentration on the swelling of the hydrogels, certain amount of potassium chloride was introduced to the buffer solution to obtain a solution with constant ionic strength of 0.1 mol/L.

Studies on the Thermo- and pH-Sensitivity of the Hydrogels. The gravimetric method was employed to measure the equilibrium swelling ratios (ESR) of the hydrogels. The equilibrium swelling studies were performed in buffer solutions of different pH (3.0, 5.0, 7.0) at different temperatures (from 11 to 51 °C) and in buffer solutions of different pH (from 2.0-8.0) at room temperature. The ionic strength of the buffer solutions was fixed at 0.1 mol/L. The hydrogels were immersed in buffer solution to reach a swollen equilibrium at each predetermined temperature or predetermined time intervals, and the weights of the equilibrated swollen hydrogels were weighed after excess surface water was wiped off carefully with moistened filter paper. The equilibrium swelling ratio (ESR) was calculated according to the following equation:

$$\mathrm{ESR}(\%) = [(W_e - W_d)/W_d] \times 100 \quad (1)$$

where W_e and W_d denote the weights of the equilibrated swollen hydrogels and dried gels, respectively.

Oscillatory Swelling Kinetics of the Hydrogels. The oscillatory swelling behavior was observed in buffer solution (pH 7.0, I=0.1 mol/L) maintained at alternate temperatures of 20 and 40 °C, and in buffer solutions (I=0.1 mol/L) with pH between 4.0 and 7.0. The weight of the hydrogels was weighed at a predetermined time intervals at the temperatures and pH quoted.

Hydrolytic Degradation Study of the Hydrogels. The hydrolytic degradation of the photocrosslinked hydrogel was carried out in a pH 7.4 phosphate-buffered saline solution (PBS) at 37 °C. The dried gels were weighed and immersed in enough buffer solution to maintain the bulk pH at 7.4 throughout the degradation experiment. At specified time intervals (one time per two weeks), three disks were removed from the degradation medium, washed throughly with distilled water, and dried at room temperature for 2 days and then dried in vacuum for 3 days at 60 °C. The average value of three measurements was taken. The percent weight loss of each sample was determined by the following equation:

$$\text{Weight loss}(\%) = [(W_0 - W_t)/W_0] \times 100 \quad (2)$$

where W_0 and W_t denote the initial dried gels and the final dried gels after complete drying in a vacuum oven.

***In vitro* Drug Release Studies of the Hydrogels.** For drug release experiments, the drug-loaded hydrogel was formed by *in situ* photopolymerizing a solution of F127/PCL macromer and AA comonomer, in which 0.5 wt% BSA was dissolved to ensure homogenous dispersion throughout the hydrogel matrix after photopolymerization. After the photocrosslinking, the disk-shaped gels (10 mm in diameter and 3 mm in thickness) were placed in a tube containing 12 mL of fresh buffer solution (pH 7.4 or 2.0, 37 °C). At predetermined time intervals, the samples were taken out and replaced in another 12 mL of fresh buffer solution. The concentration of BSA release was analyzed using UV spectrophotometer (UV-1800, SHIMADZU, Japan) at the maximum absorbance wavelength of BSA at 278 nm. The experiment was performed in triplicate for each of the samples. The release mechanism of BSA was investigated using the Peppas equation:[25]

$$M_t/M_\infty = Kt^n \quad (3)$$

where M_t/M_∞ is the fraction of drug released, K is a constant dependent on the system, t is the release period and n is the diffusional exponent, indicative of the release mechanism for matrices of varying shape and swelling or non-swelling systems. An n value of 0.5 indicates Fickian diffusion, where the drug is released by the usual molecular diffusion through the system. An n>0.5 is indicative of Case II diffusion related to polymer relaxation and/or erosion.

