Microwave-Assisted Preparation of Temperature Sensitive Poly(*N*-isopropylacrylamide) Hydrogels in Poly(ethylene oxide)-600

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ABSTRACT: In this article, a series of poly(*N*-isopropylacrylamide) (PNIPAM)-based hydrogels were prepared under microwave irradiation using poly(ethylene oxide)-600 (PEO-600) as reaction medium and microwave-absorbing agent as well as pore-forming agent. All of the temperature measurements, gel fractions, and FTIR analyses proved that the PNIPAM hydrogels were successfully synthesized. Within 1 min, the PNIPAM hydrogel with a 98% yield was obtained under microwave irradiation. The PNIPAM hydrogels thus prepared exhibited controllable properties such as pore size, equilibrium swelling ratios, and swelling/deswelling rates when changing the feed weight ratios of monomer (*N*-isopropylacrylamide, NIPAM) to PEO-600. These properties are well adapted to the different requirements for their potential application in many fields such as biomedicine. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 4177–4184, 2006

Key words: poly(*N*-isopropylacrylamide) hydrogel; microwave; temperature sensitive; poly(ethylene oxide); macroporous

INTRODUCTION

The temperature sensitive hydrogel can swell or deswell in aqueous solution in response to environmental temperatures without dissolution. The environmental temperature causing the hydrogel an abrupt discontinuous volume phase transition is defined as its lower critical solution temperature (LCST). The well-known poly(*N*-isopropylacrylamide) (PNIPAM) hydrogel, for example, exhibits a LCST behavior at about 33°C,[1] which is near the body temperature. Above the LCST, PNIPAM hydrogel shrinks due to loss of water; while it hydrates and expands below the LCST. Because of the unique temperature sensitivity, PNIPAM hydrogel has been extensively studied in many fields such as controlled drug release,[2] tissue engineering,[3] and immobilization of enzymes.[4]

To improve the temperature sensitive properties of PNIPAM hydrogel, studies mainly focused on two aspects: adjustment of its LCST and enhancement of its temperature responsive rates. The latter is of significant importance in some cases like on–off control, where the fast response rates of PNIPAM hydrogel are indispensable. For the purpose of accelerating the temperature responsive rates of PNIPAM hydrogel, many techniques were employed, mainly including the formation of porous structure, the incorporation of water-releasing channels,[5] the breakage of dense skin layers,[6] etc. Kabra and Gehrke[7] prepared a class of fast responsive porous PNIPAM hydrogels by carrying out polymerization reaction above its LCST. Wu et al.[8] combined pore-forming technique with phase separation method to synthesize macroporous PNIPAM hydrogel, which displayed fast deswelling rate. Chen and Park[9] reported a new method to prepare superporous hydrogels with tremendously fast swelling and deswelling rate using surfactant-stabilized CO_2 gas bubbles as pore-forming agent. Zhang and Zhuo[10] decreased the temperature of polymerization/crosslinking reaction below the freezing point (−18°C) to achieve a novel fast responsive PNIPAM hydrogel, which had a porous and regularly arranged network. Cheng et al. conducted polymerization reaction of PNIPAM hydrogel in NaCl,[11] glucose,[12] or sucrose solution[13] and due to phase separation the PNIPAM hydrogels thus prepared had macroporous structures and exhibited fast responsive rates. It is clear that the porous structure is closely related to the fast responsive properties of PNIPAM hydrogel.

Because of the unique properties of high efficiency, low energy consumption, and homogeneity, microwave-assisted heating has attracted wide attention and been studied as energy source in almost all kinds of chemical reactions.[14] For example, microwave-assisted polymerization has been used to synthesize hydrogels. Murry et al.[15] prepared PNIPAM microgel under microwave irradiation, which shortened the reaction time of

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6 h down to 1 h. Maue and Moll[16] reported microwave-assisted accelerated preparation of cellulose and polyacrylate-based hydrogels and found that microwave demonstrated excellent bactericidal property.

Hydrogels are usually prepared in solutions, especially in an aqueous solution. Based on the solubility of monomers and crosslinkers, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, etc. and their mixtures are chosen as solvent to synthesize hydrogels. They can be used as media for microwave-assisted polymerization in an open and atmospheric system because of their polar and microwave-absorbing nature. But in terms of safety they are not proper reaction media for microwave-assisted preparation of hydrogels in a sealed system due to their volatility. The latter reaction system requires such a nonvolatile solvent as poly(ethylene oxide) (PEO). There exists a series of PEO with a molecular weight range of 400–100,000, and among them PEOs with a low molecular weight such as poly(ethylene oxide)-600 (PEO-600) are liquids at $\sim 25^{\circ}$C and can effectively absorb microwave. PEO has been used as pore-forming agent to prepare macroporous PNIPAM hydrogel.[17] Kim et al.[18] synthesized semi-interpenetrating networks of crosslinked PNIPAM and linear PEO-100,000. These results suggest that PEO is compatible with PNIPAM. Meanwhile, we find that the monomer, the crosslinker, and the initiator to synthesize PNIPAM hydrogel can all dissolve in PEO-600 at high temperature.

