Preparation and Characterization of Dual Responsive Sodium Alginate-*g*-Poly(vinyl alcohol) Hydrogel

Cunping Xia, Congming Xiao

Department of Polymer Science and Engineering, College of Material Science and Engineering of Huaqiao University, Quanzhou 362021, China

Received 20 December 2010; accepted 26 April 2011
DOI 10.1002/app.34751
Published online 23 August 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: Poly(vinyl alcohol) (PVA) was chosen as a controllable gelator to prepare sodium alginate (SA)-based physically cross-linked dual-responsive hydrogel by three steps. First, polyvinyl acetate (PVAc) was grafted onto SA via radical copolymerization. Then, the copolymer was subsequently converted into SA-*g*-poly(vinyl alcohol) (SAPVA) by alcoholysis reaction. PVA content of SAPVA was tailored by controlling the graft percentage of PVAc, i.e. through varying the amount of vinyl acetate during copolymerization. Finally, SAPVA hydrogels were formed by freezing-thawing cycles. The structure of the graft copolymers was verified with FTIR spectroscopy. X-ray diffraction analysis results revealed that the crystallinity of SAPVA hydrogels depended on the PVA content of SAPVA. The swelling test showed that SAPVA hydrogels were pH-responsive, and the swelling was reversible. SAPVA hydrogels also behaved electric-responsive. In addition, the pH-sensitivity of SAPVA hydrogels was able to be controlled with the composition of the hydrogels. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 123: 2244–2249, 2012

Key words: sodium alginate-*g*-PVA; physical hydrogel; controllable; response

INTRODUCTION

Hydrogels are hydrophilic polymer networks that are capable of absorbing large amount of water when they are submersed in aqueous solution or biological fluids. They can be either chemically or physically cross-linked. Biodegradable hydrogels exhibit many unique physicochemical properties and have been widely used in biomedical applications such as tissue engineering and drug delivery.[1–3] Smart hydrogels are those respond to environmental stimuli including chemical and physical activations. They are of valuable for various applications.[4,5] To use such a kind of hydrogels in the area consisting of bioactive substances, it is preferential to fabricate responsive hydrogels under mild conditions.

Alginate is extracted from brown algae. It is a natural linear biopolyelectrolyte and is composed of 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) units.[2,6] The reversible protonation and deprotonation of the carboxyl groups on the backbone make alginate a good candidate for preparing pH-responsive matrices.[7] It is usually cross-linked with multivalent metallic cations or polycations such as water-soluble *N*,*O*-carboxymethyl chitosan.[8] However, the stability of these alginate-based hydrogels is poor when the environment is changed. The cations will dissolve into the medium after pH-stimulation,[9] which leads to the network structure of alginate-based hydrogels formed in these ways is difficult to turn back to its original one. As a result, the hydrogel is difficult to keep their reversible sensitivity and cannot be used repeatedly.

Various chemically cross-linking approaches have been presented to improve the mechanical properties of alginate-based hydrogels.[10] But, the reagents and reaction conditions are invasive and unfavorable for some biomedical applications. To obtain physically cross-linked responsive hydrogel that not only exhibits the unique properties of alginate but also possess enhanced mechanical strength, a strategy via incorporating a gelator onto alginate backbone is proposed and examined in this article.

Poly(vinyl alcohol) (PVA) is water-soluble and biocompatible. Its mechanical strength is well enough. The utilization of PVA in medical and pharmaceutical applications is well documented.[11,12] PVA hydrogel is easily prepared via freezing/thawing cycles.[13,14] This mild procedure has been successfully used to prepare physically cross-linked starch-*g*-PVA and chitosan-*g*-PVA hydrogels in our lab.[15,16] Being encouraged by these facts, we choose PVA as a physical gelator to attain the goal mentioned earlier.

Evidently, the combination of PVA and alginate will generate a new kind of alginate-based hydrogel.

Correspondence to: C. Xiao (xcm6305@yahoo.com.cn).
Contract grant sponsor: Natural Science Foundation of Fujian Province of China; contract grant numbers: 2010J01291, E1010026.
Contract grant sponsor: Basic Research Item of Central Universities; contract grant number: JB-JD1001.