Results and Discussion

Synthesis of Photocrosslinkable Pluronic F127/PCL Macromer. The biodegradable and photocrosslinkable Pluronic F127/PCL macromer was synthesized via ring-opening polymerization of ε-caprolactone using Pluronic F127 as a macroinitiator and stannous hexanoate as a catalyst, and subsequently reacted with acryloyl chloride. The ^{1}H NMR of the macromer in $CDCl_3$ is presented in Figure 1. The signals at 5.8-6.2 ppm belong to protons of the carbon-carbon double bonds attached to the both ends of the block copolymer. The signals at 4.1, 2.3, 1.4 and 1.6 ppm correspond to the chain protons of PCL segments. The signals at 4.2 and 3.6 ppm result from the protons of PEO segments, and the signals at 3.3-3.5 ppm are attributed to the protons of PPO segments. The actual CL units and the degree of acrylation in the macromer could be calculated from the signal intensities of the CH_3 protons in Pluronic F127 and the related signal intensities of CL units and carbon-carbon double bonds, and were found to be 7.4 and 94.8%, respectively. These results indicate that the biodegradable and photocrosslinkable macromer was successfully synthesized.

Preparation of Dual-Sensitive Photocrosslinked Hydrogels. When the mixture solutions of the F127/PCL macromer and AA with different feed compositions were exposed to UV light in the presence of a photoinitiator, a rapid *in situ* gelation was observed to form hydrogel for all systems (including the system without AA comonomer) in several

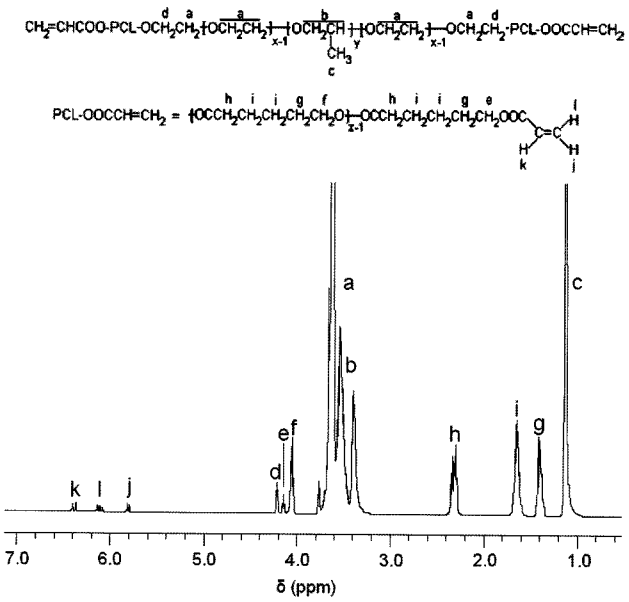

Figure 1. ^{1}H NMR spectrum of Pluronic F127/PCL macromer in $CDCl_3$.

seconds, and exposition for 10 min was kept to ensure the enough copolymerization of the macromer and AA comonomer. The hydrogels obtained in this study are listed in Table I. Compared to the large and bulky macromer, AA is a small and mobile monomer, having only one double bond. It will incorporate itself into the polymeric backbone of the hydrogel as PAA components along the polyacrylate chains which were crosslinked by F127/PCL in the network. As illustrated in Figure 2. Due to the incorporation of biodegradable PCL segments, thermo-sensitive F127 segments and the ionizable groups of PAA components, the resultant hydrogels could respond to both temperature and pH changes and be labile to hydrolytic degradation.

pH Sensitivity of the Hydrogels. The effect of pH values on ESR of the hydrogels was determined in buffer solutions in the pH range from 2.0 to 8.0 with a constant ionic strength of 0.1 mol/L at 25 °C. As shown in Figure 3, the swelling ratio of the hydrogels increased obviously with the increasing pH of the solution, and ESR of the hydrogels exhibited a dramatic transition between pH 3.0 and 5.0. This phenomenon can be attributed to the ionization behavior of carboxylic acid groups in response to external pH changes. At lower

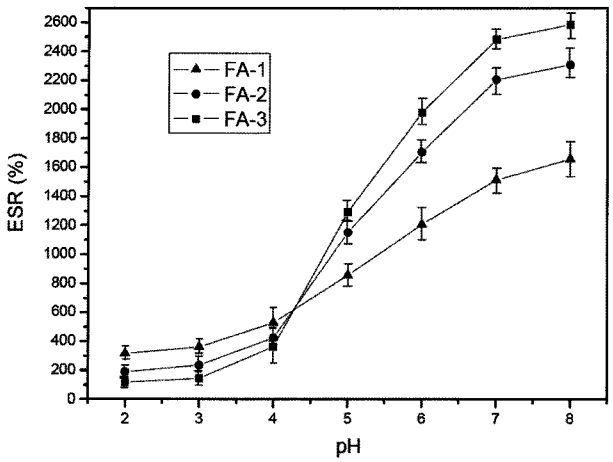

Figure 3. Effect of pH on ESR of the hydrogels at 25 °C.