In our present work, PEO-600 was chosen as reaction medium to prepare PNIPAM hydrogel under microwave irradiation. Here PEO-600 acted as reaction solvent and microwave-absorbing agent as well as pore-forming agent. PNIPAM hydrogel could successfully be prepared in PEO-600 under microwave irradiation. After polymerization and crosslinking reaction, PEO-600 could simply be removed via immersing in water. The microwave-assisted preparation of PNIPAM hydrogel is a rapid and safe process with a high yield and the PNIPAM hydrogel thus produced is uniform and porous. Furthermore, the microwave output power could be modulated conveniently to control the increasing rate and magnitude of temperature in the sealed reaction environment, so that the interior heating property of microwave, in contrast to classical convection heating, could have sufficient influence on the reaction. Finally, the pore size of the PNIPAM hydrogel could be controlled when changing the feed composition ratios of monomer to PEO-600, therefore, the temperature responsive rates of the PINPAM hydrogel became controllable.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAM) (99%) was purchased from Acros Organics (Beijing, China) and used as received. *N*,*N*′-methylenebisacrylamide (BIS) (99.5%) was purchased from Fluka BioChemika and not further purified prior to use. *N*,*N*′-azobisisobutyronitrile (AIBN) (CP) and poly(ethylene oxide)-600 (PEO-600) (CP) was purchased from Shanghai Chemical Reagents (Shanghai, China). AIBN was recrystallized from methanol and then kept at 4°C. PEO-600 was used without further purification.

Preparation of PNIPAM hydrogels

Keeping constant the feed weight ratio of NIPAM (monomer) to BIS (crosslinker) and AIBN (initiator) (NIPAM : BIS : AIBN = 800 : 50 : 3), NIPAM, BIS, AIBN, and PEO-600 were weighted according to the feed compositions listed in Table I. The reaction mixture was sufficiently ground in a mortar and then transferred into a glass ampoule. The glass ampoule was charged into highly pure N_2 gas and degassed with vacuum pump for three times. After the removal of O_2 gas the glass ampoule was torch-sealed under vacuum.

The microwave-assisted polymerization/crosslinking reaction was performed in a microwave oven of Panasonic NN-K542WF with a 2450 MHz frequency and a changeable output power ranging from 75 to 800 W. The temperatures in the reaction system were measured using a tin-paper-shielded thermocouple. The hermetic ampoule sealed as above was irradiated by microwave with different output powers for 15 min. The formed hydrogel was carefully cut into pieces with 12 mm in diameter and ~ 1 mm in thickness and immersed in distilled water, and the water was refreshed every several hours to remove unreacted chemicals and PEO-600. The hydrogel samples were swollen to equilibrium at 25°C for the following measurements.

The PNIPAM hydrogel was prepared using the conventional thermal heating method by placing the sealed ampoule in oil bath at 125°C for 15 min. The feed composition of this PNIPAM hydrogel was the same as the sample MH2. The other operations were the same as above.

The PNIPAM hydrogels prepared by the microwave-assisted heating method and the conventional heating

TABLE I
Feed Compositions and Maximum Yields for Preparing Poly(*N*-isopropylacrylamide) Hydrogel in PEO-600 under Microwave Irradiation

Sample	MH1[a]	MH2	MH3
NIPAM (mg)	1600	800	400
BIS (mg)	100.0	50.0	25.0
AIBN (mg)	6.0	3.0	1.5
PEO-600 (mg)	1200	2400	3600
Maximum yield (%)	95	98	92

[a] MH1 stands for No. 1 hydrogel prepared under microwave irradiation (M, microwave, H, hydrogel; 1 is a number).

one were designated as MH and CH (M = microwave, H = hydrogel, C = conventional), respectively.

Measurement of the gel fractions

To investigate the gel fractions of microwave-assisted synthesis of PNIPAM hydrogel and compare the difference from the conventional thermal heating one, the polymerization/crosslinking reactions were stopped quickly by breaking the ampoules and transferring these PNIPAM hydrogels into an ice-NaCl bath at once. The reaction yield was gravimetrically measured and defined as 100% × the weight of the obtained dry gel/the total weight of monomer (NIPAM) and crosslinker (BIS) in the feed composition.

