ELSEVIER

Polymer 43 (2002) 4823–4827

polymer

www.elsevier.com/locate/polymer

Polymer Communication

Synthesis and properties of thermosensitive, crown ether incorporated poly(*N*-isopropylacrylamide) hydrogel

Xian-Zheng Zhang[a,b,*], Jian-Tao Zhang[a], Ren-Xi Zhuo[a,*], Chih-Chang Chu[b]

[a]*Key Laboratory of Biomedical Polymers (LBMP) of the Ministry of Education, Department of Chemistry, Wuhan University, Wuhan 430072, People's Republic of China*
[b]*Department of Textiles and Apparel and Biomedical Engineering Program, Cornell University, Ithaca, NY 14853-4401, USA*

Received 14 September 2001; received in revised form 24 April 2002; accepted 26 April 2002

Abstract

A crown ether derivative (4′-allyldibenzo-18-crown-6, CE) was covalently incorporated into the network of temperature sensitive poly(*N*-isopropylacrylamide) (PNIPA) hydrogels by copolymerization in a mixed solvent of water and tetrahydrofuran (H_2O/THF). The poly(*N*-isopropylacrylamide-*co*-4′-allyldibenzo-18-crown-6) (poly(NIPA-*co*-CE)) hydrogels exhibited dramatically faster deswelling rates than normal PNIPA hydrogels at a temperature (50 °C) above their lower critical solution temperatures. The effect of the solvent component ratio in the mixed solvent during the copolymerization on the swelling properties of the poly(NIPA-*co*-CE) hydrogel was investigated. The thermosensitive poly(NIPA-*co*-CE) hydrogels have potential applications in the extraction of cations and separation of chiral drugs. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: *N*-isopropylacrylamide; Crown ether; Temperature sensitive hydrogel

1. Introduction

Intelligent hydrogels can change their volumes abruptly in response to the changes of the external environmental factors, such as temperature [1], pH [2], photofield [3], and antigen [4], etc. Because of their intelligent nature, these hydrogels have attracted increasing interest and considerable research attention in recent years [5–10]. Poly(*N*-isopropylacrylamide) (PNIPA) is a typical thermosensitive polymeric material and demonstrates a transition temperature (T_{tr}) or lower critical solution temperature (LCST) at ~32 °C in aqueous solution [11]. This temperature sensitive polymer can be crosslinked to produce an insoluble, but swellable hydrogel through redox radical polymerization [12–14]. This three-dimensional PNIPA network undergoes phase separation as the external temperature cycles across its LCST (~33 °C) [15]. Below this temperature, the PNIPA hydrogel absorbs a lot of water in its network, and thus exhibits a swollen state. But its swollen state collapses and displays an abrupt reduction in volume as the temperature is increased above its LCST. This process of phase separation is thermoreversible.

Due to their unique properties, PNIPA hydrogels have been widely used in many fields [16–19]. For example, a PNIPA hydrogel has been used to recognize and capture a target molecule [20]. By incorporating a crown ether into the temperature sensitive PNIPA network, we speculated that PNIPA hydrogel could be used to extract cations owing to the excellent ion-solvating capability of crown ethers [21–23]. Furthermore, one of the important applications of crown ethers is in enantiomeric separation in the pharmaceutical industry [24–26]. Huang et al. showed that the addition of a crown ether for cyclodextrin-based separation also could promote enantiomeric separations [27–29]. Based on above considerations, we wish to synthesize a new hydrogel, which can combine the temperature sensitive

---

Abbreviations: LCST, lower critical solution temperature; T_{tr}, phase transition temperature; NIPA, *N*-isopropylacrylamide; CE, 4′-allyldibenzo-18-crown-6; BIS, *N*,*N*′-methylenebisacrylamide; APS, ammonium persulfate; TEMED, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; THF, tetrahydrofuran; CG, poly(*N*-isopropylacrylamide-*co*-4′-allyldibenzo-18-crown-6) hydrogel or poly(NIPA-*co*-CE) hydrogel; CG–$X_{y/z}$, X, content of the crown ether in the poly(NIPA-*co*-CE) hydrogel, *y*/*z*, the volume ratio of water to tetrahydrofuran (H_2O/THF = *y*/*z*) of the mixed solvent during the copolymerization process.