pH value, most -COOH groups were kept in the form of COOH, which may induce the formation of hydrogen bond between -COOH groups and F127 segments. Such enhancement of interactions between polymer chains caused the decrease in ESR of the hydrogels. It also was observed that ESR of samples decreased with the increasing feed ratio of AA to the macromer at lower pH value, which may be attributed to more -COOH groups to form hydrogen bonds leading to a much more compact hydrogel network structure. On the other hand, with the increase of pH values, -COOH groups were ionized, and the hydrogen bonds between the polymeric chains were broken. Meanwhile, the COO^- groups' electrostatic repulsion force led to the polymeric network' expanding, these attracted more water into the hydrogel network.[26,27] In addition, as seen from Figure 3, with the increase of -COOH groups, pH sensitivity of ESR of the hydrogels increased both in acid and alkaline media. The above-mentioned results clearly indicated that the prepared hydrogels exhibited pH-sensitive characteristic.

Temperature Sensitivity of the Hydrogels. Pluronic F127 is one of the most extensively investigated thermo-sensitive materials due to its unique thermo-reversible gelation property. The chemically crosslinked hydrogels containing F127 segments also exhibited phase transition behavior in response to external temperature.[18,19] However, when -COOH groups were introduced into such hydrogels, the temperature sensitivity of the hydrogels should be affected by the pH of medium.

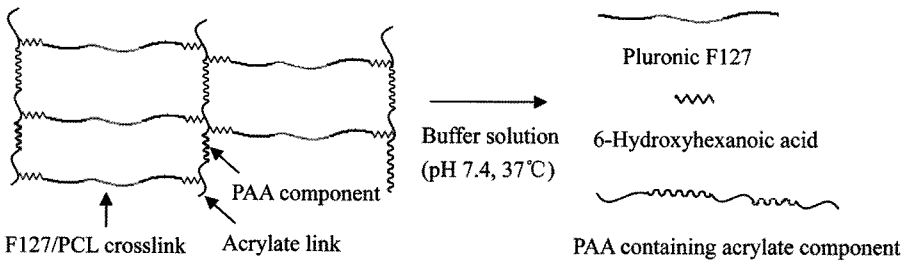

Figure 2. The illustration for the idealized structure of cross-linked hydrogel, and its hydrolytic degradation products.