FTIR analyses of PNIPAM gels

The FTIR spectra of PNIPAM gels were analyzed using a Nicolet Avator 330FTIR spectrophotometer (Thermo Electron, USA) in the region of 4000–400 cm^{-1}. Before the analyses, the hydrogel samples were dried in vacuum for several days until constant weights. The dried PNIPAM gel sample (3.0 mg) was mixed with KBr (300 mg) by grinding and compressed into a pellet for FTIR measurement.

Interior morphology of PNIPAM gels

The hydrogel samples having swollen to equilibrium at 25°C were taken out from water and the excess surface water was carefully wiped with moistened filter paper. These samples were transferred into refrigerator to freeze at −18°C for 1 h and then quickly into a FD-1 freeze drier (Beijing Tianyou Sci. Techn.). The hydrogel sample was freeze-dried under vacuum at −40°C for 3 days until no water appears in the dried gel sample. The freeze-dried gel sample was fractured carefully, fixed on a metal bar, and coated with gold. The cross sections of the gel samples were observed under a scanning electron microscope (Hitachi-X650, Japan) and the interior morphology of the gels was studied.

Measurement of equilibrium swelling ratios of PNIPAM hydrogels

The hydrogel samples were equilibrated in water at temperatures ranging from 10 to 50°C. They were taken out and wiped with moistened filter paper to remove excess surface water. Their weights were measured in a 1/10000 Sartorius BS124S balance (Beijing Sartorius Instrument, CN). Equilibrium swelling ratio (ESR) is defined as ESR = W_T/W_D, where W_T is the weight of hydrogel sample reaching equilibrium at T°C and W_D is the weight of dry gel sample.

Measurement of swelling kinetics of PNIPAM hydrogels at 25°C

The hydrogel samples having reached equilibrium in 25°C water were freeze-dried at −40°C under vacuum until constant weight and then transferred into 25°C water to allow them to swell. At predetermined time, the hydrogel samples were taken out and weighted after wiping the excess surface water with moistened filter paper. The water uptake value (WU) is defined as WU (%) = $100 \times (W_T - W_D)/(W_{25} - W_D)$, where W_t is the weight of hydrogel sample at time t, W_{25} is the wet weight of hydrogel sample reaching equilibrium at 25°C, and W_D is the same as defined above.

Measurement of deswelling kinetics of PNIPAM hydrogels at 37°C

The hydrogel samples having reached equilibrium in 25°C water were placed into 37°C water to allow them to deswell. At predetermined time, the hydrogel samples were taken out and weighted after wiping the excess surface water with moistened filter paper. The water retention value (WR) is defined as WR = $100 \times (W_T - W_D)/(W_{25} - W_D)$, where all the symbols are the same as above.

RESULTS AND DISCUSSION

Temperature changes in reaction systems

Figure 1 illustrates the temperature changes under microwave irradiation with different output powers and incubated in oil bath (125°C). It can be found that the temperature under microwave irradiation increased rapidly from room temperature to a maximum value irrespective of output power, but the maximum temperatures are dependent upon the output powers. When the output power of microwave irradiation is lower than 75 W, the temperature of the reaction mixture increases from 20 to 114°C within 3 min and then keeps approximately constant. It only takes 3 and 1.5 min respectively, for the mixtures irradiated by 170 and 340 W microwaves to reach the maximum temperatures (148 and 188°C, respectively). However, it takes nearly 14 min for the reaction mixture incubated in oil bath to increase from 20 to 114°C and then remains constant. The rapid increase of temperature under microwave irradiation is probably ascribed to the unique interior heating property of microwaves in contrast to the conventional convection heating method. The high viscosity of PEO-600 limits the convection–diffusion rate of thermal energy and results in a slow temperature increase in the thermal heating reaction system. Different from our previous studies on microwave-assisted ring-opening polymerization,[19]

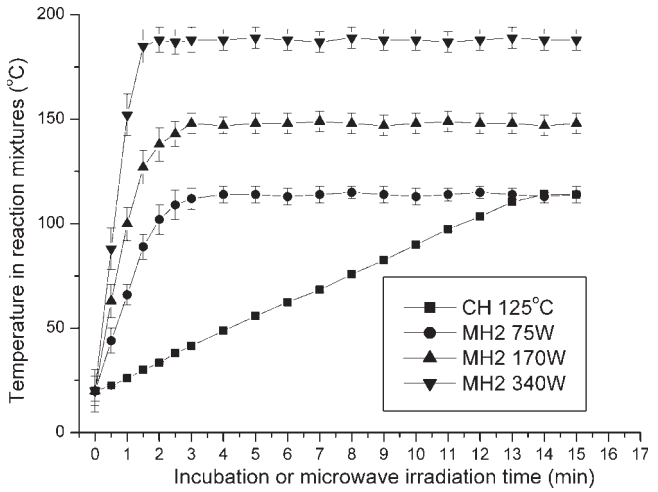

Figure 1 Temperature changes in reaction mixtures under microwave irradiation with different output powers and incubated in 125°C oil bath.

no additional temperature increase induced by reaction energy is observed.

