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Effect of Pore-Forming Agent Type on Swelling Properties of Macroporous Poly(*N*-[3-(dimethylaminopropyl)]-methacrylamide-co-acrylamide) Hydrogels

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Macroporous poly(N-[3-(dimethylaminopropyl)]methacrylamide-co-acrylamide) [P(DMAPMA-co-AAm)] hydrogels were prepared by free-radical crosslinking copolymerization of corresponding monomers in water using two different pore-forming agents such as hydroxypropyl celluose (HPC) and poly(ethylene glycol) (PEG). The effect of these pore-forming agents on the volume phase transition temperature (VPT-T), interior morphology and swelling/deswelling kinetics of the P(DMAPMA-co-AAm) hydrogels was investigated. Scanning electron micrographs revealed that the interior network structure of the hydrogel matrix became more porous due to the presence of HPC or PEG pore-forming agents. The more porous matrix provided numerous water channels for water diffusion in or out of the matrix and, therefore, an improved response rate to the external stimuli. Particularly, due to its unique macroporous structure, the *PEG*-modified hydrogel showed a tremendously faster response to the external temperature changes during deswelling process and the swelling process at 22°C.

Keywords: poly(*N*-[3-(dimethylaminopropyl)]methacrylamide-co-acrylamide), hydrogel, morphology, pore-forming agent, temperature sensitive

1 Introduction

The temperature sensitive hydrogels have attracted great attention in the last years due to both fundamental and technological interests (1–3). These hydrogels are useful for biomedical and bioengineering applications such as protein-ligand recognition (4), on-off switches for modulated drug delivery (5) or artificial organs (6), and immobilization of enzyme (7). In these applications, a fast response rate of the hydrogel to external stimuli is needed. For this purpose, several techniques have been proposed. One technique is to form a heterogeneous network structure of the hydrogel through a phase separation method (8, 9). Wu et al. (9) synthesized macroporous poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogels above the VPT-T in the absence or presence of HPC acting as a pore forming agent. Use of PEGs with different molecular weights during the network formation process was also suggested for the preparation of macroporous PNIPAAm hydrogels (10–11). Okano et al. (12) suggested a graft-copolymerization technique to synthesize rapid responsive hydogels with a comp-like structure. In recent years, Zhuo et al. (13) also reported that the response rate of PNIPAAm hydrogel could be improved via incorporating siloxane linkage, cold polymerization, and crosslinking methods. In addition to these techniques, another idea is to apply a radiation induced polymerization method (14, 15) Huang et al. (16) prepared macroporous pol(vinyl methyl ether) (PVME) hydrogels by γ-irradiation of 30 wt% PVME solution mixed with 15 wt% ferric oxide powder, which was used to enhance the heat transfer. However, to our knowledge, the systematic investigations of the effect of pore-forming agent type on swelling properties, especially volume phase transition behavior and response dynamics of poly(*N*-[3-(dimethylaminopropyl)]methacrylamide-co-acrylamide) [P(DMAPMA-co-AAm)] hydrogels have not been reported before. In this study, a porosigen technique was employed to improve the response rate of P(DMAPMA-co-AAm) hydrogels by using hydroxypropyl cellulose (HPC) and poly(ethylene glycole) (PEG) aqueous solutions as the polymerization solvent. The effect of the pore-forming agent type on the properties of resulting P(DMAPMA-co-AAm)

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hydrogels was examined in terms of chemical composition and morphology via by Attenuated Total Reflectance Fourier Transformed Infrared (ATR-FTIR), scanning electron microscopy (SEM) and swelling capability at 22°C, as well as deswelling kinetics upon temperature increase.

2 Experimental

2.1 Materials

Monomers *N*-[3-(dimethylaminopropyl)]methacrylamide (DMAPMA), acrylamide (AAm), the crosslinker *N*,*N*-methylenebisacrylamide (MBAAm), initiator ammonium persulfate (APS), the accelerator *N,N,N′,N′*-tetramethylethylenediamine (TEMED), pore forming agents poly(ethylene glycole (PEG) (MW = 1000 g/mol) and hydroxypropyl cellulose (HPC) (MW = 1000 g/mol) were purchased from Aldrich Chemical Co. The chemicals were used as received. All aqueous solutions were prepared using deionized water.

