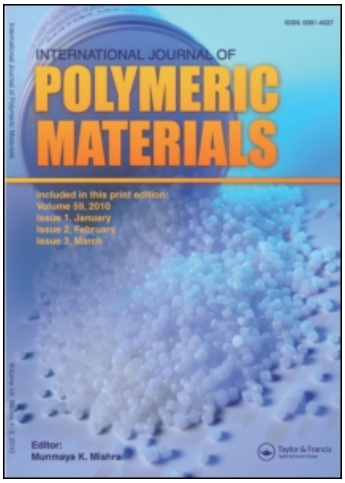

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Synthesis and Properties of Temperature-Sensitive Hydrogel Based on Hydroxyethyl Cellulose

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Synthesis and Properties of Temperature-Sensitive Hydrogel Based on Hydroxyethyl Cellulose

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Hydrogels were prepared from modified hydroxyethyl cellulose by copolymerization with N-isopropylacrylamide. The equilibrium swelling ratio of hydrogel was measured in buffer solution with pH 7.0 from 25.0 to 45.0°C and the data obtained showed that hydrogels exhibited temperature sensitivity. The results of DSC analysis revealed that the low critical solution temperature (LCST) of hydrogels was enhanced by the introduction of hydroxyethyl cellulose. SEM images suggested that the cross-section of freeze-dried hydrogels was porous. The data of adsorption and release experiments for two model drugs suggest that the controlled drug release can be achieved.

Keywords 2,4-toluene diisocyanate, hydrogel, hydroxyethyl cellulose, monoblock, N-isopropylacrylamide, temperature-sensitive

INTRODUCTION

Hydrogels, which can absorb a large amount of water while maintaining a distinct three-dimensional structure, have been applied in bioengineering, biomedicine, pharmaceuticals, agriculture, and many other fields [1,2]. Traditional hydrogels usually include copolymers of hydrophilic monomers (e.g., acrylic acid [3], acrylamide [4]). However, it is the considerable drawback

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that traditional hydrogels have difficulty in being degraded by organism. Hydrogels based on natural polymers, e.g., cellulose [5], starch [6], chitosan [7] and alginate [8], are currently of great interest because of their unique advantages of abundance, nontoxicity, biocompatibility, and biodegrability.

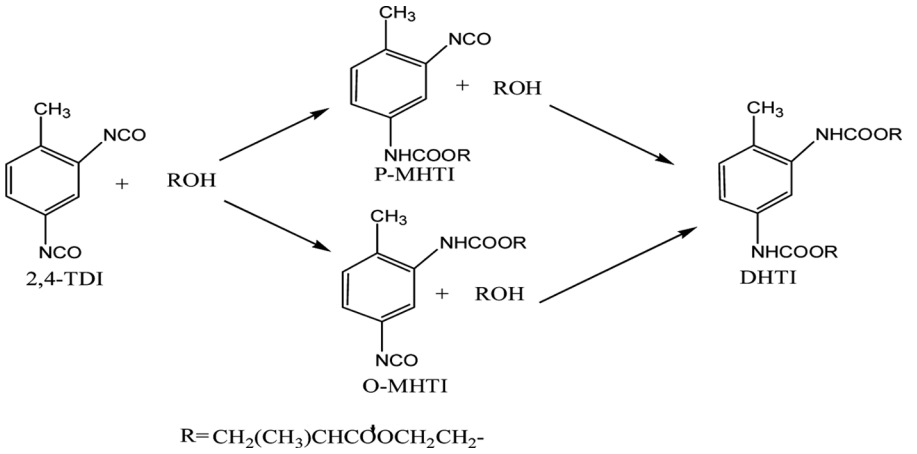
Cellulose is one of the most abundant natural polymers, which is usually used as the skeleton of the hydrogel owing to its excellent biocompatibility and biodegrability. Several methods, e.g., chemical crosslinking [9], graft copolymerization [10], and atom transfer radical polymerization [11], have been developed to prepare a cellulose-based hydrogel. Among these methods, graft copolymerization of vinyl monomers onto cellulose or its derivatives has been studied extensively, and is usually carried out by various chemical initiators or by irradiation. Li et al. [12] prepared temperature-sensitive hydrogel from hydroxylpropyl cellulose by copolymerization with N-isopropylacrylamide initiated by ceric ammonium nitrate. Ibrahim et al. [13] prepared superabsorbent hydrogels from carboxymethyl cellulose by copolymerization with acrylamide initiated by electron-beam irradiation. An alternative approach for graft reaction has been developed, which involves the introduction of carbon-carbon double bonds onto cellulose [14]. Vinyl monomers are readily grafted onto the vinyl derivatives of cellulose by solution polymerization. Trombino et al. [15] prepared hydrogel by copolymerization of cellulose acrylate and N,N-dimethylacrylamide. Esterification with acryloyl chloride and etherification with vinylbenzyl chloride are two main ways to introduce the unsaturated groups onto cellulose [14,16], where an excess of acryloyl chloride is consumed due to its volatility while a long reaction time is required due to the low reactivity of vinylbenzyl chloride. Thus, it is important to develop a new grafting monomer that is favorable to reduce the consumption of this grafting monomer and to accelerate the introduction of carbon-carbon double bonds onto cellulose.