It can also be seen from Figure 1 that it takes only about 10, 28, and 48 s respectively, for the reaction systems under 340, 170, and 75 W microwave irradiation to reach 56°C, at which the reaction mixtures start to form hydrogel networks. However, it takes 300 s for the conventional heating to attain the temperature.

Gel fractions

The gel fractions of microwave-assisted polymerization and conventional thermal heating one were studied and shown in Figure 2. The samples with 1 : 3 feed weight ratio were discussed here. The rate of network formation of the PNIPAM hydrogel prepared under microwave irradiation increased with increasing output microwave powers and was faster than that prepared by conventional thermal heating method. Under 75 W microwave irradiation, the PNIPAM hydrogel began to form within 50 s, and when the microwave output power increased to 170 and 340 W, the time for the formation of the hydrogel shortened to ~ 30 and ~ 10 s, respectively. But in 125°C oil bath, the PNIPAM hydrogel formed after 5 min. At all these time intervals the temperature in reaction mixtures arrived at ~ 56°C as shown in Figure 1. Therefore, the polymerization/crosslinking reaction of PNIPAM hydrogel in PEO-600 media is a temperature-triggered process and once *N*,*N*′-azobisisobutyronitrile (AIBN) is initiated at 56°C to produce free radicals, the polymerization/crosslinking reaction goes on at a tremendously fast rate due to fast chain prolongations. When the output power increased to 340 W, AIBN is quickly and thoroughly decomposed due to rapid increase of temperature in reaction mixtures, some NIPAM and BIS can not timely participate the polymerization and lead to a relatively lower yield (90%). If the temperature increases too slowly, AIBN is initiated at ~ 56°C, but NIPAM and BIS can not completely dissolve at this temperature, the yield will also be low. It is the case for the conventional heating reaction system at 125°C in oil bath (87% yield). So there seems to be an optimal increasing rate of temperature like those under 170 and 75 W microwave irradiation where the preparations of PNIPAM hydrogel give maximum yields (98 and 97%).

Reaction yield is also related to the feed ratio of NIPAM to PEO-600 as illustrated in Table I, and decreased feed weight ratio of NIPAM to PEO-600 results in a decreased yield. This is ascribed to the formation and following wash-away of some network fragments when too much PEO-600 was used, e.g., in MH3. From the viewpoint of high yield, the optimum feed weight ratio of NIPAM to PEO-600 is 1 : 3 for

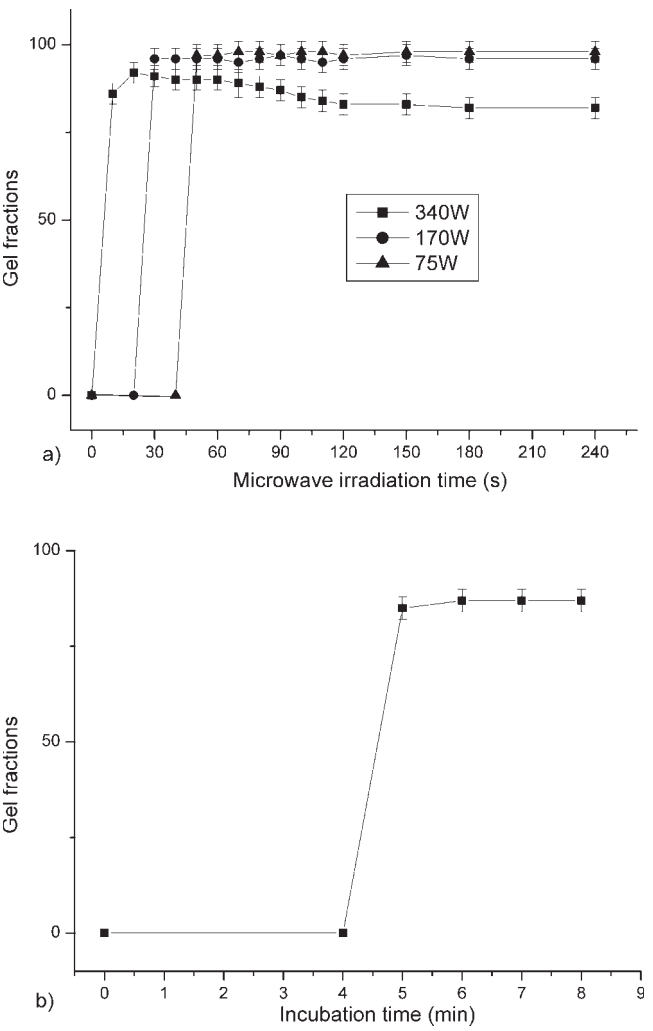

Figure 2 Gel fractions of (a) microwave-assisted polymerization and (b) conventional thermal heating polymerization in 125°C oil bath.