As PVA and alginate are chemical bonded, the resistance to environmental changes of such a hydrogel is superior to that of calcium alginate or physical blend of alginate and PVA. This novel hydrogel will be not only smart but also really reversible. To our best knowledge, no similar ideas and result have been reported. In addition, the hydrogel is an anionic one. Its properties are probably quite different from those of neutral starch- or cationic chitosan-based hydrogels.

To carry out this intention, the physical gelator PVA is first incorporated onto alginate backbone by two steps. Then, the obtained alginate-*g*-PVA is physically cross-linked to form a novel anionic polyelectrolyte hydrogel. Its responsive behavior in various environments are examined and presented.

EXPERIMENTAL

Materials

Vinyl acetate (VAc, Sinopharm Chemical Reagent Co., China) was purified by distillation. Potassium persulphate (KSP) was purified by recrystallization from distilled water. Sodium alginate (SA, its weight molecular weight is ca. 33000, Wenzhou Chemical Agent Factory, China) was dried before use. Sodium hydroxide (NaOH), hydrochloric acid (HCl), ethanol, and methanol were all analytical grade reagents and used as received.

Synthesis of SA-*g*-PVA of various PVA%

Sodium alginate-*g*-poly(vinyl alcohol) (SAPVA) was prepared according to the literature[15] with some minor improvements. Briefly, 1.0 g SA was dissolved in 20 mL distilled water in a three-necked flask under stirring at 55°C. It was mixed with 7 mL ethanol to form a homogenous mixture. Nitrogen purging for 10 min was carried out to remove the dissolved oxygen from the mixture. A predetermined amount of KSP was added and allowed to react with alginate for 15 min. Subsequently, a certain volume of VAc was added in drops at the speed of one drop every 3 s. The mixture was allowed to react for another 6 h. The crude product was separated from solution after cooling down the reaction mixture in an ice/water bath. It was washed with distilled water, dried, and then extracted with ethanol for 24 h. The dried white product was pure SA-*g*-polyvinyl acetate (PVAc). As SA is undissolvable in ethanol, the graft percentage of PVAc was calculated as $G\% = (W_1 - W_0)/W_0 \times 100$, where W_0 and W_1 were the weight of SA and SA-*g*-PVAc, respectively.

SAPVA was derived from alcoholysis of SA-*g*-PVAc. SA-*g*-PVAc powder and 3% NaOH/methanol solution were mixed at the ratio of 1 : 10 (wt/v) and kept at 55°C with agitating for 6 h. The product, that is, SAPVA, was filtered and dried to constant weight. The PVA content of SAPVA (PVA%) equaled approximately to *G*% of PVAc.

Formation of SAPVA hydrogels

One gram of SAPVA samples of various PVA% was dissolved in 10 mL distilled water and poured into moulds, respectively. Then, they were subjected to three repeated freezing/thawing cycles, 16 h at −16°C and 4 h at ambient temperature. The obtained hydrogels were dried under vacuum at 37°C to constant weight. To measure the gel content of SAPVA hydrogels, the samples were kept in distilled water at 37°C for 12 h. The gel percentage was calculated as $\text{gel}\% = W_r/W_o \times 100$, where W_r and W_o were the weight of the original dried SAPVA hydrogel samples and the remained, respectively.

Characterization of SAPVA and its precursor

Powdered SA, purified SA-*g*-PVAc, and SAPVA of 31.4% PVA were mixed with dry KBr and compressed into disk, respectively. Then, Fourier transform infrared (FTIR) spectra of the samples were recorded using a Nexus 470 FTIR spectrophotometer. As SAPVA of 31.4% PVA was easily to be powdered, it was used for characterization.

X-ray diffraction (XRD) profiles of SA-*g*-PVAc, SAPVA of 31.4% PVA, and the dried hydrogel powder were collected with a Bruker D8-Advanced diffractometer using Nickel-filtered Cu Kα radiation ($\lambda = 0.15406$ nm) and scanned from 2° to 60° at a scan speed of 4°/min, respectively. The crystallinity of samples could be calculated as the ratio of the intensity of sharp peaks to the total intensity.

The Au-coated cross-section of SAPVA hydrogel was examined with a Hitachi S-3500N scanning electron microscope.