In this study, a new grafting monomer for cellulose or its derivatives was synthesized by the mono-blocking reaction of 2,4-toluene diisocyanate (2,4-TDI) with 2-hydroxyethyl methacrylate (HEM). Hydroxyethyl cellulose (HEC) was modified with this new monomer. Hydrogels were prepared by copolymerization of modified hydroxyethyl cellulose and N-isopropylacrylamide. The swelling properties of the hydrogels, and the adsorption and release performances of the hydrogels for two model drugs were examined.

EXPERIMENTAL

Synthesis of Monoblocked TDI with HEM

2,4-Toluene diisocyanate (2,4-TDI) and 1,4-dioxane were mixed in a three-necked flask equipped with a stirrer, thermometer, reflux condenser, and a gas inlet. 2-Hydroxyethyl methacrylate (HEM) containing dibutyltin



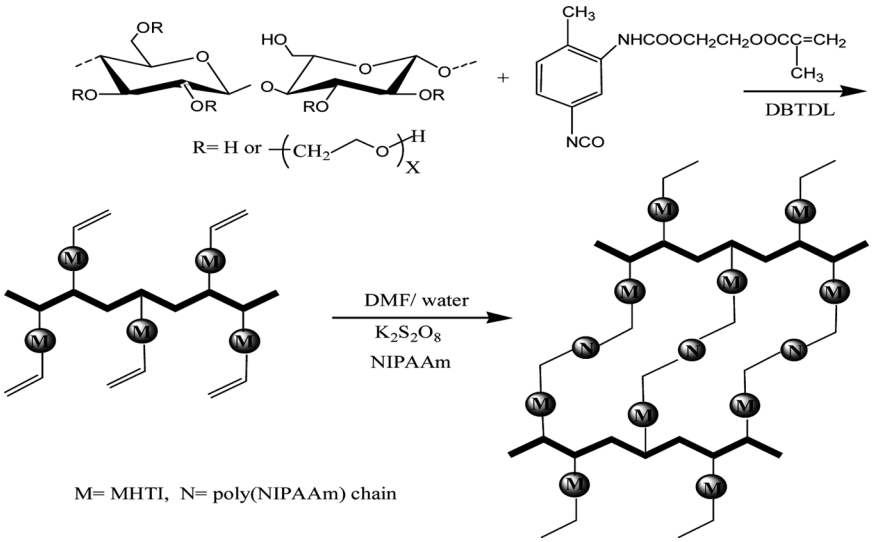
Scheme 1: Reaction of 2,4-TDI with HEM for the synthesis of HMTI.

dilaurate as a catalyst was added dropwise to the flask according to the molar ratio of n_{TDI}/n_{HEM}: 1:1.1. The reaction was carried out at 15°C for 1 h under a nitrogen atmosphere and then maintained at 20–30°C for 2 h. The reaction procedure is shown in Scheme 1. Petroleum ether was added to the reactor to precipitate the product after the reaction was finished. The blocked product was dissolved in methylbenzene and precipitated with cyclohexane for the removal of the unreacted TDI. Monoblocked diisocyanate (MHTI) was obtained.