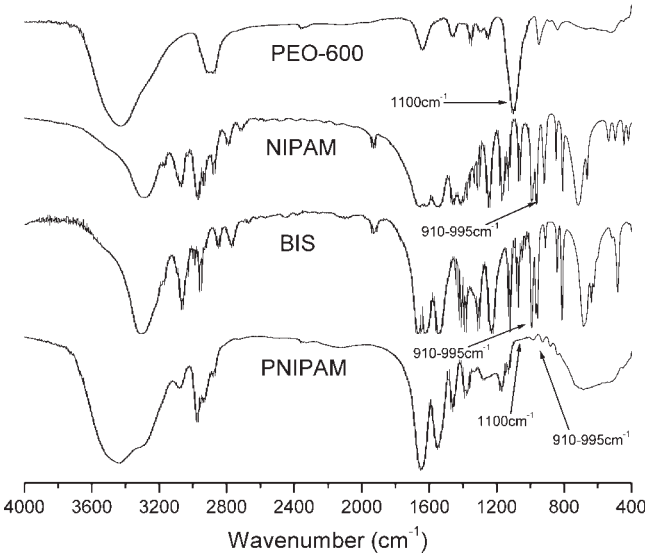

Figure 3 FTIR spectra of reaction medium (PEO-600), monomer (NIPAM), crosslinker (BIS), and the PNIPAM gel prepared by microwave-assisted polymerization.

MH2, whose maximum yield is 98%. When the feed weight ratios are 4 : 3 and 1 : 9, the corresponding maximum yields are 95 and 92%, respectively.

FTIR analyses

FTIR spectra of reaction medium (PEO-600), monomer (NIPAM), crosslinker (BIS), and the PNIPAM gels prepared under microwave irradiation are illustrated in Figure 3, and the characteristic absorbance bands are marked with numbers and arrows. NIPAM and BIS have three characteristic absorbing peaks at 917, 965, and 992 cm^{-1} belonging to the vibrations of mono-substituted C=C double bond.[18] The disappearance of these peaks in PNIPAM hydrogel demonstrates that the PNIPAM hydrogel is successfully synthesized in PEO-600 under microwave irradiation. On the other hand, PEO has a characteristic absorbance band at 1100 cm^{-1} due to the C—O stretching vibration, but the PNIPAM gel thus obtained does not include the absorbance bond, indicating that PEO-600 has been completely removed during the water-immersing and refreshing process.

FTIR spectra of PNIPAM gels prepared under microwave irradiation with different output powers or by conventional heating in 125°C oil bath are shown in Figure 4. It seems that FTIR spectrum of the PNIPAM hydrogel prepared by microwave irradiation is similar to that prepared in 125°C oil bath, suggesting that heating method and irradiation power influence neither the activities of monomer and crosslinker nor the chemical composition of the resultant PNIPAM hydrogels.

Morphology observation

Figure 5 illustrates SEM photographs of the freeze-dried PNIPAM hydrogels prepared under 75 W microwave irradiation using different feed weight ratios of NIPAM to PEO-600. All of them show honeycomb-like pores with flimsy walls. But the pore number decreases from MH1 to MH3. There are about 54 pores in the photo of MH1. However, about 13 and 4 pores can be respectively, observed in the photos of MH2 and MH3. In other words, the pores become larger and the networks turn looser from MH1 to MH3. The phenomenon is reasonable because increased content of PEO-600 is used from MH1 to MH3. The solvent acts as a three-dimensional boundary within which the hydrogel network forms accompanying with the penetration, coiling, and entanglement of polymer chains. When more amount of solvent is used, the formed polymer network is expanded and there is less penetration, coiling, and entanglement of polymer chains, leading to the enlargement of pore diameter and decrease of pore number in the prepared hydrogel.