Electric- and pH-responsive behaviors of SAPVA hydrogels

The dried SAPVA hydrogels of different PVA% were weighed and placed in vials that contained HCl (0.1*M* and pH 1.0) and NaOH (0.1*M* and pH 13.0) aqueous solutions, respectively. Both the ionic strengths of two solutions were 0.1*M*. The samples were maintained in the solution, which was changed every hour to keep its pH value constant, at 25°C and removed at timed intervals, blotted up the surface liquid of the samples with soft paper, and weighed. This procedure was repeated until the weight of the samples became constant. The swelling ratio (SR) of the samples was calculated from the weight of sample at different time (W_t) and the

weight of the corresponding dried sample (W_d): SR = W_t/W_d. An average of triplicate measurements was taken.

The dried SAPVA hydrogel of 169% PVA was immersed in 0.1 mol/L NaCl aqueous solution in the presence or absence of electric field at room temperature. The electric field was generated by maintaining the electric current at DC 250 mA. SR of the samples was tested as earlier.

RESULTS AND DISCUSSION

Synthesis of SAPVA

Because the monomer VAc is undissolved in deionized water, ethanol is used as a co-solvent for the reaction system to enhance the graft copolymerization of the monomer onto sodium alginate. However, it is found that excess ethanol increases the amount of the homopolymer PVAc. The ratio of solvents adopt is ascertained through examining the effect of the volume of ethanol on *G*%. The proper temperature and the concentration of initiator are necessary for the reaction, which produce enough active centers on the SA chain to initiate graft copolymerization with VAc.[17,18] Although these factors can be used to adjust the *G*% of PVAc, the most effective strategy to greatly vary *G*% is changing the amount of monomer whilst keeping the others properly. Herein, the *G*% is simply controlled by varying the amount of VAc.

As the alcoholysis reaction of SA-*g*-PVAc is mostly the conversion of the side groups,[19] PVA% of SAPVA is simply regarded as the *G*% of SA-*g*-PVAc. Therefore, the factors mentioned earlier are also effective to tailor the PVA% of SAPVA. In this work, SAPVA samples of different PVA% (31.4–230%) were obtained in this way. Because SA-*g*-PVAc is obtained via radical copolymerization, PVAc or PVA chains were randomly distributed on the backbone of alginate. In other words, the length of the side chains was unable to be controlled with *G*% or PVA%.

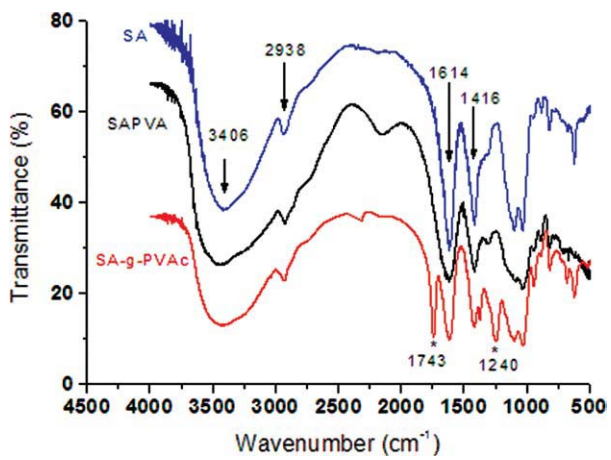

Figure 1 FTIR spectra of sodium alginate (SA), the graft copolymer SA-*g*-PVAc, and its derivative SA-*g*-PVA (SAPVA, 31.4% PVA). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

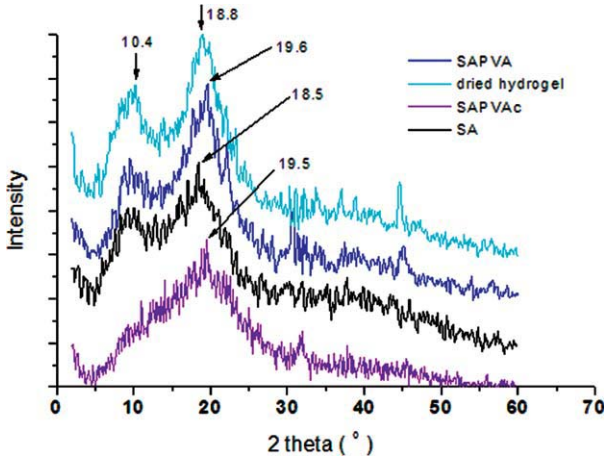

Figure 2 XRD profiles of sodium alginate-*g*-PVAc, sodium alginate-*g*-PVA (SAPVA, 31.4% PVA), and dried SAPVA hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Characterization of SA-*g*-PVAc and SAPVA