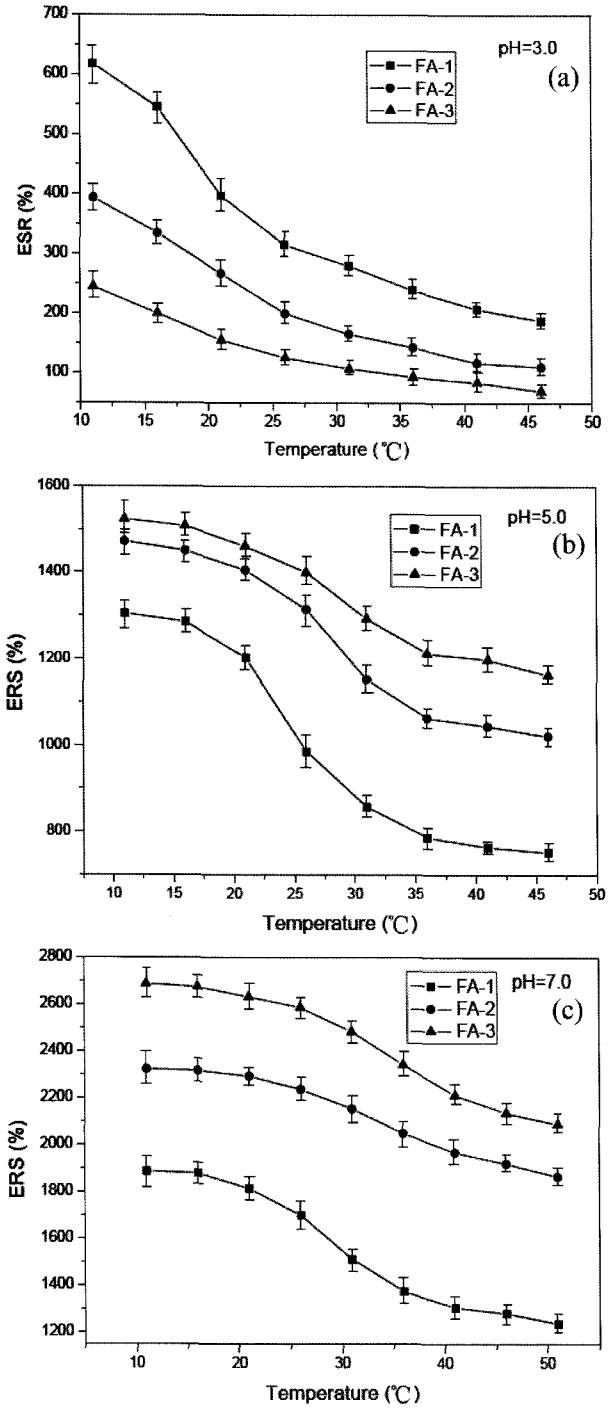

Figure 4. ESR as a function of temperature at pH 3.0 (a), pH 5.0 (b), and pH 7.0 (c) for the hydrogels.

ESR of copolymerized hydrogels investigated will be affected by both the temperature and pH of the surrounding environment. Figure 4(a)-(c) exhibits the effect of temperature on ESR of the various hydrogels in buffer solutions of different pH values (3.0, 5.0 and 7.0). First, as seen from Figure 4(a), at pH 3.0, ESR of hydrogel FA-1 shows the evident reduction around 25 °C, which is regarded as its phase transition temperature. With the increase of -COOH groups in the hydrogels, the phase transition temperature slightly increased. The results indicate that the temperature plays an important role for phase transition in response to the temperature at lower pH.[28] At pH 5.0, as seen from Figure 4(b), ESR of the hydrogels still presented a marked transition region, but the phase transition temperature shifted to higher temperature with the increase of -COOH groups in the hydrogels. This may be attributed to the ionization of -COOH groups, a part of hydrogen bonds is broken, and the electrostatic repulsive force by the $-COO^-$ groups may offset the aggregation caused by thermo-sensitive component leading the higher phase transition temperature. At pH 7.0, due to more -COOH groups' ionization, ESR presented a relatively broad and slow transition region, and the hydrogels showed relatively low temperature sensitivity. These results are still different from the poly(NIPAAm-*co*-AA) hydrogel's behavior,[27] in which the content of -COOH groups is more than 10 mol%, the resultant hydrogel can not exhibit a phase transition temperature. However, for copolymerized hydrogels of F127/PCL macromer with AA comonomer, ESR for all hydrogels exhibited a transition region at investigated conditions. The phenomenon may be attributed to the different structure distribution character of pH-sensitive component and thermo-sensitive component in the chain network of the hydrogels. In the hydrogels investigated, the polyacrylate chains containing PAA component was connected by the cross-links, F127/PCL segments, each component may keep its own property. As illustrated in Figure 2.

Oscillatory Swelling Kinetics of the Hydrogels. The oscillatory swelling-deswelling experiments were performed to investigate the response of the hydrogels prepared as smart matrixes to changes of temperature and pH. Figure 5 exhibits that the reversible response to the alternating changes

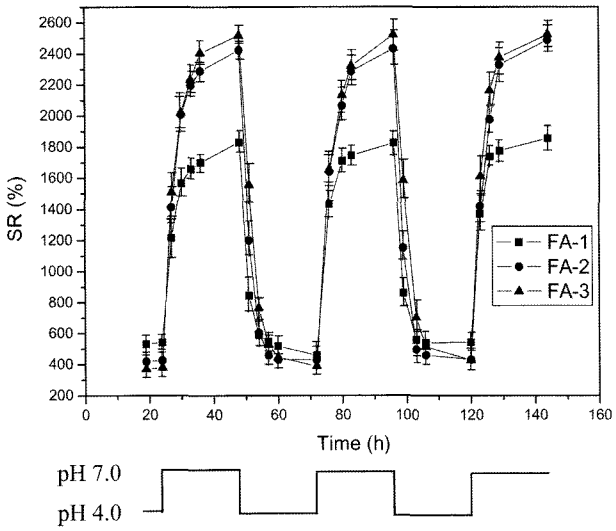

Figure 5. Oscillatory swelling behavior of the hydrogels in response to pH changes between pH 4.0 and 7.0.