Equilibrium swelling behavior

Figure 6 shows the temperature dependence of equilibrium swelling ratios of the PNIPAM hydrogels prepared under 75 W microwave irradiation using different feed weight ratios of monomer (NIPAM) to reaction solvent (PEO-600) (4 : 3 for MH1, 1 : 3 for MH2, and 1 : 9 for MH3). Two main findings can be made from Figure 6: (1) All of these PNIPAM hydrogels clearly exhibit a lower critical solution temperature (LCST) around 33°C regardless of the feed weight ratios of NIPAM to PEO-600, that is, a discontinuous

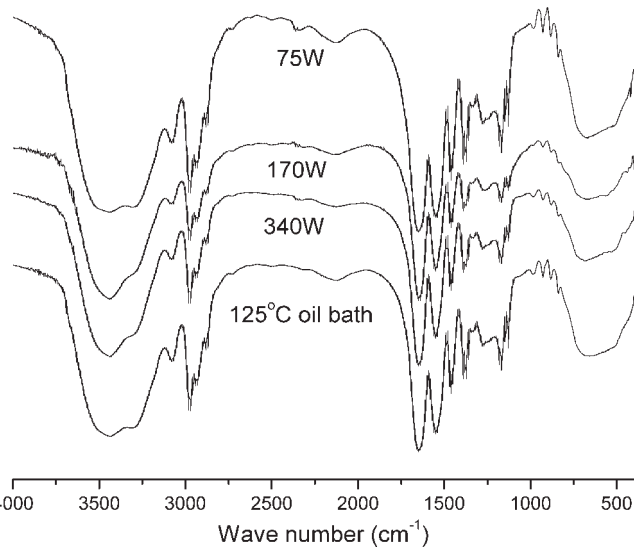

Figure 4 FTIR spectra of PINPAM gels prepared under microwave irradiation with different output powers and in 125°C oil bath.

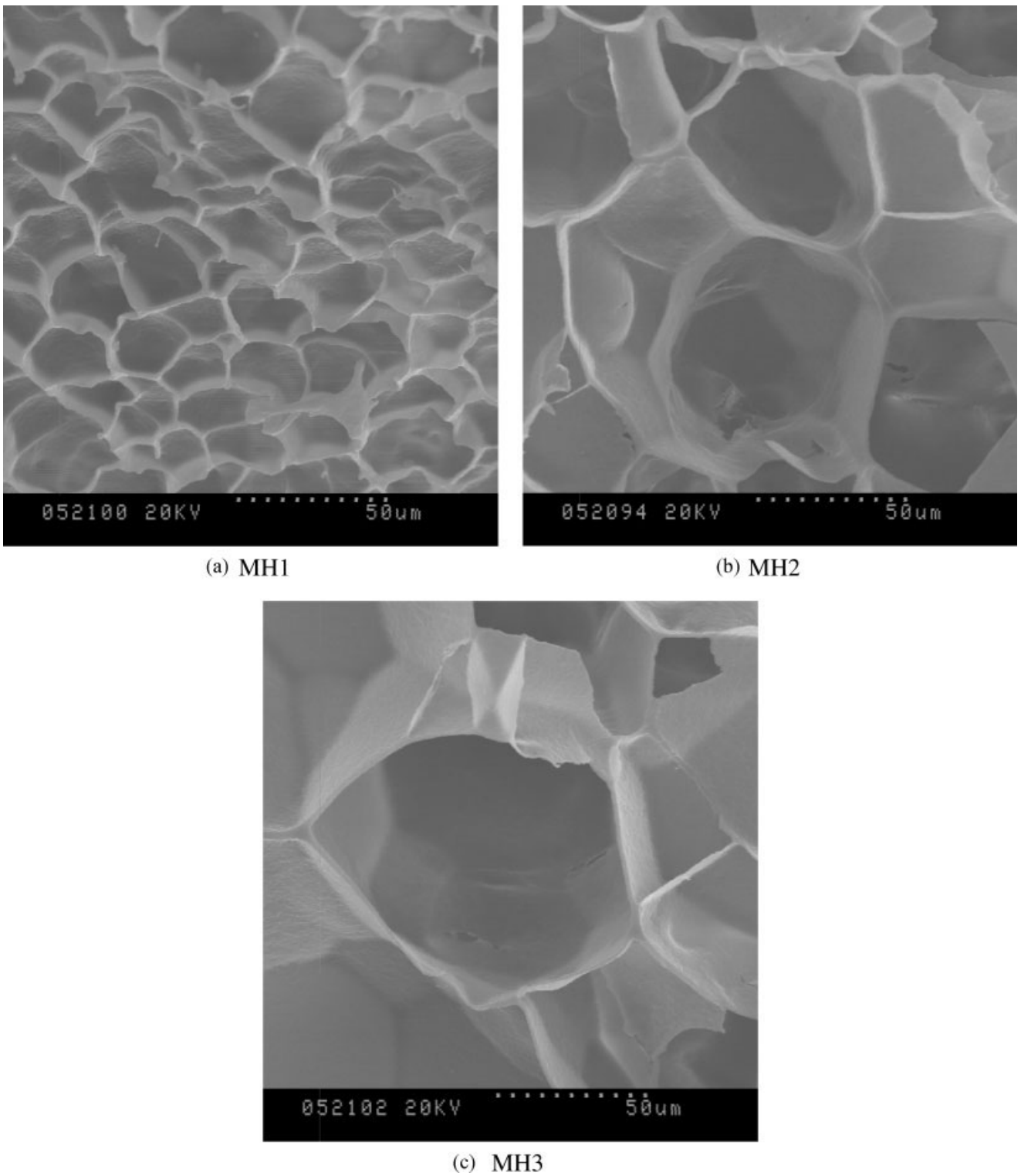

Figure 5 SEM photographs of the freeze-dried PNIPAM gels prepared by the microwave-assisted polymerization.