Preparation of Hydrogels

The synthesis of hydrogel is shown in Scheme 2. 1 g of hydroxyethyl cellulose and 0.3 g of MHTI were dissolved in DMF, separately. Then, MHTI solution was added to HEC solution under stirring. The reaction was carried out at room temperature for 1 h. Then, the catalyst, dibutyltin dilaurate, was added into the flask, the flask was heated to 45°C and maintained for 2 h. After that, diethyl ether was added to the reactor to precipitate the product, and the precipitate was washed with diethyl ether to remove diblocked diisocyanate (DHTI) and unreacted monoblocked diisocyanate (MHTI). The modified hydroxyethyl cellulose (MHEC) was obtained after removing the ether by vacuum-drying at 40°C for 24 h.

Hydrogel was synthesized by copolymerization of MHEC and N-isopropylacrylamide (NIPPAm). MHEC and various amounts of NIPPAm were dissolved in DMF, then distilled water was added to the system with continuous stirring to form a 10% emulsion based on solid. The emulsion was transferred into a plastic test tube after potassium persulfate was added. The tube was sealed after nitrogen was bubbled to remove any residual oxygen.



Scheme 2: Synthesis of hydrogel.

The reaction was conducted at 60°C for 2 h. After the gelation was finished, the samples were taken out and cut into small pieces, then immersed in deionized water for a week to remove any unreacted components. The air-dried hydrogel was prepared by allowing the water to evaporate at room temperature for a week and then vacuum-dried at 40°C for 72 h. In this study, H1, H2, H3, H4, and H5 represent the hydrogels prepared with MHEC and various amounts of NIPPAm, respectively, where the number represents the mass ratio of NIPPAm to HEC.

Thermoresponse Properties of Hydrogels

Pre-weighed dried samples were immersed in a buffer solution of pH 6.86. The swelling ratios were measured from 20 to 45°C in temperature intervals of 4°C. The samples stood for 12 h at each temperature. The swollen samples were weighed after free water was wiped with filter paper. The swelling ratio, SR, was used to evaluate the swelling performance of the hydrogels at different temperatures. SR is defined as follows:

$$SR = (W_t - W_d)/W_d,$$

where W_t represents the weight of the swollen sample at specified temperature and W_d represents the weight of the dried sample.

A typical testing cycle comprised immersing the dried sample into the buffer solution of pH 6.86 at 25°C for 12 h and then transferring the sample

into the buffer solution of pH 6.86 at 45°C for another 12 h. The swelling ratio was used to examine the temperature-sensitive swelling–deswelling properties.

Thermal Transition of Hydrogels

The low critical solution temperature (LCST) of hydrogel was determined using a TA Instruments Q-200 differential scanning calorimeter. The hydrogel sample was allowed to swell in a buffer solution of pH 6.86 at 25°C until swelling equilibrium. The sample surface was wiped with filter paper to remove free water and 10 mg of the swollen sample was placed in an aluminum pan. DSC measurement was performed on swollen samples from 25 to 50°C at a rate of 2°C/min.

Adsorption and Release Behavior of Dye

Methylene blue (MB) and methyl orange (MO) were selected as the model drugs to investigate the adsorption and release of cationic and anionic substances into/from hydrogel [17]. Pre-weighed dried samples were swollen in a buffer solution of pH 6.86 at 25°C for 24 h. The swollen hydrogels were transferred into 25 ml of methylene blue (MB) solution and methyl orange (MO) solution of various concentrations at 25°C and 37°C for 24 h, respectively. The concentration of the dye in the solution after removing the hydrogel was estimated from the absorbance at 664 nm for MB, and 446 nm for MO, respectively, using a DU-7HS spectrophotometer. The adsorption amount in each gel of the dye was calculated from the difference in the concentration before and after soaking.