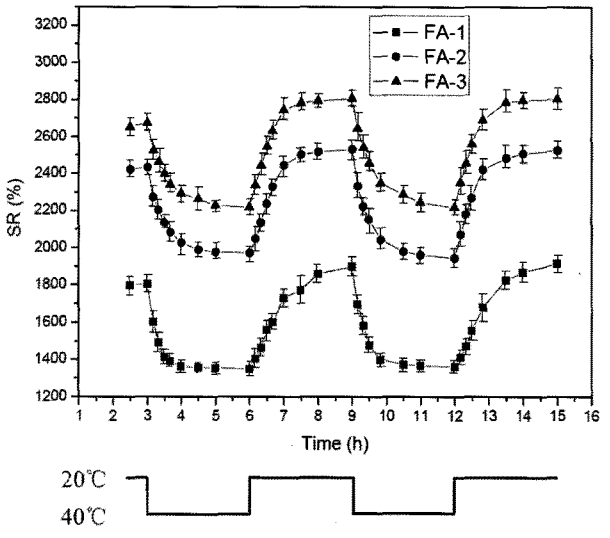

Figure 6. Oscillatory swelling behavior of the hydrogels in response to temperature changes between 20 and 40 °C.

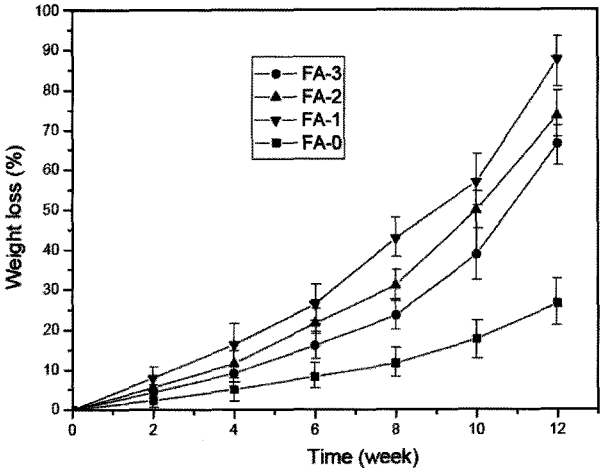

Figure 7. Hydrolytic degradation behavior of the hydrogels in PBS solutions (pH 7.4, 37 °C).

in pH. As seen from Figure 5, after the hydrogels achieved swelling equilibrium in the buffer solution of pH 4.0, and then were immersed in a pH 7.0 buffer solution, they swelled quickly, this may be attributed to hydrogen bonds' broken and the electrostatic repulsive force inducing hydrogel's expanding when -COOH groups change into $-COO^-$ ions at higher pH. When the hydrogels swelled to a certain extent, the driving force for expanding decreased, and swelling rate became slow until obtaining a new equilibrium. The hydrogels investigated possessed good repeated response to the pH changes.

Figure 6 shows that the reversibility process of temperature response between 20 and 40 °C in buffer solution of pH 7.0. After the hydrogel reach ESR at 20 °C, it began to shrink fast after being immersed into a 40 °C buffer solution. During 30 min, ESR of the hydrogel FA-1 decreased from 1,806 to 1,415. With the increase of -COOH component, the reduction rate of ESR became slow. This may be attributed to the strong electrostatic repulsion leading to slow shrinking.