The structure of the graft copolymers is confirmed with FTIR. Figure 1 shows the FTIR spectra of SA, purified SA-*g*-PVAc, and SAPVA. On the FTIR spectra of SA, the characteristic peaks of hydroxyl group and C—H bonds exhibit at 3413 and 2938 cm^{-1}, respectively. The bands showed at 1614 and 1416 cm^{-1} are attributed to the absorption of carboxyl group on SA chain. Compared to the spectra of SA, a couple of additional characteristic peaks appear at 1743 and 1240 cm^{-1} on the FTIR spectra of the purified graft copolymer of SA and VAc, and they are attributed to the absorption of carbonyl group and ester group, respectively. This suggests that the product is SA-*g*-PVAc.[16] The spectra of the derivative of SA-*g*-PVAc do not show the absorption band around 1743 cm^{-1}, which indicates that SA-*g*-PVAc has been converted into SAPVA completely. The XRD analysis results show that the peak of SA-*g*-PVAc is wider than that of SA, which also indicates that PVAc is successfully grafted onto the backbone of SA (Fig. 2).

The difference between XRD profiles of SA-*g*-PVAc and SAPVA is evident. Three peaks appear around 10.4°, 18.8°, and 19.6° on the XRD pattern of SAPVA, whereas only one peak exhibits at 19.5° on that of SA-*g*-PVAc. In addition, the peaks of SAPVA are much sharper than that of SA-*g*-PVAc, which suggests that the crystallinity of SAPVA is higher than that of its precursor. Because PVA and PVAc

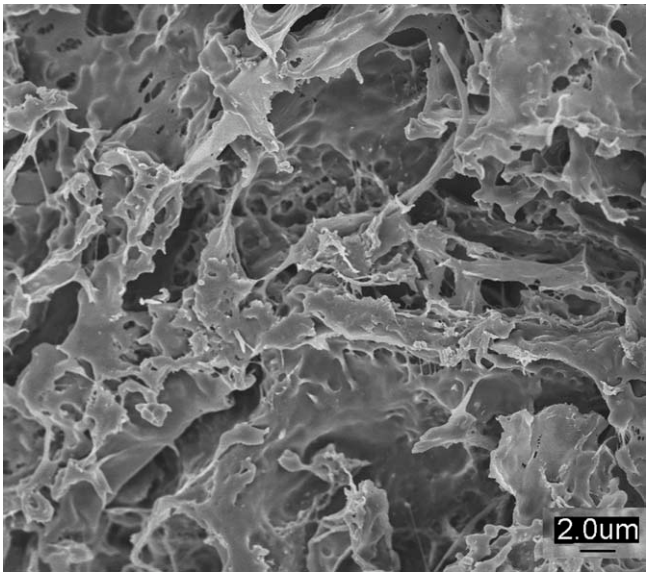

Figure 3 SEM images of the cross-section of fresh sodium alginate-*g*-PVA hydrogel (100% PVA).

are semicrystalline and amorphous, respectively, the crystallization capability of SAPVA is surely higher than that of SA-*g*-PVAc. XRD analysis results demonstrate that the alcoholysis of SA-*g*-PVAc is complete once more.

Dual-responsive behavior of SAPVA hydrogel

The XRD pattern of dried SAPVA hydrogel is similar to that of SAPVA (Fig. 2), which indicates that the hydrogel is also semicrystalline. The crystallinity of the samples can be calculated from the profiles[16] and approximate to 15.1% for SAPVA and 16.8% for the dried hydrogel, respectively, that is the crystallinity of dried SAPVA hydrogel is a little higher than that of SAPVA. According to the literature, the junction points of the PVA hydrogel formed by freezing/thawing technique are mainly the crystalline domains of PVA.[20] The XRD analysis results are consistent with this statement and confirm the idea of incorporating PVA onto SA to play as a gelator is convincible.