2.2 Hydrogel Synthesis

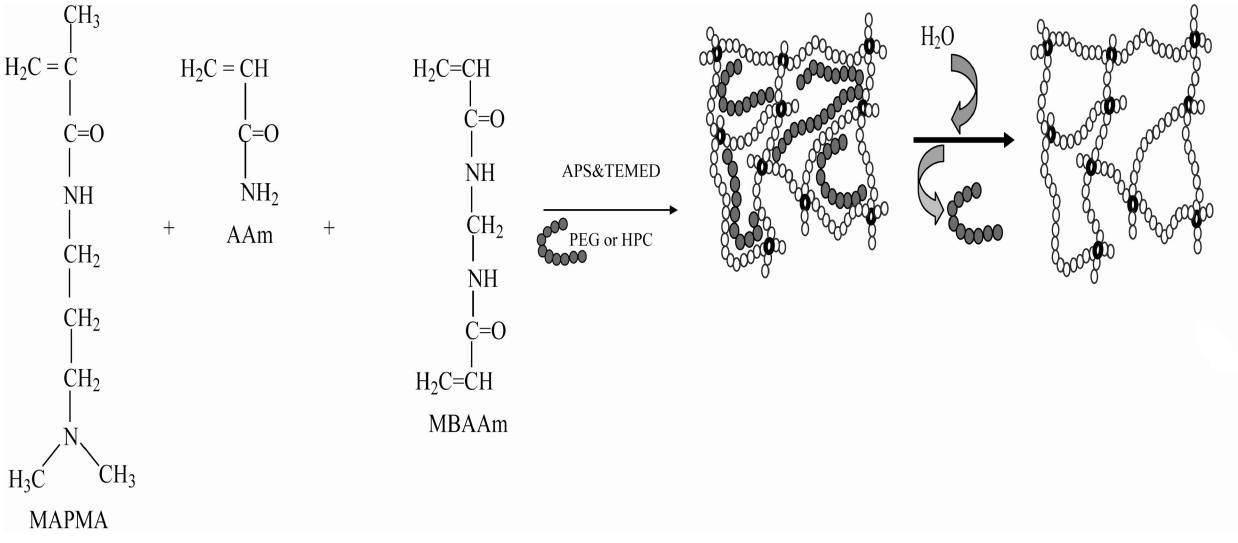
The traditional and PEG- or HPC-modified P(DMAPMA-co-AAm) hydrogels were prepared by free-radical crosslinking copolymerization of DMAPMA and AAm in aqueous solutions (Scheme 1). The hydrogels designed as T-Gel, PEG-Gel and HPC-Gel were prepared in deionized water, PEG and HPC aqueous solutions, respectively. APS (0.056 M) and TEMED (0.32 M) were used as the redox initiator system. The DMAPMA (0.7 mL), AAm (0.3 g) APS (1.0 mL) and MBAAm (0.14 g) were dissolved in deionized water (4 mL). Then, PEG or HPC (18 wt%) was added in the monomer solution. The solution was purged with nitrogen gas for 10 min. After the addition of TEMED (0.5 mL), the solution was placed in poly(vinylchloride) straws of 4 mm diameters and about 20 cm long. The poly(vinyl chloride) straws were sealed and placed in a thermostated water bath at 22°C, and the copolymerization was conducted for 24 h. The resulting hydrogels were purified by immersing in deionized water for one week to remove unreacted chemicals and pore-forming agents (PEG or HPC). The water was replaced 3–4 times every day and the purified hydrogels were then dried at room temperature under vacuum to constant weight. The traditional hydrogel was prepared in deionized water with the same recipe and fabrication condition. All the purified hydrogels were cut into disc-like pieces approximately 10 mm in length for further studies.

2.3 Attenuated Total Reflectance Fourier Transformed Infrared (ATR-FTIR) Measurements

ATR-FTIR measurements were made with a Nicolet 6700 FT-IR (USA) spectrometer equipped with a smart orbit assessor in the range of 2000–500 cm^{-1}. Before the measurements, the originally swollen hydrogels were freeze-dried in a Virtis freeze drier (Lobconco, USA) for two days to completely remove water

2.4 Internal Morphology Observation

Scanning electron microscopy (SEM, JEOL JSM-6360 LV SEM instrument) was used to study the internal or cross-section morphology of the P(DMAPMA-co-AAm) hydrogels. To prepare samples for SEM, the swollen hydrogels at 22°C were firstly freeze-dried and than fractured and sputter coated with gold.



Sch. 1. Chemical structure of the macroporous P(DMAPMA-co-AAm) hydrogels prepared in PEG or HPC aqueous solutions.

