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European Polymer Journal 43 (2007) 4975–4982
EUROPEAN POLYMER JOURNAL
www.elsevier.com/locate/europolj

Effects of synthesis-solvent on swelling and elastic properties of poly(*N*-isopropylacrylamide) hydrogels

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Received 11 July 2007; received in revised form 28 August 2007; accepted 17 September 2007
Available online 29 September 2007

Abstract

Thermosensitive *N*-isopropylacrylamide (NIPA) hydrogels were synthesized by a free radical copolymerization with *N*,*N*′-methylenebisacrylamide (MBAA) in four solvents: water, ethanol, acetone and *N*,*N*-dimethylformamide. The swelling and elastic properties of the hydrogels were affected by the synthesis-solvents; the hydrogels (e.g. NIPA/MBAA = 1000/50 mol/m^3-pre-gel solution) synthesized in water have smaller swelling volume and larger shear modulus at 10 °C than those synthesized in amphiphilic solvents. The network structure of hydrogels was estimated in terms of the conversion and two sorts of effective crosslinking density based on the Flory theory and the concentration of crosslinker. The hydrogels synthesized in water can have the microscopic inhomogeneous network arising from the entanglement of polymer chains, while the hydrogels synthesized in amphiphilic solvents can have the homogeneous network arising from the polymer concentration lower than the pre-gel solution and can be similar in network structure to the lightly crosslinked hydrogel synthesized in water.

Keywords: Poly(*N*-isopropylacrylamide); Hydrogel; Synthesis-solvent; Effective crosslinking density

1. Introduction

Thermosensitive hydrogels have attracted a great deal of attention for their potential applications to drug delivery system, biochemo-mechanical system, separation system by molecular recognition and so on [1]. Poly(*N*-isopropylacrylamide) (poly(NIPA)) has a lower critical solution temperature (LCST) in the vicinity of 33 °C [2]; it exhibits hydrophilicity and hydrophobicity in water at temperatures lower and higher than the LCST, respectively. NIPA hydrogel swells below the LCST and it shrinks as the temperature is raised.

NIPA hydrogel is generally synthesized by a free radical polymerization in water using a crosslinker and an initiator. In the last two decades, the characteristics of NIPA hydrogel synthesized in water were reported, such as equilibrium swelling [3], polymer–solvent interaction [4], elasticity [5] and

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doi:10.1016/j.eurpolymj.2007.09.016

swelling/shrinking kinetics [6]. This study concerns with synthesis-solvents for gel preparation. For the synthesis of NIPA gel, amphiphilic solvents can be used in some cases such as the copolymerization of NIPA and water-insoluble comonomer. Subsequently, NIPA hydrogels are obtained by washing with water. It has been reported that the transparency and swelling properties of NIPA hydrogel synthesized in aqueous acetone solution [7,8] or aqueous ethanol solution [8] depend on the concentration of solvent. As is clear from the above result, the synthesis-solvent is an important factor that determines the structure of gel network.

The purpose of this study is to elucidate the effects of synthesis-solvent on the network structure of NIPA hydrogels. NIPA hydrogels were synthesized in four synthesis-solvents: water, ethanol, acetone and *N*,*N*-dimethylformamide (DMF). The swelling and elastic properties of those hydrogels were investigated. The network structure of NIPA hydrogels were discussed in terms of the conversion and the effective crosslinking density.

2. Experimental

2.1. Preparation of gels

NIPA was kindly supplied by Kohjin Co. The NIPA gels with *N,N′*-methylenebisacrylamide (MBAA) as a crosslinker were synthesized in water, ethanol, acetone and DMF, respectively, by a free radical copolymerization for 24 h in a tube with 6 mm inside diameter under a nitrogen atmosphere. The concentrations of NIPA and MBAA were 600–1200 and 1–100 mol/m^3 in pre-gel solution, respectively. The polymerization in water was performed with *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TEMED, 10 mol/m^3) as an accelerator and ammonium peroxodisulfate (APS, 1 mol/m^3) as an initiator in a glass tube at 10 °C. The polymerization in ethanol, acetone and DMF was performed with 2,2′-azobisisobutyronitrile as an initiator (20 mol/m^3) in a polytetrafluoroethylene (PTFE) tube at 50 °C. The PTFE tube allows an easy removal of synthesized gels out of the tube, while the synthesized gels adhere tenaciously to the glass surface. The resulting gels were cut into 6-mm length (for the measurements of swelling diameter and shear modulus) and 50-mm length (for conversion measurement). Their gels were thoroughly washed with water to remove the unreacted monomers and to allow the gels to be the hydrogels.