The swollen hydrogels were soaked in 50 mg/l dye solution for 24 h at 25°C. The hydrogels were then transferred into a buffer solution of pH 6.86 at 25°C and 37°C, respectively. 3 ml buffer solution was added to maintain the solution volume after 3 ml buffer medium was removed in time intervals of 1 h. The cumulative release (%) was calculated according to the method of Li et al. [18].

Characterization

The reaction products of 2,4-TDI with hydroxyethyl methacrylate after derivatization with anhydrous ethyl alcohol were analyzed using an Agilent 1100 high performance liquid chromatograph with an ultraviolet absorbance detector (254 nm) and an eluent of acetonitrile–water (70%/30%).

The spectra of HEC, modified HEC, and the hydrogel were recorded in KBr pellets using a Nicolet Nexus 670 Fourier transform infrared spectrometer.

The fracture surface of freeze-dried hydrogels was sputtered with gold, and was examined with a Nova Nano 430 scanning electron microscope.

RESULTS AND DISCUSSION

Synthesis of Monoblocked TDI with HEM

The isocyanate group at the ortho position of the $-CH_3$ group in 2,4-TDI is less reactive than that at the para position due to steric hindrance and the electronic effect of the methyl group [19,20]. In addition, it is usually considered that one isocyanate group in 2,4-TDI has reacted to form urethane while the second one is less reactive due to the substitution effect [21]. Thus the reaction of a monoalcohol with a diisocyanate first forms a monoblocked diisocyanate and later forms a diblocked diisocyanate. 2, 4-TDI reacted with hydroxyethyl methacrylate according to the molar ratio of n_{TDI}/n_{HEM}: 1:1.1 and the ethanol derivatives of the reaction products were analyzed with HPLC. Figure 1(a) shows the chromatogram of the derivatives of the reaction products. The peaks at the retention time of 7.5 min, 8.7 min and 10.1 min are assigned to the derivative of unreacted 2,4-TDI, monoblocked diisocyanate and diblocked diisocyanate, respectively, by comparing the chromatogram with those of pure compounds. The ratio of peak area is 0.06/0.80/0.14, indicating that the monoblocked diisocyanate is the main product. Figure 2(b) shows the chromatogram of derivatives of the purified reaction products of 2,4-TDI with HEM. The peak at the retention time of 7.5 min disappeared, indicating that the unreacted 2,4-TDI has been removed.

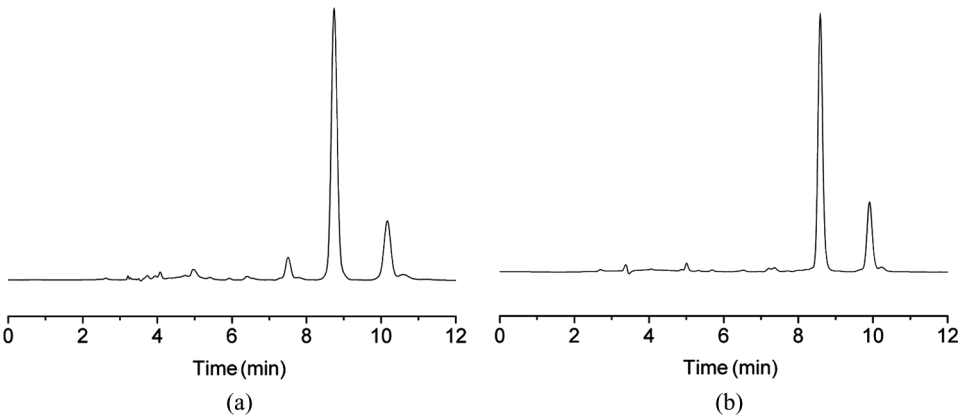


Figure 1: Chromatogram of ethanol derivatives of the reaction products of 2,4-TDI with HEM (a: reaction products; b: purified reaction products).