2.5 Measurement of Equilibrium Swelling/Deswelling Ratio

The equilibrium swelling/deswelling ratio of hydrogels was measured gravimetrically after carefully blotting the surface water with moistened filter paper in the temperature range from 10 to 60°C. The hydrogel samples were immersed in deionized water for at least 24 h at each predetermined temperature. The average value of three measurements was taken for each hydrogel, and the equilibrium swelling/deswelling ratio (ES/DR) was defined as follows:

$$\mathrm{ES/DR} = \frac{m_s - m_d}{m_d} \quad (1)$$

where m_s is the mass of swollen hydrogel at the particular temperature and m_d is the dry mass of hydrogel.

2.6 Measurement of Deswelling Kinetics

The deswelling kinetics of hydrogels was measured gravimetrically at 50°C. The hydrogel samples were first immersed in deionized water at 10°C until equilibrium was reached. Then the equilibrated hydrogels were quickly transferred to a water bath at a temperature of 50°C. At specified time intervals, the hydrogels were removed from the hot water and weighted after wiping off the excess surface water with moistened filter paper. The average value of three measurements was taken for each sample, and the normalized deswelling ratio (NDR) was defined as follows:

$$\mathrm{NDR} = \frac{m_t - m_d}{m_s - m_d} \quad (2)$$

where m_t is the mass of hydrogel at regular time intervals, m_d is the same as above and m_s is the mass of swollen hydrogel at 22°C

2.7 Measurement of Swelling Kinetics

After drying at 60°C in vacuum oven, the dried samples were then placed in deionized water at 22°C and removed from water at regular time intervals. After the water on the surfaces of the samples was wiped off with moistened filter paper, the masses of the hydrogels were recorded. The swelling ratio (SR) was defined as follows:

$$\mathrm{SR} = \frac{m_t - m_d}{m_d} \quad (3)$$

3 Results and Discussion

3.1 Synthesis and Spectral Characterization

The hydrogels made of DMAPMA alone were too fragile to handle. Therefore, we added AAm to make copolymers to improve the mechanical property of the hydrogels. Both traditional and PEG- or HPC-modified P(DMAPMA-co-AAm) hydrogels can also be easily synthesized. From the procedure of polymerization, it was observed that the pore-forming agents in the polymerization solvent significantly influenced the formation of P(DMAPMA-co-AAm) hydrogels.

The ATR-FT-IR spectra of the traditional and PEG- or HPC-modified P(DMAPMA-co-AAm) hydrogels were shown in Figures 1 and 2. The ATR-FT-IR spectra of the traditional and PEG- or HPC-modified hydrogels are almost similar. The exists a typical amide I band ($\sim$1625 cm^{-1}), consisting of the C=O stretch of DMAPMA and AAm, and the amide II band ($\sim$1545 cm^{-1}), including N—H vibration in each spectrum. In this respect, if there exists PEG or HPC in the modified hydrogels, a typical and strong peak positioned at 1096 and 1055 cm^{-1} (Figures 1c and 2c), which belongs to the C—O stretch of PEG and HPC, respectively, would appear in the difference spectra. For this purpose, the spectrum subtraction of the T-Gel from the PEG-Gel and HPC-Gel was made to compensate for the C—O stretching band of the PEG and HPC at 1096 and 1055 cm^{-1} (Figures 1d and 2d). However, there is no obvious peak appearing at around 1096 and 1055 cm^{-1} in the difference spectra of the modified hydrogels. On the other hand, the difference spectra of the modified hydrogels are not flat, as expected. This behavior may be attributed to the band shifting that originated from the interactions between the pore forming agent and P(DMAPMA-co-AAm) chains during the polymerization. These findings suggest that the modified hydrogels have the same chemical composition as the traditional P(DMAPMA-co-AAm) hydrogel and PEG and HPC do not exist in the modified hydrogels after they are extensively washed. Both PEG and HPC act as the pore-forming agent and do not participate with the polymerization.

3.2 Interior Morphology by SEM

Figure 3 shows the cross-sectional views of the internal structures of the freeze-dried traditional and PEG- and HPC-modified hydrogels. The internal morphology of the traditional hydrogel is dense and smooth, while the PEG- and HPC-modified hydrogels exhibit a porous microstructure. There are two possible reasons. First, the hydration and thus exclusion volume of PEG and HPC may provide spatial hindrance during the polymerization and crosslinking process. Thus, a more porous structure is formed with the PEG- and HPC-modified hydrogels. Second, due to the presence of PEG or HPC, phase separation of formed P(DMAPMA-co-AAm) chains occurs during the polymerization, leading to macroporous and heterogeneous structures. From Figure 3, it can also be observed that the thickness of the pore wall becomes thinner from HPC-Gel to PEG-Gel consecutively, which is attributed to the enlarged porous network structure of PEG-modified hydrogel.