[*] Corresponding authors. Address: Key Laboratory of Biomedical Polymers (LBMP) of the Ministry of Education, Department of Chemistry, Wuhan University, Wuhan 430072, People's Republic of China. Tel.: +86-27-8764-8509; fax: +86-27-8764-8509.

E-mail addresses: xz59@cornell.edu (X.Z. Zhang), bmplab@public.wh.hb.cn (R.X. Zhuo).

0032-3861/01/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0032-3861(02)00299-9

properties of PNIPA with the excellent capability of selective separation via a crown ether. However, from the standpoint of applications, the kinetics of volume changes of normal PNIPA hydrogels are found unsatisfactory and a long time is needed for a phase separation to occur. In order to improve the response rates of PNIPA hydrogels, several strategies have been proposed in this regard [30–36]. Recently, Yamaguchi et al. reported the fast responsive, molecular recognition ion gating membrane by using the temperature sensitive PNIPA linear polymer with a pendant crown ether as the receptor [37]. However, this method requires the use of a porous substrate, and the grafted polymer was formed inside the porous substrate through plasma-graft polymerization [38,39]. The fast sensing and high gating properties observed were attributed to the nature of the linear PNIPA chains grafted in the membrane.

Here, a new temperature sensitive poly(*N*-isopropylacrylamide-*co*-4′-allyldibenzo-18-crown-6) (poly(NIPA-*co*-CE)) hydrogel was prepared by copolymerization/crosslinking in a mixed solvent of water and tetrahydrofuran (H_2O/THF). This poly(NIPA-*co*-CE) hydrogel exhibited much faster deswelling rate than that of a normal PNIPA hydrogel when the temperature was raised above the LCST, and the effect of the solvent component ratio in the mixed solvent during the copolymerization process on the swelling properties of the poly(NIPA-*co*-CE) hydrogel was further investigated.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPA) was synthesized and purified according to Ref. [19]. 4′-Allyldibenzo-18-crown-6 (CE) was kindly provided by Dr Gong SL (Chemistry Department, Wuhan University, Wuhan 430072, People's Republic of China) and used as received. *N*,*N*′-methylene-bisacrylamide (BIS), ammonium persulfate (APS), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) and tetrahydrofuran (THF) were analytical grade and used without further purifications.

2.2. Synthesis of hydrogels

For the synthesis of poly(NIPA-*co*-CE) hydrogels, NIPA and CE were dissolved in 1.2 ml mixed solvent (H_2O/THF) in existence of a crosslinker (BIS). APS and TEMED were used as redox initiators. Polymerization was carried out at 25 °C for 6 h and then the hydrogels obtained were cut into discs (10 mm in diameter and 2.0 mm in thickness) for the measurement of swelling properties. Before the measurement, discs samples were immersed into distilled water at 25 °C for 48 h and the water was replaced with fresh water every several hours in order to leach out the unreacted chemicals. The feed composition for preparation of crown ether bonded PNIPA hydrogels is listed in Table 1.

Table 1
Feed composition of the thermosensitive poly(*N*-isopropylacrylamide-*co*-4′-allyldibenzo-18-crown-6) hydrogels (CG), using the mixed solvent (H_2O/THF = 1:1 in volume)

Component	Sample ID			
	CG-$I_{1:1}$	CG-$II_{1:1}$	CG-$III_{1:1}$	CG-$IV_{1:1}$
NIPA (mg)	100	100	100	100
CE (mg)	1	2	3	4
BIS (mg)	5	5	5	5
5 wt% APS (ul)	50	50	50	50
TEMED (ul)	20	20	20	20

As the volume ratio of H_2O to THF in the mixed solvent was changed into 1.4:1 or 2:1, the hydrogel sample ID was changed to be CG-$I_{1.4:1}$, CG-$II_{1.4:1}$, CG-$III_{1.4:1}$, CG-$IV_{1.4:1}$ or CG-$I_{2:1}$, CG-$II_{2:1}$, CG-$III_{2:1}$, CG-$IV_{2:1}$, respectively.

2.3. FT-IR measurement

The FT-IR analyses of hydrogel samples were measured on Nicolet 170SX FT-IR spectrophotometer. The FT-IR samples were prepared by immersing hydrogels into distilled water at 50 °C for 2 h and then further dried in vacuum for 48 h.