Characterization of Hydrogels

The infrared spectra of HEC, MHEC, and hydrogel are shown in Figure 2. The bands at 1127.6 cm^{-1} and 1047.9 cm^{-1} in the spectrum of HEC can be assigned to the stretching vibration of C–C and C–O in HEC. The band at 1715.0 cm^{-1} in the spectrum of MHEC can be assigned to the absorption of –NHCO– of urethane in modified HEC, indicating that HMTI has been bonded with HEC. The bands at 1649.5 cm^{-1} and 1542.0 cm^{-1} in the spectrum of the hydrogel can be assigned to the stretching vibrations of C=O and C–N bonds in poly (NIPPAm), respectively, and the bands at 1127.6 cm^{-1} and 1047.9 cm^{-1} represent the stretching bands of C–C, C–O in HEC. The results indicate that a copolymerization has occurred between HHEC and NIPPAm.

Figure 3 shows SEM images of the cross-section of freeze-dried hydrogels (H1 and H4). The cross-section is found to be porous. Large pores are observed in the network of H4. It is probably derived from the low crosslinking density of the network due to the great feed dosages of NIPPAm in preparation of H4.

Thermal Transition of Hydrogels

Figure 4 shows the DSC curves of swollen hydrogels in a buffer solution of pH 6.86. An endothermic peak is observed at 46°C in Curve B, 40°C in Curve C, 36°C in Curve D, 32°C in Curve E, and no endothermic peak is observed in Curve A from 25 to 50°C. The results of DSC analysis show that the LCST of

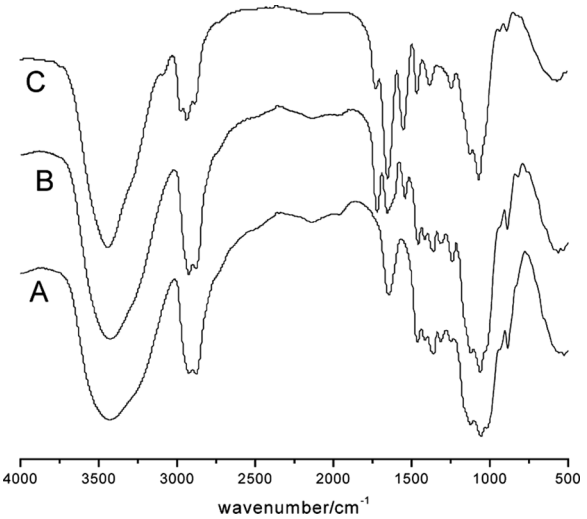


Figure 2: Infrared spectra of HEC (A), modified HEC (B), and hydrogel (C).

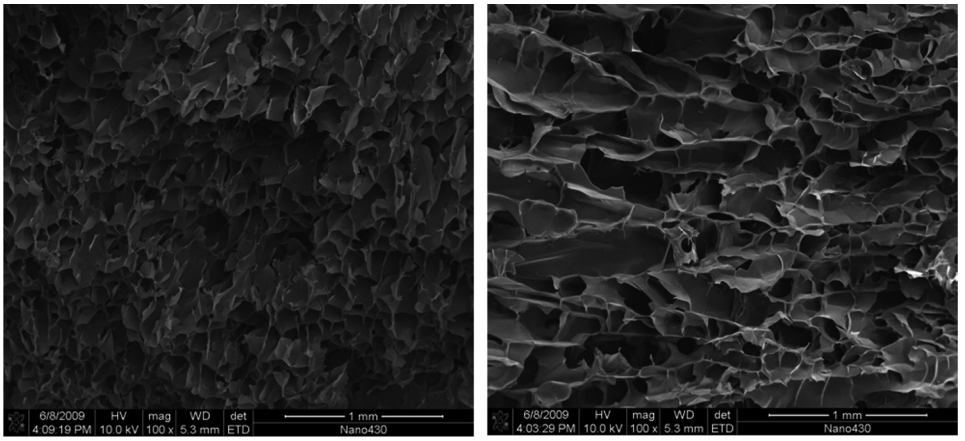


Figure 3: SEM images of the cross-section of freeze-dried hydrogels (a: H1, b: H4).

hydrogel enhances as the mass ratio of N-isopropylacrylamide to HEC decreases. It has been reported that the LCST of temperature-sensitive hydrogel can change with the ratio of hydrophilic and hydrophobic segments of the polymer [22]. In general, LCST enhances with the decrease in the hydrophobic segments in hydrogels [23]. The increase of LCST of the copolymers of NIPPAm and HEC is probably derived from the introduction of HEC, the hydrophilic segment.