The Hydrolytic Degradation of the Hydrogels. The F127/PCL cross-links in the hydrogel contain the hydrolytically labile ester bonds that provide the network with its degradable characteristic. The cleavage of ester bonds within the network leads to the weight loss. The hydrolysis of the hydrogels was studied in buffer solution of pH 7.4 at 37 °C. Figure 7 presents the hydrolytic degradation behavior of the hydrogels in buffer solution of pH 7.4 at 37 °C. The hydrogels formed from F127/PCL macromer with acrylic acid degraded much rapidly than the hydrogel formed from only pure F127/PCL macromer. Acrylic acid is a acidic in nature with a p*K*a of 4.25. Under the conditions investigated, a majority of the acrylic acid segments in the hydrogels are ionized, and the electrostatic repulsive force caused the network to expand, producing a highly swollen hydrogel. Ester bonds of PCL segment might more easily hydrolyse when exposed to water in highly swollen hydrogels. While the hydrogel formed from the pure macromer exhibited lower swelling ratio due to the thermo-sensitive property under the same conditions. According to Figure 7, the weight loss of the hydrogels containing pH-sensitive component increased with increase of F127/PCL content, the reason is that the weight loss mainly comes from the removal of F127 segments and/or F127/ε-caprolactone oligomer from the hydrogels at the initial degradation step. The hydrogels containing PAA component exhibited a substantial weight loss after 8 weeks. This result shows that the increased swelling of the hydrogels copolymerized with acrylic acid greatly accelerated the hydrolytic degradation of PCL segments.

***In vitro* Drug Release Study of the Hydrogels.** The drug release from the double-sensitive hydrogels was examined employing BSA as a model protein. Figure 8 depicts *in vitro*

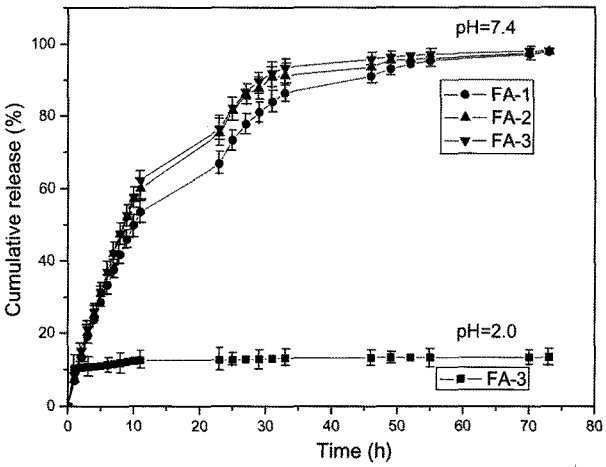

Figure 8. Release profile of BSA from the hydrogels in buffer solutions of pH 7.4 and pH 2.0 at 37 °C.

release profiles of BSA from the hydrogels in different buffer solutions (pH 7.4 and pH 2.0) at 37 °C. The amount of BSA released from hydrogel FA-3 at pH 2.0 was very low, only about 13% BSA was released from the test hydrogel due to the initial burst caused by its shrinking, this may be attributed to the low swelling ratio restricting the release of BSA in the hydrogel. However, the release of BSA from the hydrogels at pH 7.4 increased significantly. The drug-loaded hydrogels showed an initial burst (~50% of the initial loading amount) for 10 h, followed by a sustained release (~50-97% of the initial loading amount).

In order to investigate the release mechanism of BSA from the hydrogels at pH 7.4, an exponential equation (eq. (3)) proposed by Rigter and Peppas was employed.[29] Table I lists the values of n and determination coefficients. The introduction of AA comonomer resulted in great improvement of the swelling ratio of the hydrogels, an $n > 0.5$ indicates Case II diffusion related to the polymer relaxation without considering the degradation of the hydrogels, since the degradation rate of the hydrogels was very slow, as discussed above.

Conclusions

A series of thermo- and pH-sensitive hydrogels were prepared via the photopolymerization of Pluronic F127/PCL macromer and acrylic acid under UV irradiation. The resultant hydrogels exhibited biodegradable and reversible thermo- and pH-sensitive character. With the increase in pH of buffer solutions, the swelling ratio increased accordingly, while the temperature sensitivity decreased. The content of AA component in the hydrogels, and the pH and the temperature of media have great effect on the swelling ratio, degradation rate of the hydrogels and the drug release from the hydrogels. The investigated biodegradable dual-sensitive hydrogel materials might have potential in biomedical applications as smart drug delivery carriers and tissue engineering scaffolds.