2.4. Measurement of swelling ratio of hydrogels

Swelling ratios (SRs) of hydrogel samples were determined by immersing dry and known weight hydrogel samples into distilled water at each predetermined temperature for at least 24 h, removing from the water and wiping off excess water on the surfaces of hydrogel samples with moistened filter papers. The wet weight of the hydrogel sample was measured by a balance at room temperature. SR is calculated from the following formula:

$$\mathrm{SR} = W_\mathrm{s}/W_\mathrm{d} \tag{1}$$

where W_s is the weight of water in a swollen hydrogel (wet weight − dry weight) at each predetermined temperature, and W_d the dry weight of hydrogel.

2.5. Measurement of deswelling kinetics of hydrogels

The deswelling kinetics of hydrogel samples were measured gravimetrically in terms of water retention (WR) at 50 °C after wiping off the excess water on the surfaces of the hydrogel samples with moistened filter papers. Before the deswelling studies, hydrogel samples were allowed to reach equilibrium in distilled water at 15 °C, and then transferred to the hot water (50 °C). Weight changes of hydrogel samples were recorded during the shrinking period at regular time intervals. WR is defined as

$$\mathrm{WR} = 100(W_t - W_\mathrm{d})/W_\mathrm{s} \tag{2}$$

where W_t is the wet weight of hydrogel at regular time intervals and the other symbols are the same as defined earlier.

3. Results and discussion

The synthesis of crown ether incorporated, temperature sensitive poly(NIPA-*co*-CE) hydrogels is schematically shown in Fig. 1. It is well known that due to the steric hindrance of the large ring structure in a crown ether, especially the 18-crown-6, the copolymerization of crown ether derivatives with other usual monomers is a very difficult task. Here, we succeed in incorporating a crown ether into the backbone of temperature sensitive hydrogels by the use of mixed solvent (H_2O/THF) during the copolymerization reaction. Based on the experiments, we found that an obvious hindrance of the CE on the synthesis of poly(NIPA-*co*-CE) hydrogels occurred if the CE content was too high. For example, if the crown ether content reached a certain level (8.0 wt% or above based on the NIPA) in the same mixed solvent, the three-dimensional structure of a desired hydrogel will not form.

We also found that a variation of the ratio of the mixed solvent components (H_2O/THF) had a profound impact on the hydrogel formation rate. When the volume ratio of H_2O to THF was 2:1 in the mixed solvent, the hydrogel appeared within 1 min, and as this ratio changed to 1.4:1, the hydrogel appeared within 3 min. When the volume content of H_2O decreased to be comparable of THF content ($H_2O/THF = 1:1$), the formation of hydrogel required at least 8 min. If the H_2O volume content was only half of the THF volume content in the mixed solvent ($H_2O/THF = 1:2$), the expected poly(NIPA-*co*-CE) hydrogel did not form even after a long time (20 h), although some soft hydrogel pieces in the mixed solvent appeared. It was noted that all the hydrogels synthesized in this mixed solvent are opaque.

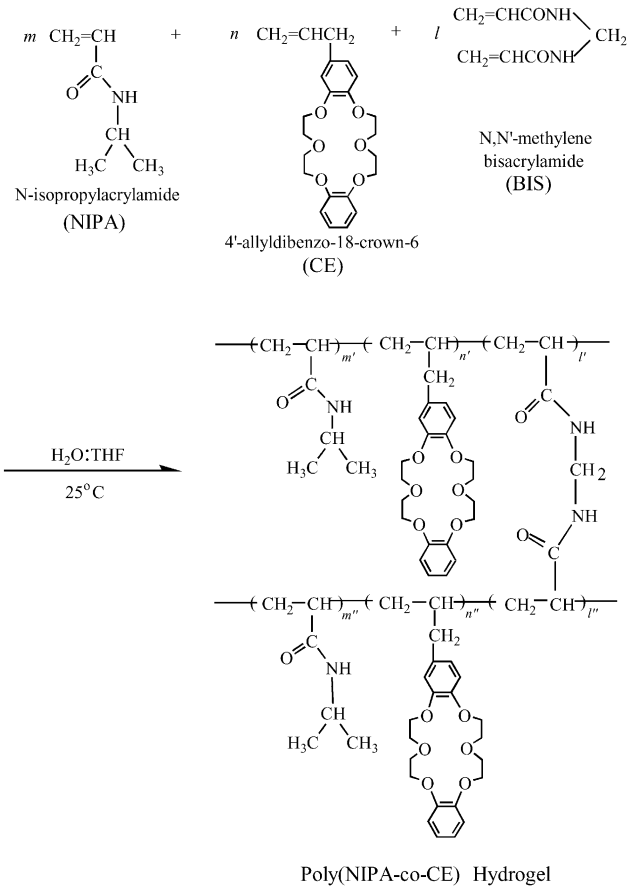

Fig. 1. The synthetic scheme of poly(NIPA-*co*-CE) hydrogels.

