Effect of Comonomer Type and Concentration on the Equilibrium Swelling and Volume Phase Transition Temperature of *N*-Isopropylacrylamide-Based Hydrogels

J. A. Cortés,[1] E. Mendizábal,[1] I. Katime[2]

[1]*Departamento de Química, Universidad de Guadalajara, Boul. M. García Barragán, 1451. Guadalajara, Jalisco 44430, México*
[2]*Grupo de Nuevos Materiales y Espectroscopia Supramolecular, Departamento de Química Física, Facultad de Ciencia y Tecnología, Universidad del País Vasco, Campus Lejona, Vizcaya, España*

Received 11 September 2007; accepted 25 October 2007
DOI 10.1002/app.27632
Published online 29 January 2008 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The effect of incorporating a hydrophilic monomer into poly(*N*-isopropylacrylamide) (polyNIPA) hydrogels on the equilibrium swelling and the volume phase transition temperature is reported here. A nonionizable monomer (acrylamide) and three ionizable monomers (itaconic acid, 2-ethoxyethyl monoitaconate, and 2,2-(2-ethoxyethyl) monoitaconate) were studied. Hydrogels with larger swelling capacity than that of the polyNIPA hydrogel were obtained. With the exception of the hydrogel containing 2,2-(2-ethoxyethyl) monoitaconate, which did not exhibit the deswelling phenomena, the rest showed a volume phase transition. The hydrogels containing 85 wt % acrylamide and 15 wt % comonomer presented the higher shrinking ratio. For some compositions, the T_c of the polyNIPA hydrogel was within the desired temperature range (38–41°C) for controlled-drug delivery in the human body. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 108: 1792–1796, 2008

Key words: hydrogel; transition temperature; *N*-isopropylacrylamide; stimuli-sensitive polymers

INTRODUCTION

Volume phase transitions in polymer gels have attracted much attention because of its scientific and technological importance.[1] Phase transitions in polymer gels depend on temperature, pH, gel composition, solvent composition, and ionic concentration.[2–6] Poly(*N*-isopropylacrylamide) (polyNIPA) gels show a volume phase transition in water from a swollen to a shrunken state by increasing temperature.[4–7] This phase transition takes place at a critical temperature (T_c) as a result of the dissociation of the hydrophobic interactions between NIPA segments and water molecules caused by the presence of an upper consolute critical transition.[8] Above T_c, the hydrogen bonds between the amide groups of the NIPA and water molecules weaken or disappear and hydrophobic interactions are promoted.[9]

Hydrogels that have phase transitions in response to surrounding conditions are being considered for biomedical applications such as controlled drug release.[10–12] In some controlled drug release applications, it is desirable to have hydrogels with volume phase transitions between 38 and 41°C, which is the temperature range of the human body in response to some diseases. *N*-Isopropylacrylamide (NIPA)-based hydrogels are excellent candidates to be used as controlled drug release devices because of their good biocompatibility.[13] However, because the T_c of polyNIPA is around 32°C,[14] it is necessary to increase its phase transition temperature.

One way to increase the transition temperature of polyNIPA hydrogels and to modify its equilibrium water swelling is by copolymerizing NIPA with an organic acid or its salts.[6,9] For instance, the transition temperature and the equilibrium water intake of polyNIPA can be raised by incorporating increasing amounts of sodium acrylate in the gel[6] and as the amount of the sodium acrylate in the hydrogel is increased, the transition changes from continuous to discontinuous. Kawasaki et al. reported that depending on the pH of the solution, the transition could be continuous or discontinuous in gels of poly(*N*-isopropylacrylamide-*co*-sodium acrylate).[15] Shibayama et al. showed that the T_c of poly(*N*-isopropylacrylamide-*co*-acrylic acid) hydrogels increases with increasing acrylic acid content and that the higher swelling degree occurs at a pH between 7.0 and 9.0.[8] At higher pH's (>9.0), produced by adding NaOH, there is a lower water intake due to the ionic screening effect, whereas at lower pH's, the hydrogel becomes less hydrophilic because the degree of ioni-