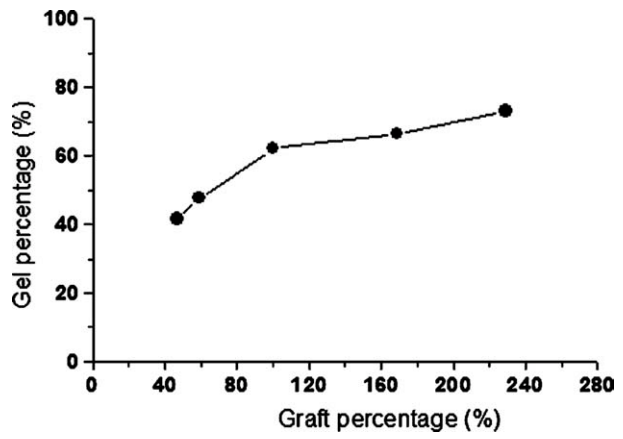

Figure 4 The effect of PVA% on gel content of sodium alginate-*g*-PVA hydrogels.

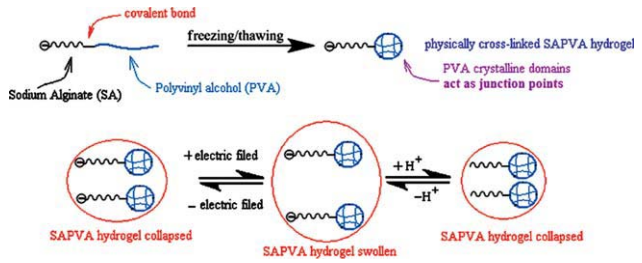

Figure 5 Formation and responsive behavior of sodium alginate-*g*-PVA hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

SAPVA hydrogel is readily to be formed in such a mild physical way. Because SA and PVA are conjugated by chemical bonds, no macroscopical phase separation is found (Fig. 3). The gel content of SAPVA hydrogel depends on the PVA%. The gel% of the hydrogel of 230% PVA is about 73% (Fig. 4). SAPVA is water-soluble, and it can form Ca-SAPVA hydrogel with calcium ions as well. It is able to be observed directly that the strength of SAPVA hydrogel obtained via freezing/thawing is higher than that of Ca-SAPVA. Moreover, the strength of SAPVA hydrogel will be enhanced by further cross-linking with calcium ions. It is true that the hydrogel contains both SA and PVA can be prepared by blending two components and subjecting to freeze/thaw cycles,[21] but it is not as stable as SAPVA hydrogel when the hydrogel contacts with multivalent ions. After immersing the samples in 0.5*M* $CaCl_2$ solution for 24 h, it is found that the weight of SA/PVA hydrogel (40 : 60, wt/wt) and SAPVA hydrogel of 60% PVA loses $\sim$ 11.7% and increases about 14.1%, respectively. The interaction between two components of the blend is physical, and it is difficult to prevent some of SA from being eroded with calcium ions in the solution, whilst the covalent combination of PVA and alginate protect SAPVA hydrogel well.

SAPVA consists of SA and PVA. Therefore, it is surely a polyelectrolyte. The carboxyl groups of SAPVA are capable of behaving reversible protonation and deprotonation. Thus, the SA segments will endow the hydrogel with pH- and electrical-sensitivity. On the other hand, PVA network is inert to the stimuli and stable enough to keep the hydrogel from disintegrating. Thus, such a network can guarantee the hydrogel stable enough and the alginate segments to behave reversible stimuli–response again and again (Fig. 5).