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References

(1) S. Shinji, O. Masayuki, and I. Isao, *Macromolecules*, **40**, 3394 (2007).
(2) D. T. Pual, R. H. Jonathan, J. C. Colin, P. A. Steven, A. L. J. Richard, and J. R. Anthony, *Macromolecules*, **40**, 4393 (2007).
(3) T. Tanaka, I. Nishio, S. T. Sun, and S. Ueno-Nishio, *Science*, **218**, 467 (1982).
(4) S. P. Jin, M. Z. Liu, F. Zhang, S. L. Chen, and A. Z. Niu, *Polymer*, **47**, 1526 (2006).
(5) M. Akira, Y. Ryo, and K. Kazunori, *Biomacromolecules*, **5**, 1038 (2004).
(6) Y. H. Bae, T. Okano, R. Hsu, and S. W. Kim, *Macromol. Chem. Rapid Commun.*, **8**, 481 (1987).
(7) K. S. Soppimath, L. H. Liu, W. Y. Seow, S. Q. Liu, R. Powell, P. Chan, and Y. Y. Yang, *Adv. Funct. Mater.*, **17**, 355 (2007).
(8) W. S. Shim, J. S. Yoo, Y. H. Bae, and D. S. Lee, *Biomacromolecules*, **6**, 2930 (2005).
(9) J. M. Suh, S. J. Bae, and B. Jeong, *Adv. Mater.*, **17**, 118 (2005).
(10) M. R. Guilherme, R. Silva, E. M. Girotto, A. F. Rubira, and E. C. Muniz, *Polymer*, **44**, 4213 (2003).
(11) L. D. Taylor and L. D. Cerankowski, *J. Polym. Sci. Part A: Polym. Chem.*, **13**, 2551 (1975).
(12) H. Chen and Y. L. Hsieh, *J. Polym. Sci. Part A: Polym. Chem.*, **42**, 6331 (2004).
(13) X. Z. Zhang, Y. Y. Yang, F. J. Wang, and T. S. Chung, *Langmuir*, **18**, 2013 (2002).
(14) R. Silva and M. G. Oliveira, *Polymer*, **48**, 4114 (2007).
(15) H. Tanii and K. Hashimoto, *Archives of Toxicology*, **54**, 203 (1983).
(16) Y. Qiu and K. Park, *Adv. Drug Deliv. Rev.*, **53**, 321 (2001).
(17) J. T. Zhang, S. W. Huang, S. X. Cheng, and R. X. Zhuo, *J. Polym. Sci. Part A: Polym. Chem.*, **42**, 1249 (2004).
(18) X. J. Loh, S. H. Goh, and J. Li, *Biomacromolecules*, **8**, 585 (2007).
(19) X. J. Loh, S. H. Goh, and J. Li, *Biomaterials*, **28**, 4113 (2007).
(20) J. C. Ha, S. Y. Kim, and Y. M. Lee, *J. Control. Rel.*, **62**, 381 (1999).
(21) P. Chandaroy, A. Sen, and S. W. Hui, *J. Control. Rel.*, **76**, 27 (2001).
(22) J. H. Ha, S. H. Kim, S. Y. Han, Y. K. Sung, Y. M. Lee, I. K. Kang, and C. S. Cho, *J. Control. Rel.*, **49**, 253 (1997).
(23) S. C. Woodward, P. S. Brewer, F. Moatamed, A. Schindler, and C. G. Pitt, *J. Biomed. Mater. Res.*, **19**, 437 (1985).
(24) S. P. Zhao, L. M. Zhang, D. Ma, C. Yang, and L. Yan, *J. Phys. Chem. B*, **110**, 16503 (2006).
(25) S. S. Kim, Y. M. Lee, and C. S. Cho, *Polymer*, **36**, 4497 (1995).
(26) E. Kokufuta, B. Wang, R. Yoshida, A. R. Khokhlov, and M. Hirata, *Macromolecules*, **31**, 6878 (1998).
(27) G. H. Chen and A. S. Hoffman, *Nature*, **373**, 49 (1995).
(28) S. Beltran, J. P. Bakai, H. H. Hooper, H. W. Blanch, and M. Prausnitz, *Macromolecules*, **24**, 549 (1991).
(29) P. L. Rigter and N. A. Peppas, *J. Control. Rel.*, **5**, 37 (1987).