2.2. Measurements of conversion

The conversion from monomers, NIPA and MBAA, to gel was investigated. The conversion is defined as the mass ratio of gel in dry state to monomers initially contained in the pre-gel solution. The hydrogel was slowly dried at room temperature for one week, followed by heating at 70 °C in an oven for 24 h. Then the mass of the resulting dry gel was measured.

2.3. Measurements of swelling diameter

The swelling diameter of cylinder-shaped hydrogel was measured as a function of temperature. The hydrogel was initially immersed in water at 10 °C. The diameter at equilibrium was measured with a microscope. The temperature was then increased and the diameter was measured at each temperature. In addition, the swelling ratio defined as V/V_p was determined where V is the volume of gel at equilibrium swollen state and V_p is the volume of polymer. V_p is estimated from the mass of dry gel sample and the densities of NIPA polymer (1.070 g/cm^3 [4]) and MBAA (1.235 g/cm^3 from catalogue).

2.4. Measurements of shear modulus

The shear modulus of cylinder-shaped hydrogel was measured by the compression [9,10]. The hydrogel was vertically placed in water at 10 °C. A weight was loaded to the hydrogel in a length direction. After several seconds, which is the sufficient time to attain the equilibrium deformation under the condition of no change in volume, the length of hydrogel, l, was measured with a digital inductive displacement sensor. The stress, P (Pa), was determined from the weight loaded and the cross-sectional area of hydrogel in the equilibrium deformation. The shear modulus, μ (Pa), of hydrogel was evaluated from the linear relation $dP = 3\mu$ (dl/l) between changes in stress dP and length dl/l.

3. Results and discussion

3.1. Swelling property

Fig. 1 shows the temperature dependence of swelling diameter of the cylinder-shaped NIPA hydrogels in water. The hydrogels have the compositions of NIPA/MBAA = 1000/50 mol/m^3 in pre-gel solution and were synthesized in water, ethanol,

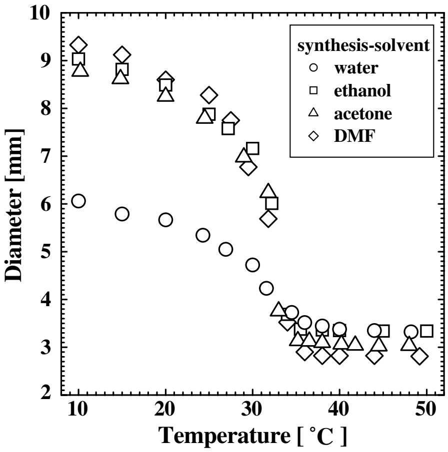

Fig. 1. Swelling diameter of the cylinder-shaped NIPA hydrogels (NIPA/MBAA = 1000/50 mol/m^3 in pre-gel solution) synthesized in water, ethanol, acetone and DMF.

acetone and DMF. The diameter of these hydrogels decreases with an increase in temperature, and a drastic change in diameter is observed around 30 °C due to the hydrophilic/hydrophobic transition of poly(NIPA). It is noted that the diameters vary by synthesis-solvent; for the hydrogel synthesized in water, the diameter at 10 °C is ca. 6 mm and for other solvents ca. 9 mm. In the case of compositions different from the above (e.g. NIPA/MBAA = 1000/100 and 1200/60 mol/m^3), the thermosensitive pattern of swelling diameter is similar to that in Fig. 1 for each synthesis-solvent, although the diameter of swollen hydrogel below the LCST decreases to some extent with an increase in MBAA concentration.

Fig. 2 shows the swelling ratio of NIPA hydrogels in water as a function of temperature. The swelling ratio also depends on the synthesis-solvents. At 10 °C, the swelling ratios of hydrogels synthesized in ethanol, acetone and DMF are quite larger than those synthesized in water due to the larger swelling diameter as shown in Fig. 1. However the attention needs to be paid to the conversion (see Section 3.3) as an important factor affecting the swelling ratio, since the amounts of NIPA and MBAA copolymerized is different from those in the pre-gel solution. The swelling ratio at 10 °C for each synthesis-solvent decreases with an increase in MBAA and/or overall monomer concentrations in the pre-gel solution. This is because the crosslinker and the entanglement of polymer chains (see Section 3.5) prevent the hydrogel swelling.