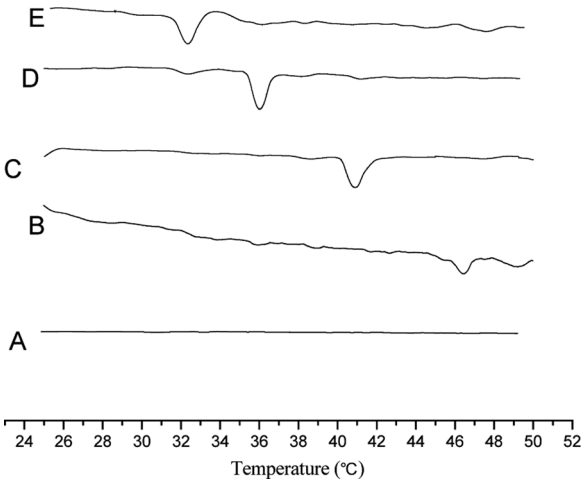


Figure 4: DSC curve of the swollen hydrogels from 25°C to 50°C (A: H1, B: H2, C: H3, D: H4, E: H5).

Thermosensitive Properties of Hydrogels

Figure 5 shows the equilibrium swelling ratios as a function of temperature for the hydrogels. The results show that all the hydrogels are temperature-sensitive and the swelling ratio of the hydrogel decreases as the temperature increases. The hydrogen bonds between water and hydrophilic segments of the polymer chain in poly (NIPPAm) hydrogel have significant effects on the swelling ratio of hydrogel [24]. The hydrogen bonds dominate at relatively low temperatures while hydrogen bonds become weak and hydrophobic interactions among hydrophobic groups become strengthened at relatively high temperatures [22,24]. The hydrogels swell in water due to the strong hydrogen bond between hydrophilic segments of the polymer chain and water molecules at low temperature, while the hydrogels shrink due to interpolymer chain association through hydrophobic interactions at high temperature [22].

As is well-known, the human body temperature is approximately 37°C. Therefore, the swelling/de-swelling behavior of H3 and H4 were investigated owning to their LCST being close to the human body temperature. Figure 6 shows swelling/de-swelling behavior of H3 and H4 in the temperature range 25–45°C in a buffer solution of pH 6.86. The hydrogels shrink at 45°C and swell at 25°C. The swelling ratios of hydrogel at 45°C and 25°C change little after repeated cycle. The results indicate that the swelling/de-swelling of hydrogels is almost reversible.

Adsorption and Release Properties of Hydrogels

The drug release from hydrogel was investigated at 37°C and H4 is selected as the carrier for the adsorption and release experiment. The adsorption

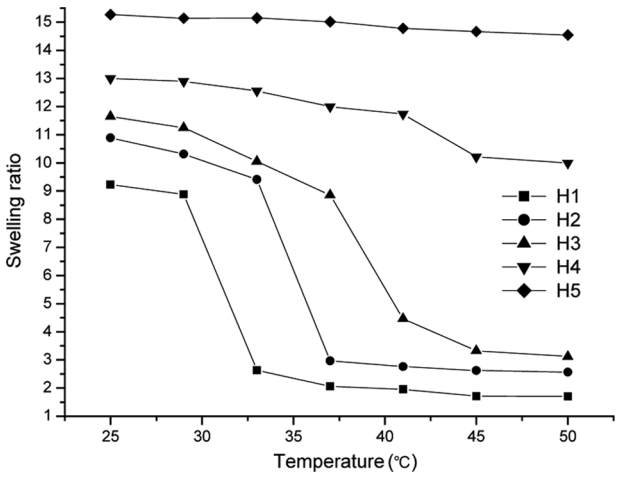


Figure 5: Equilibrium swelling ratio as functions of temperature for the hydrogels.