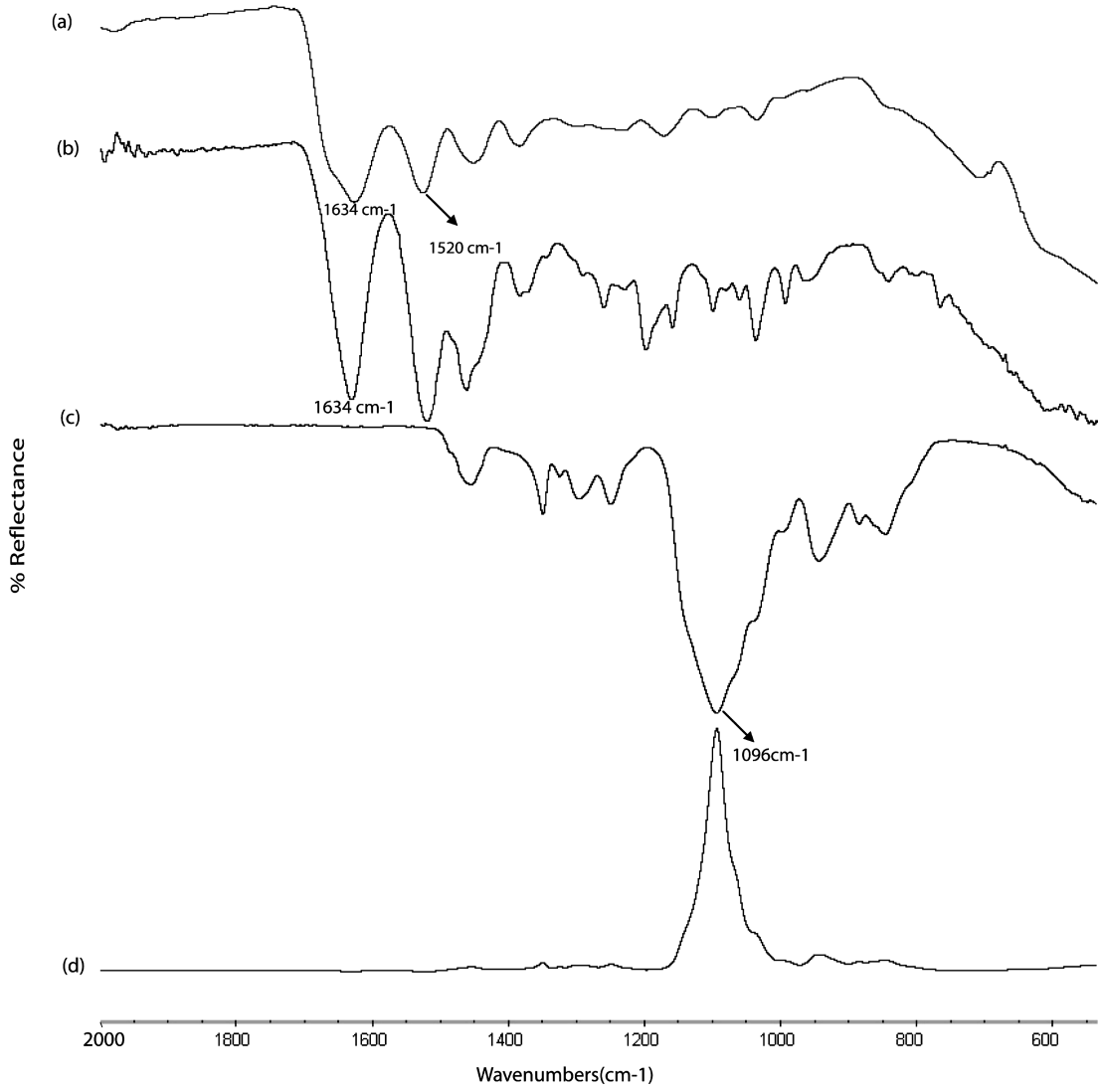


Fig. 1. ATR-FTIR spectra of the P(DMAPMA-co-AAm) hydrogels prepared in PEG aqueous solution (PEG-Gel) (a), in deionized water (T-Gel) (b), PEG (c) and difference spectrum (a–b) (d).