The FT-IR spectra of poly(NIPA-*co*-CE) hydrogel samples (CG-$I_{1:1}$, CG-$II_{1:1}$, CG-$III_{1:1}$, CG-$IV_{1:1}$) are showed in Fig. 2. We found that the FT-IR spectra of all the hydrogel samples were similar, although the spectrum of each hydrogel showed slight changes with different crown ether content. Every spectrum showed a broad band in the range of 3600–3200 cm^{-1}, which belongs to N–H stretching vibration of the PNIPA. The typical amide I band (A, ~1643 cm^{-1}), consisting of C=O stretch of PNIPA and amide II band (B, ~1534 cm^{-1}), including N–H vibration were evident in every spectrum. The existence of CE was evident by the presence of the typical band of unsymmetrical crown ether (C, ~1217 cm^{-1}), consisting of C–O–C stretch, although this band was weak due to the low CE content in hydrogels. The peak intensity at ~1217 cm^{-1} increased gradually from CG-$I_{1:1}$ to CG-$IV_{1:1}$, which confirmed that the crown ether content increased from CG-$I_{1:1}$ to CG-$IV_{1:1}$.

Fig. 3 shows the equilibrium SRs of poly(NIPA-*co*-CE) hydrogels (CG-$I_{1:1}$, CG-$II_{1:1}$, CG-$III_{1:1}$, CG-$IV_{1:1}$) as a

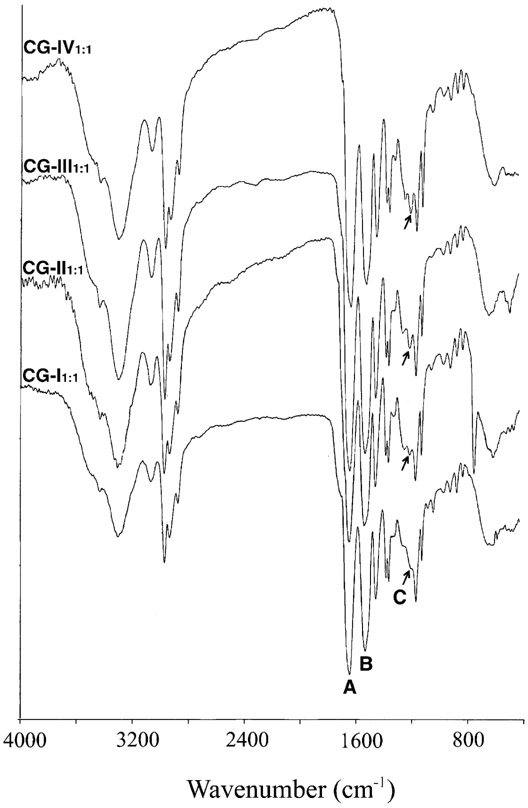

Fig. 2. FT-IR spectra of poly(NIPA-*co*-CE) hydrogels (CG-$I_{1:1}$, CG-$II_{1:1}$, CG-$III_{1:1}$, CG-$IV_{1:1}$) (A: ~1643 cm^{-1}, B: ~1534 cm^{-1}, C: ~1217 cm^{-1}).

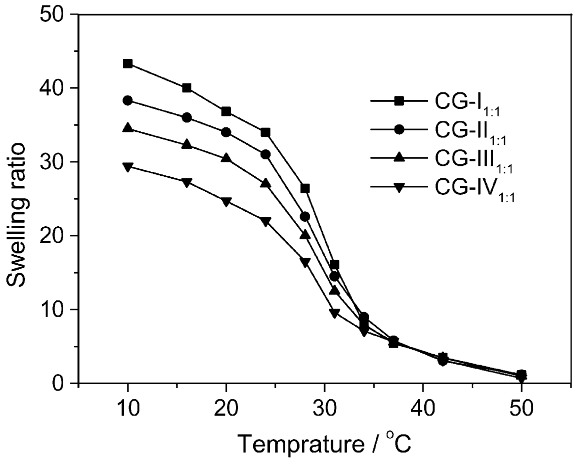

Fig. 3. Temperature dependence of equilibrium SR of poly(NIPA-*co*-CE) hydrogels (CG-$I_{1:1}$, CG-$II_{1:1}$, CG-$III_{1:1}$, CG-$IV_{1:1}$) at the temperature range from 10 to 50 °C.