The effects of synthesis-conditions other than synthesis-solvent, i.e. initiator, substrate of reactor and temperature, on the swelling properties were investigated. The NIPA gel was synthesized in DMF under the conditions of APS/TEMED, glass tube and 35 °C. The swelling diameter of the obtained hydrogel is ca. 9 mm at 10 °C and the thermosensitive pattern of diameter is in close agreement with that in Fig. 1. Therefore the initiator and the substrate can have no influence on the gelation in amphiphilic solvents, although the PTFE wall causes the poor gelation in water [11,12]. The investigations mentioned below are discussed in terms of only synthesis-solvent.

3.2. Elasticity

Table 1 shows the shear modulus of the cylinder-shaped NIPA hydrogels in water at 10 °C. In Table 1, “incomplete gel” denotes that the gel was not synthesized. There are also differences in the shear modulus among synthesis-solvents. The shear modulus of hydrogel synthesized in water is one order of magnitude larger than that synthesized in other solvents. This means that the rigid hydrogel is obtained by the polymerization in water. The shear modulus increases with an increase in MBAA and/or overall monomer concentrations in the pre-gel solution, which results in the increase in crosslinking point (the crosslinker and the entangling point of polymer chains).

3.3. Conversion

The synthesis-solvent give the large influence on the swelling and elastic properties of NIPA hydrogels. However, prior to discussing the effect of synthesis-solvent, we need to know the concentrations of NIPA and MBAA copolymerized in the as-synthesized gel, i.e. polymer concentration. Table 2 shows the conversion from monomers, NIPA and MBAA, to gel. The conversion increases with an increase in MBAA and/or overall monomer concentrations in the pre-gel solution. The conversion for the synthesis in water is still higher than that in the others and is close to unity. In addition, the gelation in water was faster than that in amphiphilic solvent, where ca. ten minutes for the former and a few hours for the latter were taken to the time of approximate completion of gelation from the observation by eyes. These results demonstrate that water gives the good reactivity for the copolymerization of