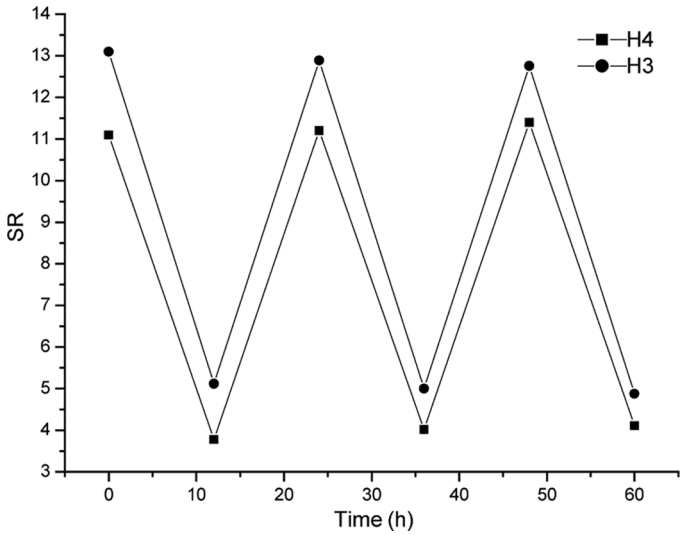


FIGURE 6: Reversible changes in the swelling ratio of two hydrogels between 25°C and 45°C.

amounts for MB and MO at various temperatures are shown in Table 1. The adsorption amount of MB in hydrogel is greater than that of MO at the same initial concentration. Possible reason is that the strong interaction between cationic MB and hydroxyl groups in HEC in hydrogel network results in the great adsorption amount of MB to hydrogel. In addition, the adsorption amount of dye below LCST is greater than that above LCST. The swollen hydrogel is effective in the diffusion of dye into the polymer matrix and increases the adsorption amount. The hydrogel shrinks in water above the LCST of hydogel, the collapse structure of hydrogel decreases the adsorption amount of dye in hydrogel.

Figure 7 shows the cumulative release of dyes from hydrogels at 25°C and 37°C. The cumulative release of MO from hydrogel within the first 8 h is about 39.0% at 37°C and 54.1% at 25°C, while the cumulative release of MB from hydrogel within the first 12 h is about 21.0% at 37°C and 25.7% at 25°C.

Table 1: Adsorption amount of dye in hydrogel.

	Absorption amount (mg/g of dry gel)			
	25°C		37°C	
Concentration (mg/g)	MB	MO	MB	MO
10	2.39	0.26	2.10	0.12
30	5.30	0.77	4.45	0.51
50	6.67	1.28	5.20	0.86

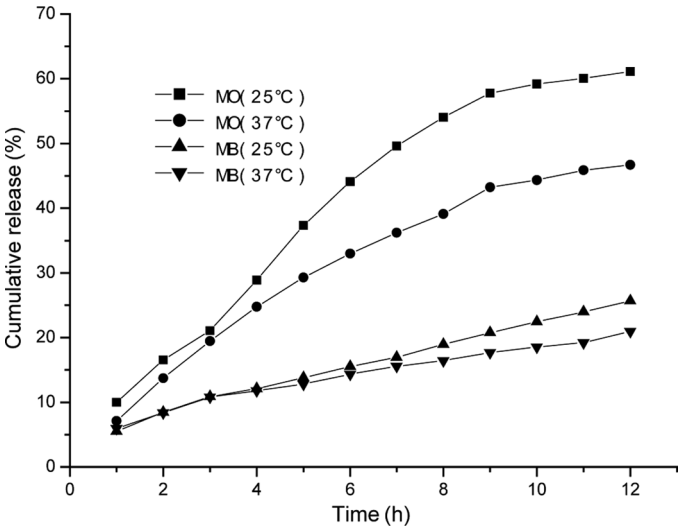


Figure 7: Cumulative releases of dyes from H4 at 25°C and 37°C.

The results show the release rate of dyes above LCST is lower than that below LCST. Possible reason is that the collapsed structure of hydrogels above LCST may greatly entrap the residual dyes in hydrogels and hence retard dyes release. In addition, the release rate of MB from hydrogel is slower than the release rate of MO. Possible reason is that the strong adsorbing capability of hydrogels toward cationic MB slows the release from hydrogels.