volume phase transition occurs at $\sim 33^{\circ}C$ for all these PNIPAM hydrogels. The feed weight ratios of NIPAM to PEO-600 do not change LCST behavior of the formed PNIPAM hydrogels; (2) The feed weight ratios of NIPAM to PEO-600 have an impact on the equilibrium swelling ratios of the PNIPAM hydrogels. At temperatures below the LCST, the resultant PNIPAM hydrogels show increasing equilibrium swelling ratios with decreasing feed ratios of NIPAM to PEO-600 (MH1 < MH2 < MH3). For example, at room temperature ($25^{\circ}C$), the equilibrium swelling ratios of MH1, MH2, and MH3 are 8.3, 13.4, and 16.4, respectively. At temperatures above the LCST, their equilibrium swelling ratios slightly decrease with decreasing feed

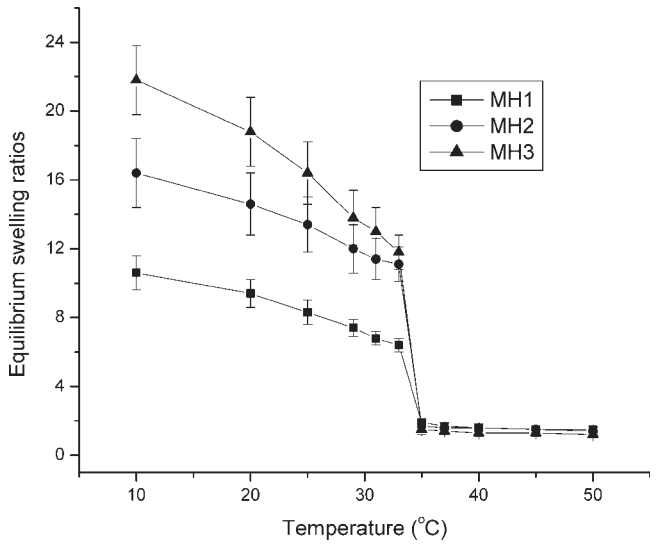

Figure 6 Equilibrium swelling ratios at different temperatures of the PNIPAM hydrogels prepared under 75 W microwave irradiation by using different feed weight ratios of NIPAM to PEO-600 (4 : 3 for MH1, 1 : 3 for MH2, and 1 : 9 for MH3).

ratios of NIPAM to PEO-600. Therefore, the equilibrium swelling ratios of the prepared PNIPAM hydrogels can be controlled when modulating the feed weight ratios of monomer (NIPAM) to reaction medium (PEO-600). The equilibrium swelling behavior is in agreement with the morphology observation above. The mechanism to control equilibrium swelling ratios via using different quantities of PEO is similar to those using other solvents such as water.[20,21]

Swelling kinetics at 25°C

Swelling kinetics of the PNIPAM hydrogels prepared under 75 W microwave irradiation using different feed weight ratios of NIPAM to PEO-600 (4 : 3 for MH1, 1 : 3 for MH2, and 1 : 9 for MH3) are displayed in Figure 7. It can be found that the swelling rates of the formed PNIPAM hydrogels increase when more PEO-600 added to the reaction system. MH1 absorbs only 41% water in 30 min, while MH2 and MH3 take up $\sim$ 49 and $\sim$ 64% water respectively, within the same time interval. MH1 needs 120 min to attain swelling equilibrium state, and MH2 and MH3 take only 90 min and 60 min to reach equilibrium.

The promoted swelling rate of the PNIPAM hydrogel prepared in increasing amount of PEO-600 is related to the expanded and looser network structure as described in the above paragraphs. The addition of more PEO-600 into the reaction mixtures results in a volume increase or a larger three-dimensional boundary on the one hand, and PEO-600 can act as a pore-forming agent due to its amphiphilicity and pliability on the other hand. PEO-600 interacts with PNIPAM chain segments by hydrogen bonds and hydrophobic interactions and entangles around the PNIPAM chains, and thus breaks the entanglements among PNIPAM chains. After the removal of PEO-600, voids or pores are left. PEO has been used as pore-forming agent to prepare macroporous PNIPAM hydrogel in aqueous solution.[17] In our present study, pure PEO-600 can also play a role of pore-forming agent just like PEO in its aqueous solution.