Correspondence to: I. Katime (issa.katime@ehu.es).
Contract grant sponsor: the MCYT; contract grant number: MAT2006-11662-C03-01.

zation is very low. Erbil et al. studied the effect of copolymerizing three organic acids (itaconic, acrylic, and maleic acids) with NIPA and found that the hydrogels containing maleic acid showed the largest T_c and largest equilibrium swelling.[9]

In this work, we present the effect of copolymerizing hydrophilic monomers with NIPA on the amount of equilibrium water intake and volume phase transition temperature. The following four monomers were studied because it has been reported that they have good biocompatibility[16,17]: acrylamide (AM), which is nonionizable, and itaconic acid (IA), 2-ethoxyethyl monoitaconate, and 2,2-(2-ethoxyethyl) monoitaconate, which are ionizable.

EXPERIMENTAL

IA, NIPA, AM, and *N*,*N*-methylenbisacrylamide (NMBA) all from Aldrich, were purified by recrystallization. 2-Ethoxyethyl monoitaconate (EMI) and 2,2-(2-ethoxyethyl) monoitaconate (EEMI) were prepared in our laboratory with the procedure described elsewhere.[16] The initiator, potassium persulfate (KPS), 99.6% pure from J.T. Baker, was used as received. Water was double distilled.

The hydrogels were prepared by the following procedure. First, 2 g of a mixture of monomers (NIPA/hydrophilic monomer) of the desired composition (100/0; 85/15; 70/30; 55/45 w/w) were dissolved in 7 mL of double distilled water; then the crosslinking agent (2 wt % NMBA with respect to monomers) and KPS (1 wt % with respect to monomers) were added and the solutions were transferred into 10 mL ampoules. These ampoules were sparged with nitrogen for 3 min, sealed and transferred to a water bath at 60°C where the polymerization was carried out for 2 h to produce the hydrogels. Conversions higher than 96% were achieved in all cases.

The hydrogels were cut into 1 mm width discs. The discs were immersed in distilled water for three periods of 24 h to remove residual initiator and monomers. Then, the disks were bloated with filter paper and dried under vacuum at 40°C to constant weight. The xerogels were put in sealed plastics bags and stored in a desiccator jar with silica gel until they were used.

The equilibrium swelling capacity of the hydrogels was measured as a function of temperature as follows: first each dried disk was weighed (m_0) and then immersed in distilled water maintained at constant temperature, T, with a thermostated bath; after a certain period of time, each swollen disc was withdrawn, bloated with a filter paper, and weighed. This procedure was repeated until the weight of the disc remained constant and equal to $m_\infty(T)$. The equilibrium swelling at the temperature T, $W_{eq}(T)$, was calculated by:

$$W_{eq}(T) = \frac{m_\infty(T) - m_0}{m_0}$$

Once the hydrogel reached its equilibrium swelling at a given temperature, the temperature of water was changed and the procedure described above was repeated. Swelling experiments were carried out at a pH around 6.0.

The criterion to determine the critical temperature of de-swelling was the midpoint between the temperature where the equilibrium swelling starts to diminish drastically and the temperature at which the equilibrium swelling is practically constant.

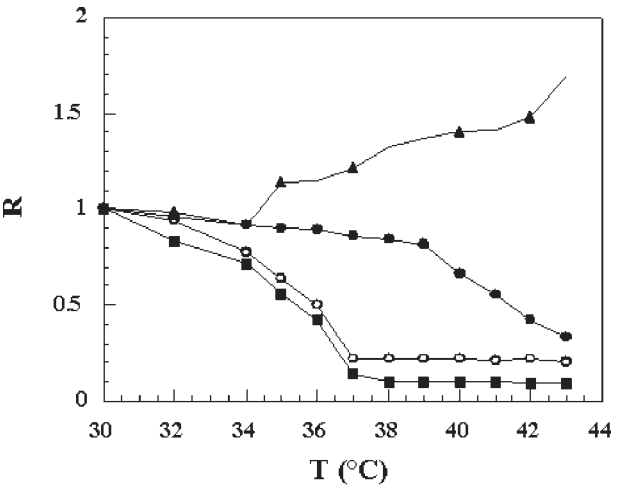

Figure 1 Ratio of the equilibrium swelling at a given temperature to that at 30°C for hydrogels of NIPA/IA: (O) 100/0; (■) 85/15: (●) 70/30; (▲) 55/45.