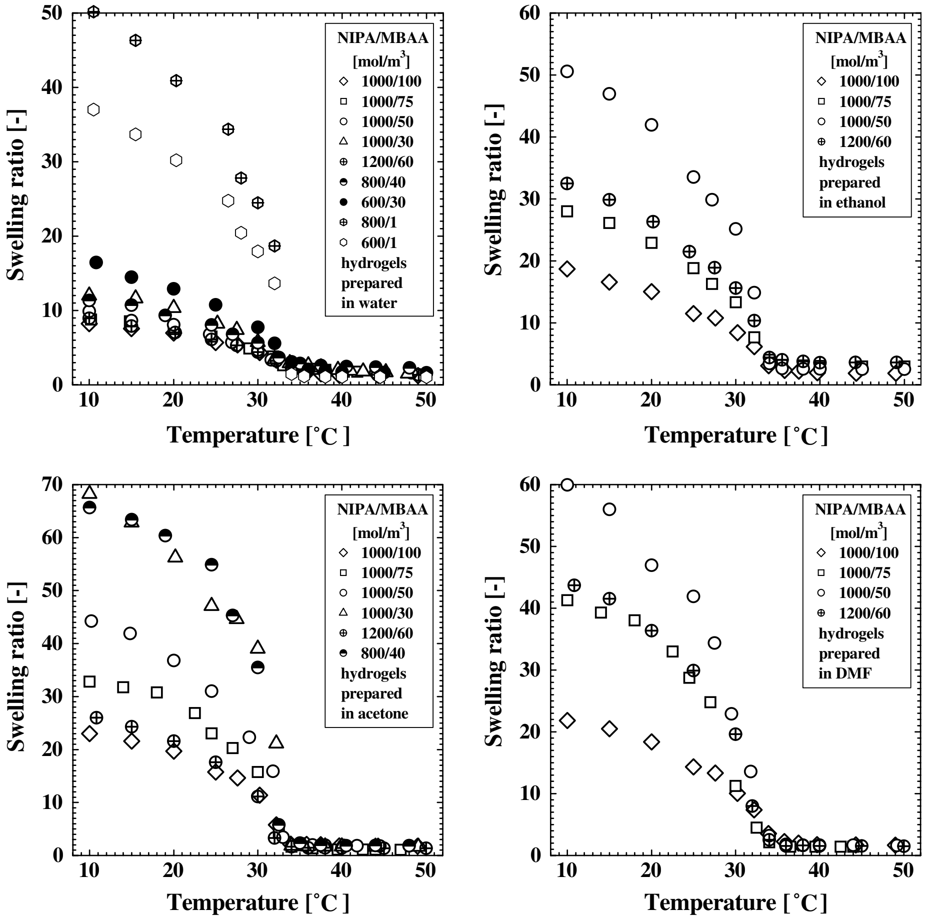

Fig. 2. Swelling ratio of the cylinder-shaped NIPA hydrogels synthesized in water, ethanol, acetone and DMF. The compositions of NIPA/MBAA in pre-gel solution are shown.

NIPA/MBAA, while the other solvents do the poor reactivity, which results in the “incomplete gel” in Table 2.

The polymer concentration can be estimated by multiplying the concentrations in the pre-gel solution by the conversion. Several sets exist in which the polymer concentration in gel synthesized in water equals to that in gel synthesized in amphiphilic solvent; NIPA/MBAA = 1000/50 mol/m^3-water and 1200/60 mol/m^3-acetone, 800/40 mol/m^3-water and 1200/60 mol/m^3-ethanol, and 600/30 mol/m^3-water and 1000/50 mol/m^3-DMF. In above each case, the hydrogel synthesized in water has smaller diameter and swelling ratio below the LCST, and larger shear modulus at 10 °C despite approximately the same polymer concentration. As shown in Fig. 2 and Table 1, the swelling ratio and the elastic modulus are strongly affected by MBAA concentration (or crosslinking point). It could be said that the amount of MBAA copolymerized in amphiphilic solvents is much lower than that in the pre-gel solution. On conclusion, there should be a dominant factor other than the polymer concentration to determine the swelling and elastic properties.

3.4. Crosslinking density

The effective crosslinking density of NIPA gels, ν_e, was investigated as a factor determining the network. The ν_e was determined by the following equation on the basis of the Flory theory [5,13,14].

$$\phi + \ln(1-\phi) + \chi\phi^2 - v_1\nu_e[\phi/(2\phi_0) - (\phi/\phi_0)^{1/3}] = 0, \tag{1}$$

where ϕ is the volume fraction of polymers at an equilibrium swollen state, ϕ_0 the volume fraction

Table 1
Shear modulus, μ (Pa), of the cylinder-shaped NIPA hydrogels in water at 10 °C

NIPA/MBAA (mol/m^3-pre-gel solution)	Synthesis-solvent			
	Water	Ethanol	Acetone	DMF
1000/100	3.77×10^4	5.44×10^3	2.07×10^3	3.01×10^3
1000/75	3.24×10^4	2.19×10^3	1.69×10^3	1.45×10^3
1000/50	2.73×10^4	0.71×10^3	1.03×10^3	0.68×10^3
1000/30	2.31×10^4	Incomplete gel	0.69×10^3	Incomplete gel
1200/60	4.74×10^4	1.93×10^3	2.44×10^3	0.97×10^3
1000/50	2.73×10^4	0.71×10^3	1.03×10^3	0.68×10^3
800/40	2.39×10^4	Incomplete gel	0.67×10^3	Incomplete gel
600/30	1.00×10^4	Incomplete gel	Incomplete gel	Incomplete gel

The gels were synthesized in water, ethanol, acetone and DMF.