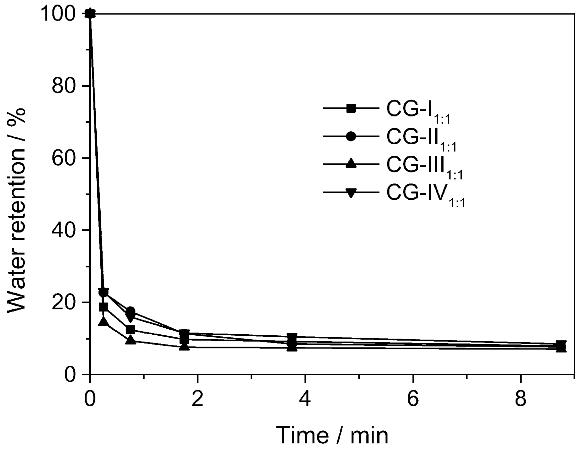

Fig. 4. Deswelling kinetics of poly(NIPA-*co*-CE) hydrogels (CG-$I_{1:1}$, CG-$II_{1:1}$, CG-$III_{1:1}$, CG-$IV_{1:1}$), measured gravimetrically at 50 °C from the equilibrated swelling condition at 15 °C in distilled water.

function of the external temperature in distilled water. The data show that these CE containing hydrogels absorbed water and became swollen at low temperatures. As the temperature increased, hydrogels lost water and shrank in volume. When the temperature increased above the hydrogels' LCSTs, the SRs of hydrogels decreased rapidly and a phase separation occurred. The level of the CE content in poly(NIPA-*co*-CE) hydrogels also exerted an effect on their SRs; at a low temperature, the SRs of hydrogels decreased (from CG-$I_{1:1}$ to CG-$IV_{1:1}$) as the content of the crown ether increased in a corresponding hydrogel network, which is attributed to the increasing hydrophobic nature of the crown ether.

The de-swelling kinetics (the change of water content with time) of poly(NIPA-*co*-CE) hydrogels (CG-$I_{1:1}$, CG-$I_{1:1}$, CG-$I_{1:1}$ and CG-$I_{1:1}$) at a temperature (50 °C) above the LCST are showed in Fig. 4. The most important observation is an unusually fast deswelling/shrinking rate. All the hydrogels lost more than 80% of their original water contents within 1 min and quickly reached their stable WRs within 4 min, compared to even more than a month to reach its stable WR with a normal PNIPA hydrogel [32].

This unusually fast response rate of poly(NIPA-*co*-CE) hydrogels is attributed to the heterogeneous network structure produced in the mixed solvent during copolymerization [40–42]. Briefly, PNIPA chains collapse in the mixture of two solvents, even though each solvent in the mixture is a good solvent to the PNIPA chains. During the polymerization in a mixed solvent, growing polymer chains become insoluble and collapse together. Thus, the reaction in this study was actually carried out in a two-phase reaction system, which would lead to a heterogeneous network structure of the final hydrogel. The opaque appearance of the poly(NIPA-*co*-CE) hydrogels also suggests their heterogeneous structures. Since the heterogeneous structure can provide lots of connective water channels and the excluded water can diffuse out of the hydrogel timely and quickly [30,31], these PNIPA-based hydrogels would exhibit fast deswelling rates at a temperature above its phase transition temperature.

We further studied the effect of the solvent component ratio in the mixed solvent on the swelling and deswelling properties of poly(NIPA-*co*-CE) hydrogels (CG-$II_{2:1}$, CG-$II_{1.4:1}$ and CG-$II_{1:1}$) (Figs. 5 and 6). The equilibrium SR of that hydrogel (CG-$II_{1:1}$), synthesized in the mixed solvent with the highest THF content (50 vol%) was the largest, while the hydrogel (CG-$II_{2:1}$) synthesized in the mixed solvent with the lowest THF content (33 vol%) was the smallest at temperatures below 30 °C (Fig. 5). In a mixed solvent having high contents of THF, the heterogeneous property of the produced polymer network becomes more profound and the hydrogel network is also enlarged correspondingly [33,36], which would result in a larger capacity to retain more water at a low temperature (below the LCST).