RESULTS

Figure 1 shows the ratio of the equilibrium swelling at a given temperature to that at 30°C, R [$\equiv W_{eq}(T)/W_{eq}(30°C)$], for hydrogels made by copolymerizing NIPA with increasing amounts of IA. The temperature of 30°C was chosen as a reference because it is below the volume phase transition temperatures of all the hydrogels examined here. Two effects can be clearly observed as the IA content increases. One is that T_c shifts to higher temperatures; the other is that the swelling capacity as a function of temperature varies. In fact, with the highest IA content, the equilibrium swelling of the hydrogel increases with increasing temperature, in contrast to the equilibrium swelling behavior of the other three. Notice also that the hydrogel with the lowest IA-content deswells more than the pure polyNIPA hydrogel.

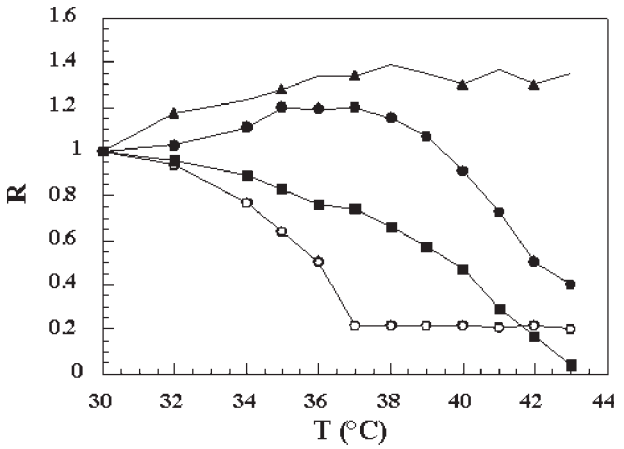

Figure 2 Ratio of the equilibrium swelling at a given temperature to that at 30°C for hydrogels of NIPA/EMI: (O) 100/0; (■) 85/15: (●) 70/30; (▲) 55/45.

Figure 2 displays R as a function of temperature for hydrogels of NIPA copolymerized with increasing amounts of EMI. Here, the de-swelling temperature also shifts to higher values and the de-swelling becomes less sharp with increasing EEMI content. At the highest EMI content, no de-swelling behavior is observed.

Figure 3 depicts R as a function of temperature for the hydrogels made of NIPA and varying amounts of 2,2-(2-ethoxyethyl monoitaconate). In this case, in contrast to the polyNIPA hydrogel, the equilibrium swelling of all the hydrogels containing EMI augments with increasing temperature.

The R versus temperature behavior of hydrogels made with NIPA and AM is shown in Figure 4. In all cases, the equilibrium swelling of the hydrogels decreases with increasing AM content. However, only the hydrogel containing 15 wt % AM shows a discontinuous de-swelling at a temperature higher than that of the polyNIPA hydrogel. The other hydrogels containing higher amounts of AM show a monotonic decrease in their equilibrium swelling with temperature.

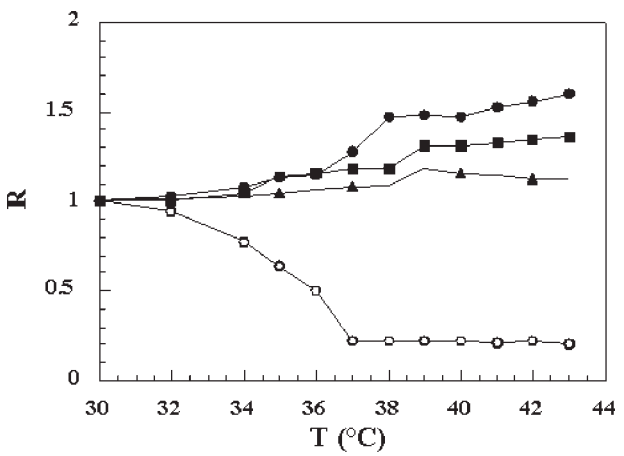

Figure 3 Ratio of the equilibrium swelling at a given temperature to that at 30°C for hydrogels of NIPA/EEMI: (O) 100/0; (■) 85/15: (●) 70/30; (▲) 55/45.