3.3 Equilibrium Swelling/Deswelling Ratio of Hydrogels

The poly(N-[3-(dimethylaminopropyl)]methacrylamide [P(DMAPMA)] hydrogel swollen in water has a positive temperature-sensitive property and exhibit a upper critical solution temperature (UCST) in response to temperature changes around 34°C (17). However, the poly(acrylamide) [P(AAm)] hydrogel does not show a VPT-T in water (18). The introduction of the AAm component into P(DMAPMA) chains changes the temperature response property of the P(DMAPMA-co-AAm) hydrogels. Figure 4 shows the temperature-dependent swelling behaviors of the traditional and PEG- and HPC-modified hydrogels when the temperature of the aqueous media increased from 10 to 60°C. As shown in Figure 4, the P(DMAPMA-co-AAm) hydrogels exhibit a negative temperature-sensitive property, that is, swelling at a lower temperature and shrinking at a higher temperature. At 10°C, the equilibrium swelling ratio of traditional hydrogel is lower than those of the modified hydrogels. For example, equilibrium swelling ratio of T-Gel is around 5.6, while those of the HPC-Gel and PEG-Gel are around 6.6 and 8.2, respectively.

Upon heating, all the hydrogels exhibit a temperature-stimulant decreasing in swelling ratio up to 60°C, but with different magnitudes of the thermo-induced decreasing in swelling ratio, As the temperature changes from 10 to 60°C, the swelling ratio of the traditional hydrogel (T-Gel) reduces from 5.6 to be around 4.0, with a ΔESR(ΔESR = $ESR_{10°C} - ESR_{60°C}$) of around 1.6. The increased ΔESR observed in the HPC- (2.5) and PEG-modified (4.0) hydrogels appears to be attributed to expanded network structure and subsequently the larger amount of contained water at 10°C. Thus, more water would be extruded upon heating,