Deswelling kinetics at 37°C

Figure 8 illustrates the deswelling kinetics of the PNIPAM hydrogels prepared under 75 W microwave irradiation using different feed weight ratios of NIPAM to PEO-600. It can be seen from Figure 8 that deswelling rates increase from MH1 to MH2 and MH3. Within 30 min, MH loses only less than 50% of water; however, MH2 and MH3 lose more than 80 and 90% respectively, within the same duration. MH1 needs 6 h to reach deswelling equilibrium, while MH2 and MH3 only need 3 and 2 h, respectively.

The increase of the deswelling rates from MH1 to MH2 and MH3 is owing to the same reason as discussed above. Because of dilution and pore-forming action of PEO-600, porous and looser networks are formed as shown in Figure 5. The porous and looser networks facilitate the outflow of water molecules from the PNIPAM hydrogel.

CONCLUSIONS

A series of poly(*N*-isopropylacrylamide) (PNIPAM)-based hydrogels were prepared under microwave irradiation in the presence of poly(ethylene oxide)-600 (PEO-600). PEO-600 was used here as reaction solvent, microwave-absorbing agent, and pore-forming agent.

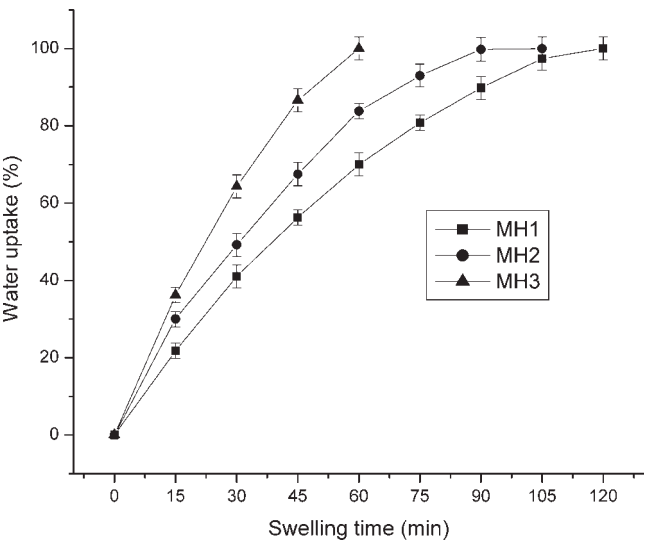

Figure 7 Swelling kinetics of the PNIPAM hydrogels prepared under microwave irradiation.

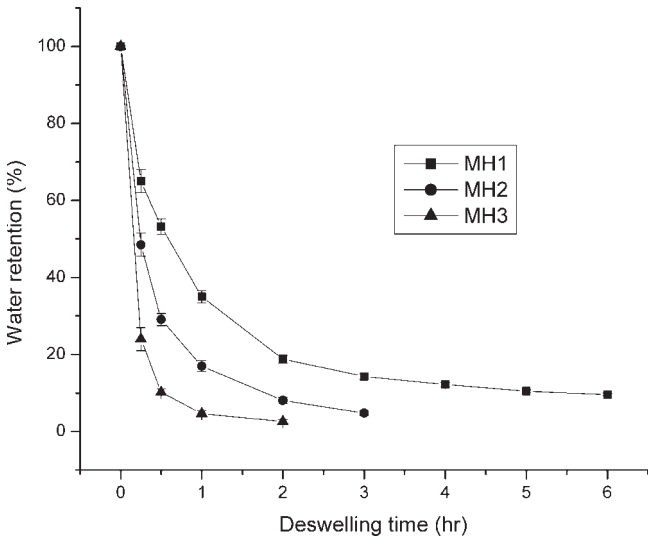

Figure 8 Deswelling kinetics of the PNIPAM hydrogels prepared under microwave irradiation.

The temperature changes in the reaction systems under microwave irradiation with different output powers and in 125°C oil bath were investigated and the gel fractions were studied. The increasing rate and magnitude of temperature in microwave-assisted reaction system could be controlled when changing microwave output powers. Within 1 min, the PNIPAM hydrogel with a 98% yield was prepared under microwave irradiation. FTIR analyses demonstrated that the PNIPAM hydrogels were successfully synthesized and PEO-600 was completely removed from the hydrogels. Furthermore, the pore size, the equilibrium swelling ratios, and the swelling and deswelling rates of the PNIPAM hydrogel prepared under 75 W microwave irradiation could be well controlled via changing the feed weight ratios of monomer (*N*-isopropylacrylamide, NIPAM) to reaction medium (PEO-600).

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