As expected, the pH-dependent swelling behaviors of SAPVA hydrogels containing different PVA%

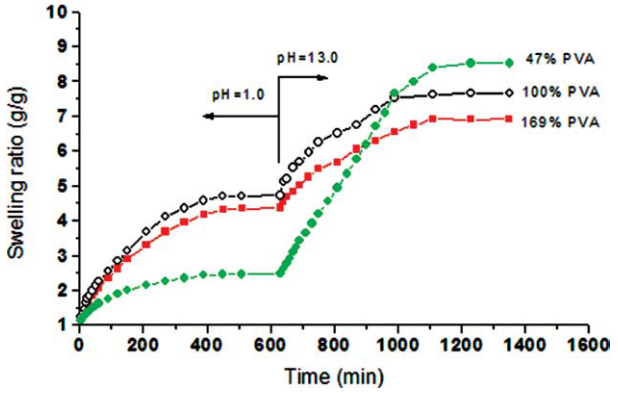

Figure 6 The effect of pH and PVA% on the swelling behavior of sodium alginate-*g*-PVA hydrogels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

are observed (Fig. 6). The dried hydrogels swell in the acidic solution to reach the equilibrium, and then they continue to swell after being transferred into a medium of higher pH. In addition, the SRs of the hydrogels are affected with PVA%. The higher PVA% of the SAPVA hydrogel, the fewer carboxyl groups existed in the hydrogel and the weaker the electrostatic repulsion is. Moreover, PVA segment of SAPVA is crystalline. Its capacity of absorbing water is poorer than that of SA segment. As a result, the SRs of the hydrogels decrease with increasing PVA%, and the pH-sensitivity of the hydrogel is enhanced as PVA% is decreased. To demonstrate its reversibility, the dried SAPVA hydrogel has been immersed in the solution of pH 1.0 to reach the equilibrium swelling, and then it is transferred into the solution of pH 13 and 1.0 subsequently. It is found that the SR decreases gradually when the sample is placed in a more acidic medium and increases again as it is surrounded in a higher pH environment (Fig. 7).

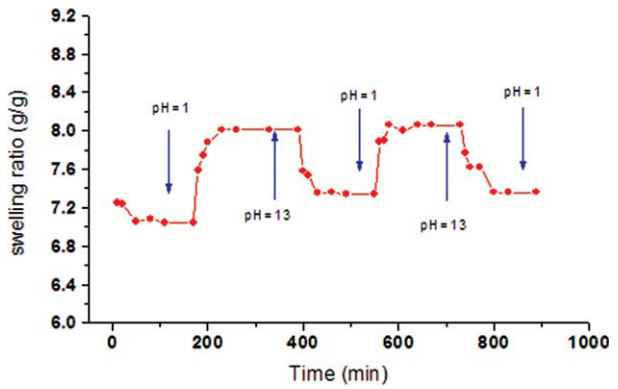

Figure 7 The reversible swelling behavior of sodium alginate-*g*-PVA hydrogel of 100% PVA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

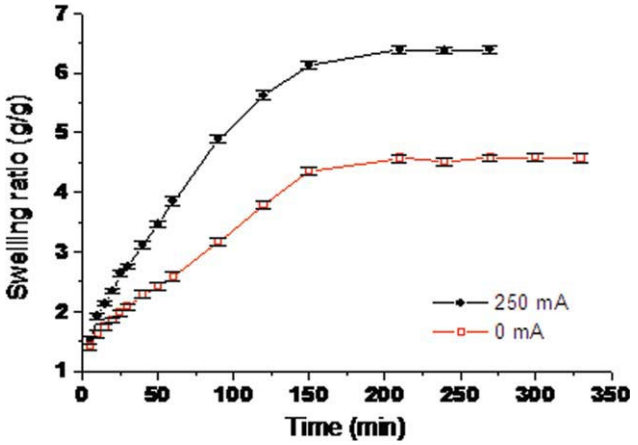

Figure 8 The swelling behavior of sodium alginate-*g*-PVA hydrogel with or without electric field. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Higher PVA% provides a SAPVA hydrogel higher strength, which is convenient to prepare sample for examining its electric response. The mechanical strength of the hydrogel that contains 169% PVA is enough and is used for this purpose. The swelling behavior of the hydrogel in the presence of electric field is quite different from that in the absence of electric field (Fig. 8). Both the swelling rate and equilibrium SR in the presence of the electric field are higher than those without applying electric field. The slopes of the initial linear part of two curves are 0.0351 and 0.01964 (min^{-1}) for 250 and 0 mA, respectively, and the equilibrium SRs of the sample at 250 and 0 mA are 6.43 and 4.59, respectively. As SAPVA hydrogel is a polyelectrolyte, even a weak electric field generated by 250 mA, electric current can drive Na^+ to transform toward the negative electrode and the dissociation of carboxyl groups is consequently enhanced. As a result, both the swelling rate and SR of hydrogel are improved.