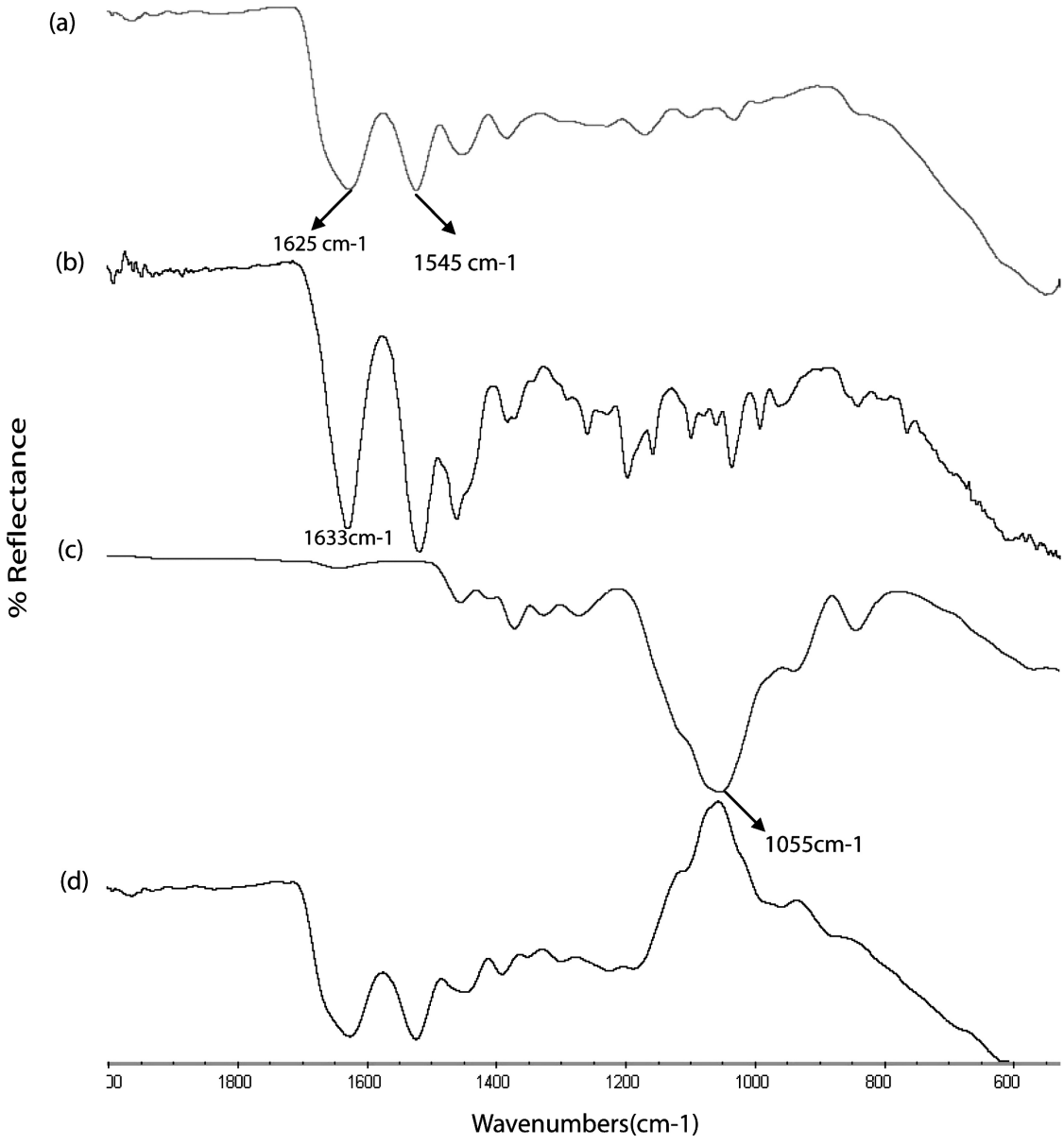


Fig. 2. ATR-FTIR spectra of the P(DMAPMA-co-AAm) hydrogels prepared in HPC aqueous solution (HPC-Gel) (a), in deionized water (T-Gel) (b), HPC (c) and difference spectrum (a–b) (d).

which result in the increased ΔESR.The T-Gel and PEG-Gel exhibited the discontinuous swelling behavior and their VPT-Ts were determined as 34°C. However, the deswelling for the HPC-Gel is not discontinuous due to its condensed structure caused by the extremely strong binding interactions between HPC and P(DMAPMA-co-AAm) chains, it is not easy to assign an exact value to VPT-T and cognizance of this difficulty is rarely taken in the literature. Hence, we have used a computer program to afford the derivative dQ_v/dT at each temperature. (Figure 4B). As shown in Figure 4B, the VPT-T of the HPC-Gel hydrogel is indicated clearly at the minimum of the curves as 41°C.

There vas no obvious effect of the pore-forming agents on the swelling ratio of the P(DMAPMA-co-AAm) hydrogels at 60°C. This suggests that, regardless of the pore-forming agent type, all the P(DMAPMA-co-AAm) hydrogels would collapse into similar collapsed structure at 60°C.

3.4 Deswelling Kinetics of Hydrogels

The macroporous hydrogels were also subjected to deswelling kinetics measurements. For this purpose, they were first swollen in water at 10°C to their equilibrium state. Thereafter, the swollen macroporous hydrogels were immersed in water at 50°C and deswelling process was monitored by measuring the hydrogel weight as a function of the time of deswelling (Figure 5). The swelling/deswelling behavior of the P(DMAPMA-co-AAm) hydrogels was