Table 2
Conversion (–) of the NIPA gels synthesized in water, ethanol, acetone and DMF

NIPA/MBAA (mol/m^3-pre-gel solution)	Synthesis-solvent			
	Water	Ethanol	Acetone	DMF
1000/100	0.950	0.765	0.753	0.702
1000/75	0.938	0.661	0.740	0.655
1000/50	0.928	0.602	0.629	0.559
1000/30	0.893	Incomplete gel	0.527	Incomplete gel
1200/60	0.915	0.659	0.783	0.604
1000/50	0.928	0.602	0.629	0.559
800/40	0.960	Incomplete gel	0.577	Incomplete gel
600/30	0.946	Incomplete gel	Incomplete gel	Incomplete gel

of polymers when the gel network is in a random walk configuration, χ the polymer–solvent interaction parameter, and v_1 the molar volume of solvent. The ϕ_0 can be estimated by dividing the volume of polymer by the volume of gel at the preparation state. The ϕ is the reciprocal number of swelling ratio at 10 °C. The v_1 of water at 10 °C is determined from its density and molecular weight. The parameter of χ is 0.227 for poly(NIPA)–water at 10 °C [5].

Table 3
Effective crosslinking density, ν_e (mol/m^3), of the NIPA hydrogels synthesized in water, ethanol, acetone and DMF

NIPA/MBAA (mol/m^3-pre-gel solution)	Synthesis-solvent			
	Water	Ethanol	Acetone	DMF
1000/100	519	95.0	54.9	58.5
1000/75	457	42.0	27.3	17.4
1000/50	346	21.3	15.1	8.38
1000/30	222	Incomplete gel	7.60	Incomplete gel
1200/60	419	28.0	43.9	15.8
1000/50	346	21.3	15.1	8.38
800/40	245	Incomplete gel	6.86	Incomplete gel
600/30	118	Incomplete gel	Incomplete gel	Incomplete gel

The values of ν_e obtained are listed in Table 3. The ν_e of the gel synthesized in water is one or two orders of magnitude larger than that synthesized in other solvents. In the case of homogeneous gel, the ν_e is proportional to the concentration of crosslinker. In addition to the Flory theory, the effective crosslinking density can be theoretically estimated from the concentration of MBAA, C_{MBAA}, in as-synthesized gel as $\nu_{e,MBAA} = 2C_{MBAA}$. C_{MBAA} can be determined by multiplying the concentration of MBAA in pre-gel solution by the conversion, on the assumption that the molar ratio of NIPA and MBAA copolymerized is the same as that in the pre-gel solution. The values of $\nu_{e,MBAA}$ obtained are listed in Table 4. The $\nu_{e,MBAA}$ of the gel synthesized in water is also larger than that synthesized in the other solvents, but the difference in $\nu_{e,MBAA}$ between water and the other synthesis-solvents is small compared with that of ν_e.

3.5. Estimation of network structure

The network structure of NIPA gels synthesized in water and amphiphilic solvent is discussed in

Table 4
Effective crosslinking density, $\nu_{e,MBAA}$ (mol/m^3), of the NIPA hydrogels synthesized in water, ethanol, acetone and DMF

NIPA/MBAA (mol/m^3-pre-gel solution)	Synthesis-solvent			
	Water	Ethanol	Acetone	DMF
1000/100	190	153	151	140
1000/75	141	99.1	111	98.2
1000/50	92.8	60.2	62.9	55.9
1000/30	53.6	Incomplete gel	31.6	Incomplete gel
1200/60	110	79.1	93.9	72.4
1000/50	92.8	60.2	62.9	55.9
800/40	76.8	Incomplete gel	46.2	Incomplete gel
600/30	56.8	Incomplete gel	Incomplete gel	Incomplete gel

terms of the two sorts of effective crosslinking density. In the gels synthesized in water, the relation $\nu_e > \nu_{e,MBAA}$ was obtained. This fact indicates that the gel network is extensively crosslinked over the amounts of MBAA copolymerized. On the contrary, the relation $\nu_e < \nu_{e,MBAA}$ was obtained for the gels synthesized in amphiphilic solvent. This means that the crosslinking points or effective polymer chains are smaller than that theoretically estimated.