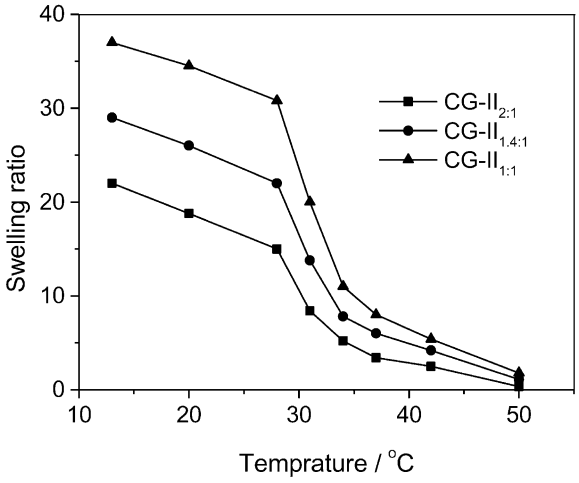

Fig. 5. Temperature dependence of equilibrium SR of poly(NIPA-*co*-CE) hydrogels (CG-$II_{2:1}$, CG-$II_{1.4:1}$, CG-$II_{1:1}$) at the temperature range from 10 to 50 °C.

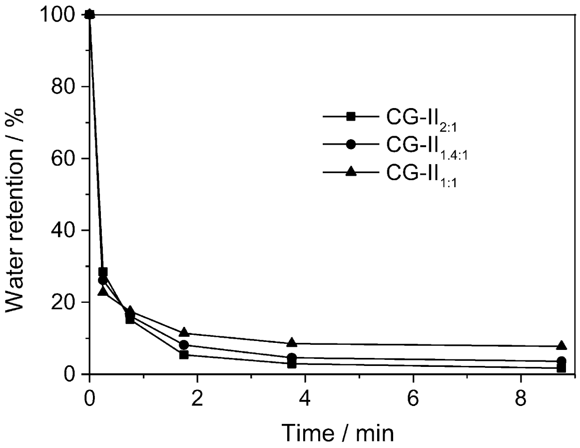

Fig. 6. Deswelling kinetics of poly(NIPA-*co*-CE) hydrogels (CG-II$_{2:1}$, CG-II$_{1.4:1}$, CG-II$_{1:1}$), measured gravimetrically at 50 °C from the equilibrated swelling condition at 15 °C in distilled water.

For the same reason, the deswelling rate of poly(NIPA-*co*-CE) hydrogels synthesized in the mixed solvent with a higher content of THF would be expected to be faster and Fig. 6 indicated that the deswelling rate of CG-II$_{1:1}$ was the fastest as evident. The deswelling rate profiles in Fig. 6 shows that the deswelling rate of CG-II$_{1:1}$ was the fastest in the first 15 s and then reached a stable WR the earliest. While the other two hydrogels (CG-II$_{1.4:1}$ and CG-II$_{2:1}$) reached their stable states relatively slower when comparing with the CG-II$_{1:1}$, although the disparity was not apparent.

4. Conclusions

By using a mixed solvent of H_2O and THF as the copolymerization solvent, a crown ether derivative was incorporated into the backbone of the PNIPA hydrogel. The ratio of the solvent components in the mixed solvent was critical for the feasibility of synthesizing poly(NIPA-*co*-CE) hydrogel networks. These crown ether incorporated PNIPA hydrogels showed dramatically fast deswelling rates and strong temperature-sensitivity as the external temperature increased above the phase transition temperature. This rapid response property might be attributed to a heterogeneous structure generated during the copolymerization in the mixed solvent. The thermosensitive poly(NIPA-*co*-CE) hydrogels have potential applications in the extraction of cations and separation of chiral drugs.

Acknowledgments

We thank the National Natural Science Foundation of China for the financial support. We are grateful to Dr Gong SL for kindly providing the crown ether.