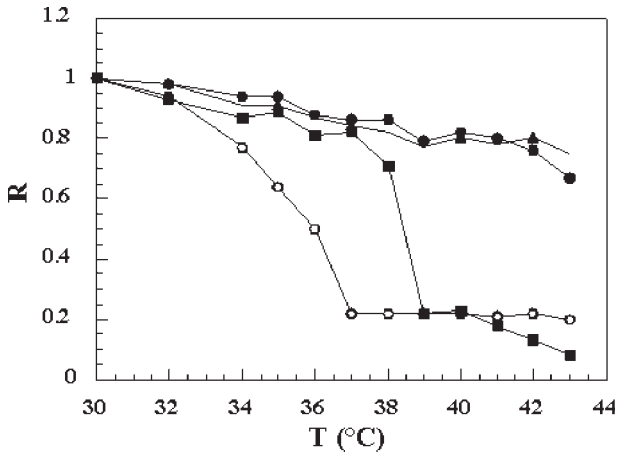

Figure 4 Ratio of the equilibrium swelling at a given temperature to that at 30°C for hydrogels of NIPA/AM: (O) 100/0; (■) 85/15: (●) 70/30; (▲) 55/45.

The values of the critical temperatures as well as the absolute values of the equilibrium swelling at the reference temperature, W_{eq} (30°C), for all hydrogels examined are reported in Table I.

DISCUSSION

NIPA is a monomer with low hydrophilicity, whose polymer exhibits a T_c around 32°C.[14] It has been reported that the equilibrium swelling as well as the volume phase transition temperature of polyNIPA hydrogels can be modified by the incorporation of more hydrophilic monomers.[6,8,9]

In this work, four hydrophilic monomers of different chemical structure were used to modify the T_c and the equilibrium swelling of polyNIPA hydro-

TABLE I
Equilibrium Swelling Temperature at 30°C and Critical Temperature of the Hydrogels

Hydrogel composition	W_{eq} (30°C) (g water/g xerogel)	T_c (°C)
100/0 (NIPA/Copolymer)	7.8	34
85/15 (NIPA/IA)	16.4	36
70/30 (NIPA/IA)	27.9	41
55/45 (NIPA/IA)	28.0	–
85/15 (NIPA/EMI)	24.4	38
70/30 (NIPA/EMI)	22.9	41
55/45 (NIPA/EMI)	29.8	–
85/15 (NIPA/EEMI)	13.8	–
70/30 (NIPA/EEMI)	22.9	–
55/45 (NIPA/EEMI)	40.0	–
85/15 (NIPA/AM)	26.9	38
70/30 (NIPA/AM)	36.3	–
55/45 (NIPA/AM)	46.1	–

gels. The monomers were IA, which has two acid groups, 2-etoxyethyl monoitaconate (EMI) and 2,2-(2-etoxyethyl) monoitaconate, which have only one acid group, and AM, which is a nonionizable hydrophilic monomer.

For many thermo-sensible polymeric hydrogels, especially for those produced by the polymerization of two or more monomers, it has been reported that the phase transition is not discontinuous, since there are always present composition inhomogeneities[9,18,19] Because in many cases the transition occurs in a range of 4–9°C, the T_c is commonly chosen as the middle point of the transition. To obtain a more accurate value of T_c, Katime et al. used the maximum of the derivative of the curve of swelling degree versus temperature[20]; however, it is necessary to obtain many experimental data points with high accuracy to use this method. This is difficult since experimental errors can occur because the hydrogel may be contaminated or some material may be lost during weight measurements; also when measuring volume changes by optical methods, errors can be introduced due to asymmetrical volume variations.[19]

To facilitate the determination of T_c as well the comparison of the swelling behavior among the hydrogels studied here, the ratio, R, of the equilibrium swelling volume at a given temperature to that at 30°C is plotted as a function of temperature.