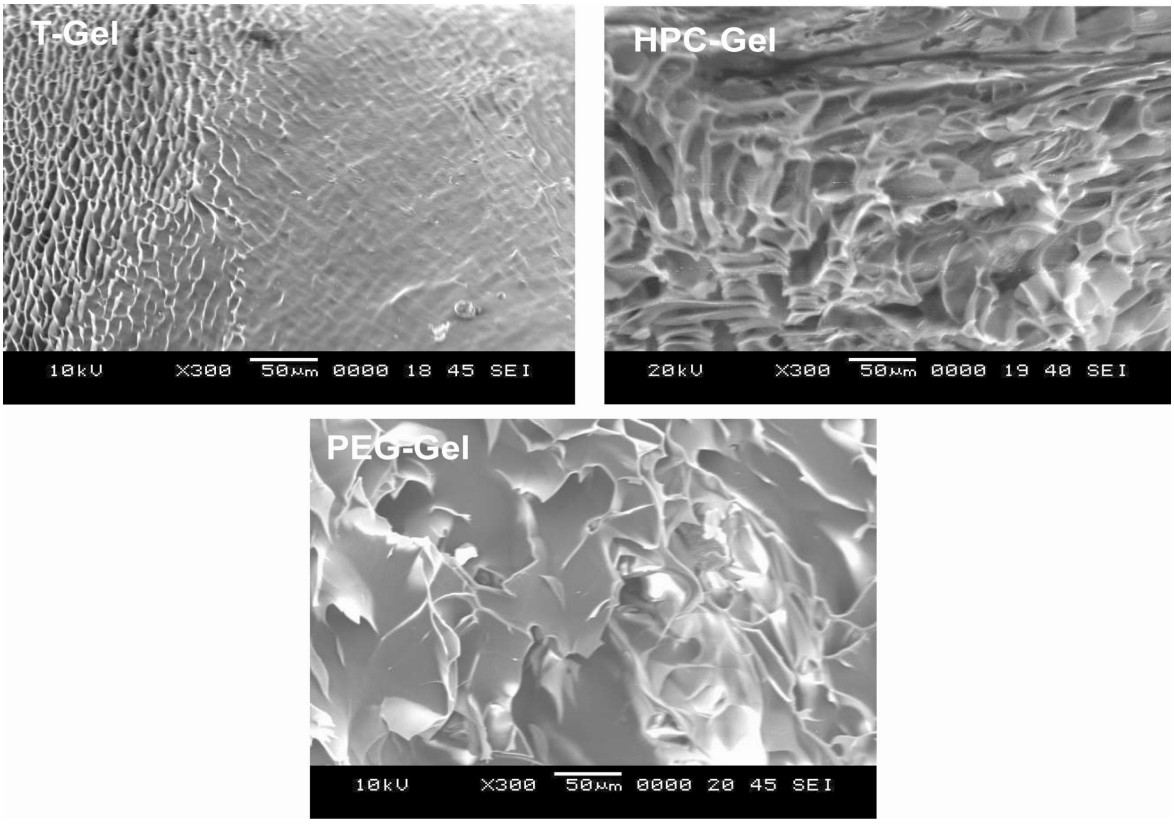


Fig. 3. Internal morphologies of the P(DMAPMA-co-AAm) hydrogels prepared in deionized water (T-Gel), in HCP aqueous solution (HPC-Gel) and in PEG aqueous solution (PEG-Gel) (300X, magnification).

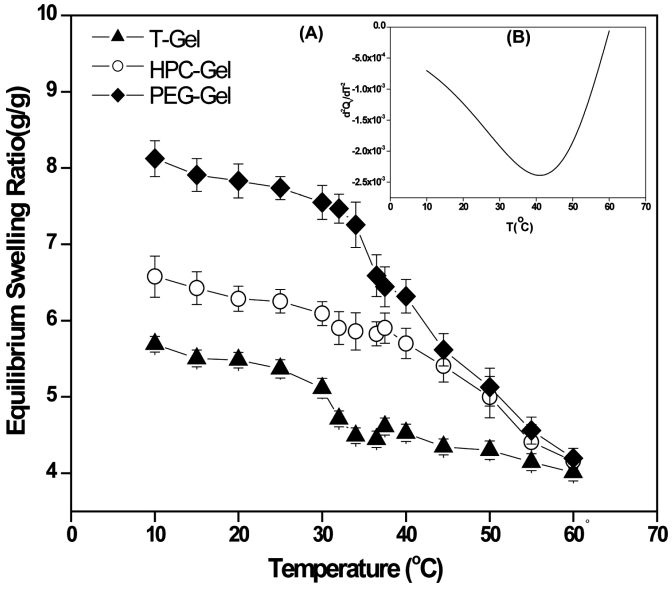


Fig. 4. (A) Temperature dependence of the equilibrium swelling/deswelling ratio of P(DMAPMA-co-AAm) hydrogels in the temperature range of 10–60°C. (B) Data for HPC-Gel in (A) plotted in the differential form of d(ES/DR)/dT versus temperature (T).

affected by the pore-forming agent type. It is obvious that PEG-Gel exhibited the fastest shrinking rate and lost water dramatically, and the normalized deswelling ratio reduced from 1.0 to about 0.82 within 50 min, and 0.43 within 100 min. HPC-Gel also showed a fast deswelling rate. However, T-Gel exhibited the slow deswelling rate and reduced from 1.0 to about 0.96 within 50 min and 0.85 within 100 min.

With respect to the deswelling kinetics, the traditional P(DMAPMA-co-AAm) hydrogel with an expanded network would demonstrate improved deswelling rate when transferred into hot water. It is regarded that, when the T-Gel hydrogel was transferred into hot water, the surface layer of the hydrogel was the first region to be affected, and a dense skin layer was generated due to hydrophobic interactions among the dimethylaminopropyl groups of P(DMAPMA-co-AAm) chains. Such a dense skin layer would greatly restrict the outward permeation of water from the hydrogel interior. However, in this study, the expanded P(DMAPMA-co-AAm) networks prepared in PEG and HPC solutions retarded the formation of such a dense skin layer during the deswelling process and the freed water might diffuse out quickly. As a result, the macroporous hydrogels with expanded network (PEG-Gel and HPC-Gel) exhibited a fast response rate at 50°C.