CONCLUSIONS

A successful combination of physical gelator PVA and ionizable biopolyelectrolyte SA is performed by facile reactions including radical copolymerization and alcoholysis. Subsequently, the physically cross-linked SAPVA hydrogels are prepared via simple and mild freezing-thawing technique. SAPVA hydrogels exhibit dual stimuli including pH- and electrical-responsive swelling behaviors. The pH-sensitivity of the hydrogel is able to be modulated with PVA%, which can be implemented by simply varying the amount of monomer.

SAPVA hydrogel composes of biocompatible and biodegradable components. Particularly, this hydrogel is able to retain its integrity when it is contacted

with electrolyte solutions that contain multivalent ions. In other words, its stability is superior to usual SA-based hydrogels such as calcium alginate or alginate/PVA blend ones. This enables the hydrogel to be a really reversible stimuli-responsive matrix. Thus, SAPVA hydrogel may find potential applications in controlled drug delivery and other fields after investigating its biocompability, biodegradability, and so on.

References

1. Hoffman, A. S. Adv Drug Deliv Rev 2002, 43, 3.
2. Drury, J. L.; Mooney, D. J. Biomaterials 2003, 24, 4337.
3. Lin, C.-C.; Metters, A. T. Adv Drug Deliv Rev 2006, 58, 1379.
4. Dai, S.; Ravi, P.; Tam, K. C. Soft Matter 2009, 5, 2513.
5. Bajpai, A. K.; Shukla, S. K.; Bhanu, S.; Kankane, S. Prog Polym Sci 2008, 33, 1088.
6. Gu, F.; Amsden, B.; Neufeld, R. J Control Release 2004, 96, 463.
7. Gopishetty, V.; Roiter, Y.; Tokarev, I.; Minko, S. Adv Mater 2008, 20, 4588.
8. Lin, Y.-H.; Liang, H.-F.; Chung, C.-K.; Chen, M.-C.; Sung, H.-W. Biomaterials 2005, 26, 2105.
9. Malafay, P. B.; Silva, G. A.; Reis, R. L. Adv Drug Deliv Rev 2007, 59, 207.
10. Jeon, O.; Bouhadir, K. H.; Mansour, J. M.; Alsberg, E. Biomaterials 2009, 30, 2724.
11. Masci, G.; Husu, I.; Murtas, S.; Piozzi, A.; Crescenzi, V. Macromol Biosci 2003, 3, 455.
12. Lozinsky, V. I.; Galaev, I. Y.; Plieva, F. M.; Savina, I. N.; Jungvid, H.; Mattiasson, B. Trends Biotechnol 2003, 21, 445.
13. Hassan, C. M.; Peppas, N. A. Adv Polym Sci 2000, 153, 37.
14. Ricciardi, R.; D'Errico, G.; Auriemma, F.; Ducouret, G.; Tedeschi, A. M.; De Rosa, C.; Lauprêtre, F.; Lafuma, F. Macromolecules 2005, 38, 6629.
15. Xiao, C. M.; Yang, M. L. Carbohydr Polym 2006, 64, 37.
16. Xiao, C. M. Gao, F.; Gao, Y. K. J Appl Polym Sci 2010, 117, 2946.
17. Shah, S. B.; Patel, C. P.; Trivedi, H. C. J Appl Polym Sci 1994, 52, 857.
18. Xiao, C. M.; Zhou, L. C. Chin J Polym Sci 2004, 22, 271.
19. Fanta, G. F.; Burr, R. C.; Doane, W. M.; Russell, C. R. J Appl Polym Sci 1979, 23, 229.
20. Yokoyama, F.; Masada, I.; Shimamura, K.; Ikawa, T.; Monobe, K. Colloid Polym Sci 1986, 264, 595.
21. Hua, S. B.; Ma, H. Z.; Li, X.; Yang, H. X.; Wang, A. Q. Int Biol Macromol 2010, 46, 517.