Fig. 3 shows the schematic illustration for networks of NIPA gels (e.g. NIPA/MBAA = 1000/50 mol/m^3) as-synthesized in water and DMF as the representative of amphiphilic solvents. In the gel synthesized in water, the good reactivity and the hydrophilic/hydrophobic transition of poly(NIPA) can cause the microscopic phase separation [15–17]. Indeed, NIPA polymer in water is more hydrophobic than NIPA monomer, since the surface tension of aqueous solution of NIPA polymer is smaller than that of NIPA monomer [12]. Therefore, the gel synthesized in water can have the entanglement of polymer chains, which plays a role of the crosslinking point, due to the aggregation of poly(NIPA). The gel synthesized in DMF has the polymer concentration lower than the pre-gel solution due to the poor reactivity. The poor reactivity can result in less amounts of MBAA copolymerized and more amounts of free ends, which allow the hydrogel to swell largely. Clear interpretation of the difference in characteristics among amphiphilic synthesis-solvents is difficult, although the reactivity in acetone is found to be somewhat larger.

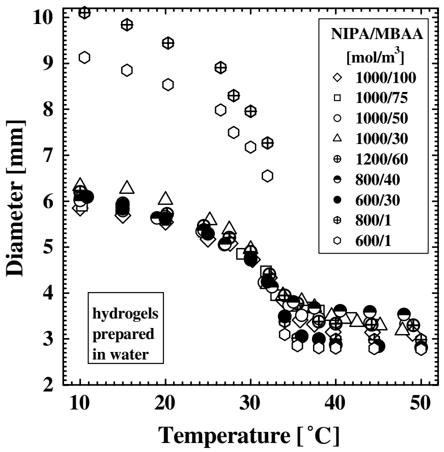

Fig. 4. Swelling diameter of the cylinder-shaped NIPA hydrogels synthesized in water at various monomer concentrations.

Table 5
Shear modulus, conversion and effective crosslinking density of the lightly crosslinked NIPA hydrogels synthesized in water

NIPA/MBAA (mol/m^3-pre-gel solution)	Shear modulus (Pa)	Conversion (–)	ν_e (mol/m^3)
800/1	0.67×10^3	0.928	8.53
600/1	0.85×10^3	0.951	8.80

3.6. Lightly crosslinked hydrogels

The molar ratio of MBAA to NIPA in the gel synthesized in DMF may be much lower than that in the pre-gel solution. From this viewpoint, the lightly crosslinked hydrogels which have the compositions of NIPA/MBAA = 800/1 and 600/1 mol/m^3

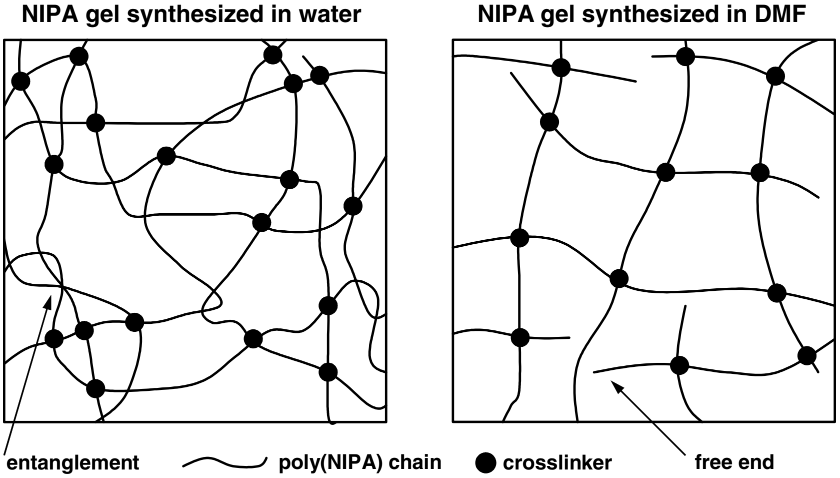

Fig. 3. Schematic illustration for networks of NIPA gels as-synthesized in water and DMF (e.g. NIPA/MBAA = 1000/50 mol/m^3).