References

[1] Chen GH, Hoffman AS. Nature 1995;373:49–52.
[2] Qu X, Wirsén A, Albertsson AC. Polymer 2000;41:4589–98.
[3] Suzuki A. Nature 1990;346:345–7.
[4] Miyata T, Asami N, Uragami T. Nature 1999;399:766–9.
[5] Sen M, Uzun C, Güven O. Int J Pharm 2000;203:149–57.
[6] Sun YM, Chen JP, Chu DH. J Biomed Mater Res 1999;45:125–32.
[7] Torres-Lugo M, Peppas NA. Macromolecules 1999;32:6646–51.
[8] Risbud MV, Hardikar AA, Bhat SV, Bhonde RR. J Control Rel 2000;68:23–30.
[9] Podual K, Doyle III FJ, Peppas NA. Polymer 2000;41:3975–83.
[10] Török G, Lebedev VT, Cser L, Zrinyi M. Physica B: Cond Mater 2000;276–278:396–7.
[11] Taylor LD, Cerankowski LD. J Polym Sci: Polym Chem Ed 1975;13:2551–69.
[12] Pekcan Ö, Kara S. Polymer 2000;41:8735–9.
[13] Oh JS, Kim JM, Lee KJ, Bae YC. Eur Polym J 1999;35:621–30.
[14] Wu S, Jorgensen JD, Skaja AD, Williams JP, Soucek MD. Prog Org Coating 1999;36:21–33.
[15] Hirokawa Y, Tanaka T. J Chem Phys 1984;81:6379–80.
[16] Hoi YJ, Yamaguchi T, Nakao S. Ind Engng Chem Res 2000;39:2491–5.
[17] Ichikawa H, Fukumori Y. J Control Rel 2000;63:107–19.
[18] Verrion B, Kim SW, Bae YH. J Biomed Mater Res 2000;51:69–79.
[19] Liu F, Tao GL, Zhuo RX. Polym J 1993;25:561–7.
[20] Oya T, Enoki T, Grosberg AY, Masamune S, Sakiyama T, Takeoka Y, Tanaka K, Wang G, Yilmaz Y, Feld MS, Dasari R, Tanaka T. Science 1999;286:1543–5.
[21] Agrawal YK, Shrivastav P, Menon SK. Sep Purif Technol 2000;20:177–83.
[22] Erk Ç, Göçmen A. Talanta 2000;53:137–40.
[23] Shoichi K, Fumiaki T, Yasuyuki T. Talanta 2000;51:637–44.
[24] Nishi H. J Chromatogr A 1996;735:57–76.
[25] Desiderio C, Fanali S. J Chromatogr A 1998;807:37–56.
[26] Peters EC, Lewandowski K, Petro M, Svec F, Fréchet JMJ. Anal Commun 1998;3:83–6.
[27] Huang WX, Xu H, Fazio SD, Vivilecchia RV. J Chromatogr B 1997;695:157–62.
[28] Huang WX, Fazio SD, Vivilecchia RV. J Chromatogr A 1997;781:129–37.
[29] Armstrong DW, Chang LW, Chang SSC. J Chromatogr A 1998;793:115–34.
[30] Kabra BG, Gehrke SH. Polym Commun 1991;32:322–3.
[31] Wu XS, Hoffman AS, Yager P. J Polym Sci, Part A: Polym Chem 1992;30:2121–9.
[32] Yoshida R, Uchida K, Kaneko Y, Sakai K, Kikuchi A, Sakurai Y, Okano T. Nature 1995;374:240–2.
[33] Kaneko Y, Nakamura S, Sakai K, Aoyaji T, Kikuchi A, Sakurai Y, Okano T. Macromolecules 1998;31:6099–105.
[34] Zhang XZ, Zhuo RX. Macromol Rapid Commun 1999;4:229–31.
[35] Zhang XZ, Zhuo RX. Macromol Chem Phys 1999;200:2602–5.
[36] Zhang XZ, Zhuo RX. Langmuir 2001;17:12–16.
[37] Yamaguchi T, Ito T, Sato T, Shinbo T, Nakao S. J Am Chem Soc 1999;121:4078–9.
[38] Yamaguchi T, Nakao S, Kimura S. Macromolecules 1991;24:5522–7.
[39] Yamaguchi T, Nakao S, Kimura S. J Polym Sci, Polym Chem Ed 1996;34:1203–8.
[40] Zhang G, Wu C. Phys Rev Lett 2001;86:822–5.
[41] Zhang XZ, Zhuo RX, Yang YY. Biomaterials 2002;23:1313–8.
[42] Zhang XZ, Yang YY, Chung TS. Langmuir 2002;18:2538–42.