CONCLUSIONS

An isocyanate-bearing unsaturated monomer (MHTI) was synthesized by the monoblocking reaction of 2,4-toluene diisocyanate with 2-hydroxyethyl methacrylate. The temperature-sensitive hydrogels were prepared by the copolymerization of N-isopropylacrylamide and modified hydroxyethyl cellulose with MHTI. The LCST of hydrogel was increased by the introduction of hydrophilic HEC. The cross-section of freeze-dried hydrogels was porous. The hydrogels have potential applications in biomedical field.

REFERENCES

[1] Kopecek, J., and Yang, J. Y. *Polym. Int.* **56**, 1078 (2007).

[2] Rudzinski, W. E., Dave, A. M., Vaishanav, U. H., Kumbar, S. G., Kulkarni, A. R., and Aminabhavi, T. M. *Des. Monomers Polym.* **5**, 39 (2002).

[3] Cutie, S. S., Smith, P. B., Henton, D. E., Staples, T. L., and Powell, C. J. *Polym. Sci. Part B* **35**, 2029 (1997).

[4] Alam, M. M., Akhtar, F., Mina, M. F., Dafader, N. C., and Mustafa, A. I. *Polym.-Plast. Technol. Eng.* **42**, 285 (2003).

[5] Chauhan, G. S., and Lal, H. *Desalination* **159**, 131 (2003).

[6] Wach, R. A., Mitomo, H., Yoshii, F., and Kume, T. *J. Appl. Polym. Sci.* **81**, 3030 (2001).

[7] Jung, B. O., Chung, S. J., and Lee, S. B. *J. Appl. Polym. Sci.* **99**, 3500 (2006).

[8] Isiklan, N., Inal, M., and Yigitoglu, M. *J. Appl. Polym. Sci.* **110**, 481 (2008).

[9] Chang, C. Y., Lue, A., and Zhang, L. *Macromol. Chem. Phys.* **209**, 1266 (2008).

[10] Xie, J. B., and Hsieh, Y. L. *J. Appl. Polym. Sci.* **89**, 999 (2003).

[11] Ifuku, S., and Kadla, J. F. *Biomacromolecules* **9**, 3308 (2008).

[12] Li, X. J., Yin, M. H., Zhang, G. L., and Zhang, F. B. *Chin. J. Chem. Eng.* **17**, 145 (2009).

[13] Ibrahim, S. M., El Salmawi, K. M., and Zahran, A. H. *J. Appl. Polym. Sci.* **104**, 2003 (2007).

[14] Akelah, A., and Sherrington, D. C. *J. Appl. Polym. Sci.* **26**, 3377 (1981).

[15] Trombino, S., Cassano, R., Bloise, E., Muzzalupo, R., Tavano, L., and Picci, N. *Carbohydr. Polym.* **75**, 184 (2009).

[16] Bojanic, V., Jovanovic, S., Tabakovic, R., and Tabakovic, I. *J. Appl. Polym. Sci.* **60**, 1719 (1996).

[17] Uraki, Y., Imura, T., Kishimoto, T., and Ubukata, M. *Cellulose* **13**, 225 (2006).

[18] Li, B. A., Jiang, Y. M., Liu, Y., Wu, Y. G., Yu, H., and Zhu, M. F. *J. Polym. Sci. Part B* **47**, 98 (2009).

[19] Ding, Y. T., Xin, Z. R., Gao, Y., Yin, J. H., and Costa, G. *J. Polym. Sci. Part B* **4**, 387 (2003).

[20] Grepinet, B., Pla, F., Hobbes, P., Swaels, P., and Monge, T. *J. Appl. Polym. Sci.* **75**, 705 (2000).

[21] Chen, J., Pascault, J. P., and Taha, M. *J. Polym. Sci. Part A* **34**, 2889 (1996).

[22] Qiu, Y., and Park, K. *Adv. Drug Deliv. Rev.* **53**, 321 (2001).

[23] Schild, H. G. *Prog. Polym. Sci.* **17**, 163 (1992).

[24] Lee, W. F., and Hsu, C. H. *Polymer* **39**, 5393 (1998).