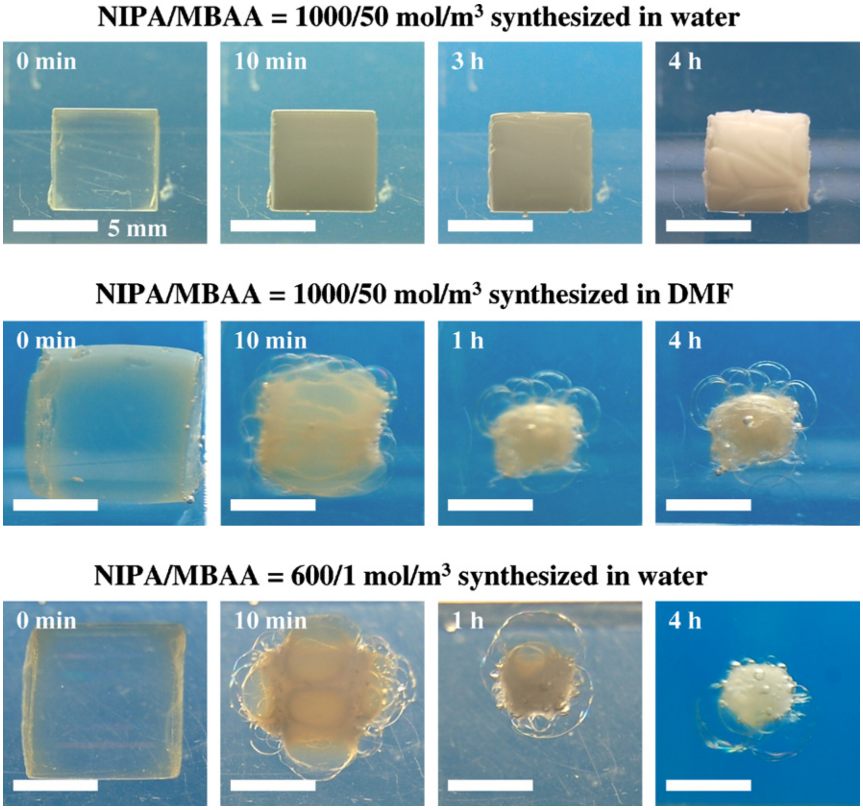

Fig. 5. Series of photographs showing the morphological changes of NIPA hydrogels in water after temperature jump from 10 °C to 50 °C.

in the pre-gel solution were synthesized in water. Fig. 4 shows the swelling diameter of the hydrogels synthesized in water at various monomer concentrations including the lightly crosslinked hydrogels and Table 5 shows the shear modulus, the conversion and the effective crosslinking density of their hydrogels. The values of the swelling diameter, the shear modulus and the effective crosslinking density for the lightly crosslinked hydrogels are in good agreement with those for the hydrogel of NIPA/MBAA = 1000/50 mol/m^3 synthesized in DMF.

The change in the morphology of the hydrogels in the shrinking process by a temperature jump across the LCST was investigated. The shrinking of the hydrogel was initiated by placing the hydrogel from water at 10 °C into water at 50 °C. Fig. 5 shows the morphological changes of the hydrogels. In the case of the hydrogel of NIPA/MBAA = 1000/50 mol/m^3 synthesized in water, a dense and shrunken network around the surface, so-called skin layer [18], was formed and subsequently a crack was appeared. On the other hand, a completely different shrinking behavior was observed for the hydrogel of NIPA/MBAA = 1000/50 mol/m^3 synthesized in DMF, that is, a thin polymer layer, bubble [19], was formed on the surface. The lightly crosslinked hydrogel of NIPA/MBAA = 600/1 mol/m^3 synthesized in water show a thermosensitive shrinking pattern similar to that of the hydrogel synthesized in DMF. These photographs strongly suggested that the hydrogel synthesized in DMF can be similar in network structure to the lightly crosslinked hydrogel synthesized in water, i.e. the amount of MBAA copolymerized in DMF is much lower than that in the pre-gel solution.

4. Conclusions

The swelling and elastic properties of NIPA hydrogels in water are affected by synthesis-solvent; the hydrogels (e.g. NIPA/MBAA = 1000/50 mol/m^3-pre-gel solution) synthesized in water have smaller swelling volume and larger shear modulus at 10 °C than those synthesized in amphiphilic solvents. The conversion shows that water gives the good reactivity for the polymerization of NIPA/MBAA and the amphiphilic solvents do the poor reactivity. From the relation between v_e and $v_{e,\mathrm{MBAA}}$, the network structure is estimated as follows; the hydrogels synthesized in water can have the microscopic inhomogeneous network arising from the entanglement of polymer chains, while hydrogels synthesized in amphiphilic solvents can have homogeneous network arising from the polymer concentration lower than the pre-gel solution and the molar ratio of MBAA to NIPA in the gel much lower than that in the pre-gel solution.

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