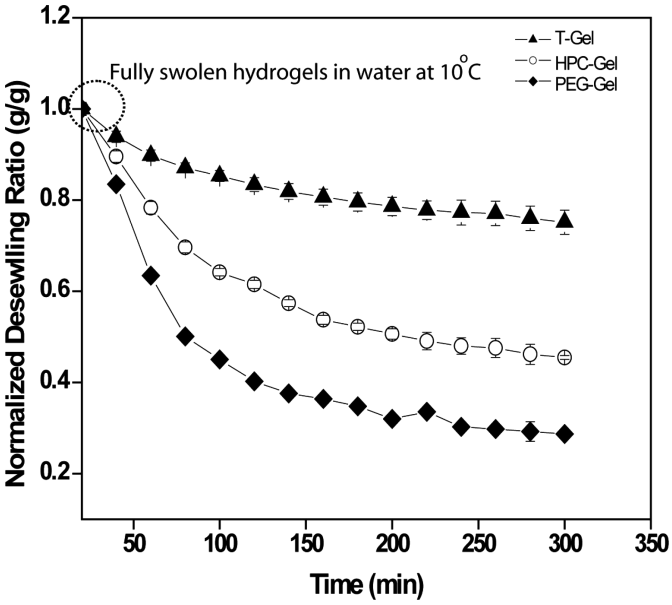


Fig. 5. The deswelling kinetics of P(DMAPMA-co-AAm) hydrogels upon temperature jumping from 10 to 50°C.

3.5 Swelling Kinetics of Hydrogels

Figure 6 displaces the swelling behaviors of the traditional and PEG- and HPC-modified samples after dried in vacuum oven at 60°C for 24 h. As shown in Figure 6, the PEG-Gel exhibited the largest swelling ratio at 22°C, while the HPC-Gel exhibited an intermediate swelling ratio due to its condensed structure caused by the extremely strong binding interactions between HPC and P(DMAPMA-co-AAm) chains. For example, the PEG-Gel had about 3.0 swelling ratio within 100 min, or 8.0 within 450 min, whereas the HPC-Gel had about 2.8 and 5.0, respectively, within the same time frames. On the other hand, the hydrogel with no added pore-forming agent (T-Gel) had about 1.3 swelling ratio within 100 min, or 3.1 within 450 min, This results showed also that the modified hydrogels absorbed water more quickly than the traditional hydrogel (T-Gel) because their macroporous structures make transfer of water molecules easier between the hydrogel matrix and the external aqueous phase.

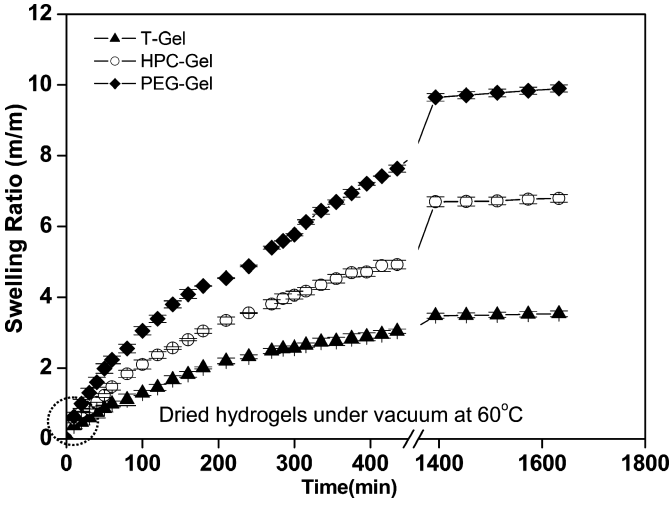


Fig. 6. The swelling kinetics of vacuum dried P(DMAPMA-co-AAm) hydrogels at 22°C.

4 Conclusions

In this study, the effect of the pore-forming agent type on the properties of P(DMAPMA-co-AAm) hydrogels, particularly the VPT-T behavior and response dynamics, were investigated. The addition of the PEG and HPC pore-forming agents does not change the chemical composition of the P(DMAPMA-co-AAm) hydrogels. The morphological data from SEM revealed that the interior network structure of the P(DMAPMA-co-AAm) hydrogel became more porous due to the presence of the PEG and HPC pore-forming agents during the polymerization. This more porous matrix provided numerous water channels for the water diffusion and, therefore, an improved response rate to the external temperature change during the deswelling process at 50°C and swelling process at 22°C. The data obtained in this study are useful to us for controlled release of macromolecular active agents.

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