Table I shows that when increasing the IA content, the equilibrium swelling at 30°C increases. This increase is because IA is more hydrophilic than NIPA and so, stronger hydrogen bonding interactions between the hydrogel and water molecules are promoted. Erbil et al. reported similar results for NIPA/IA hydrogels with IA content up to 10%.[9]

Table I and Figure 1 show that T_c raises from 36 to 41°C as the amount of IA is increased. Then, hydrogels with compositions between 15 and 30 wt % IA should have the desired T_c range, i.e., 38–41°C. At the highest IA content (45%) studied, the hydrogel does not shrink upon increasing temperature. The phase transition temperature, T_c, is a result of the competitive balance between the repulsive forces (electrostatic interaction between the charges of the same kind) and the attractive forces (van der Waals, hydrophobic interactions, hydrogen bonding, and ionic interactions between charges of opposite kind).[9,20] The replacement of hydrogen bonds by van der Waals hydrophobic interactions of the NIPA is the cause of the shrinking of the hydrogel above the phase transition temperature. However, as the amount of the hydrophilic monomer is increased, the hydrophobic interactions decreases and, as a consequence, the volume phase transition can completely disappear. Figure 1 also shows that with 15 wt % IA in the hydrogel, the shrinking ratio is higher than that of polyNIPA. In as much as hydrogels with a high shrinking ratio are desired for efficient drug release, this type of material may be of interest. However, by increasing the IA content above 15 wt %, the shrinking ratio now decreases because the hydrophobic interaction diminishes.

Because EMI and EEMI are both much more hydrophilic than NIPA, the equilibrium swelling volume of the hydrogels augments by increasing either of these esters content (Table I). Figure 2 and Table I show that T_c increases when the content of EMI increases. However, at the highest EMI concentration studied here, the collapsing of the hydrogel does not occur. The T_c obtained by the copolymerization of NIPA with 15 or 30 wt % EMI is within the desired temperature range (38–41°C). When 15 wt % EMI is used in the synthesis of the hydrogels, a large increase on the shrinking ratio is obtained. However, higher concentrations of this monomer produces a decrease in the shrinking ratio and, at the highest EMI concentration used, the hydrogels swells with temperature instead of collapsing because a decrease in the hydrophobic interactions, as discussed above.

The hydrogels of NIPA and EEMI do not de-swell even at the lowest concentration studied; instead they swell more when increasing temperature because the long hydrophilic ester chain of this comonomer prevents the hydrophobic interactions of the NIPA (Figure 3).

AM, being a more hydrophilic monomer than NIPA, produces an increase in the equilibrium swelling capacity of the hydrogel at all compositions examined (Table I). The hydrogel containing 15 wt % AM shows a T_c equal to 38°C, which is in the desired temperature range and a large increase in shrinking ratio (Table I and Figure 4). Hydrogels with higher AM concentration show only a slight decrease in the swelling capacity of the hydrogel with temperature and even at the highest temperature studied, the collapsing of the gel did not occur. The decrease on swelling capacity with temperature indicates that hydrophobic interactions are high and that probably T_c for these compositions is above 46°C.

CONCLUSIONS

In all the cases studied here, the copolymerization of NIPA with more hydrophilic monomers produced hydrogels with a larger swelling capacity than the polyNIPA hydrogel. For some compositions, the T_c of the polyNIPA hydrogel was increased within the desired temperature range (38–41°C) for human body applications. With the exception of the hydrogel containing EEMI, which did not present the de-swelling phenomena, the hydrogels with 85/15 composition presented the higher shrinking ratio. It is

noteworthy that the hydrogels made of NIPA and the comonomers employed here are potentially attractive for controlled drug delivery in the human body inasmuch as they are biocompatible and the volume phase transition of the hydrogels can be set at the desired range.

References

1. Kawaguchi, H.; Fujimoto, K.; Mizuhara, Y. Colloids Polym Sci 1992, 270, 53.
2. Ilavsky, M. Macromolecules 1982, 15, 782.
3. Wang, C.; Cao, W. Polym Intern 1996, 41, 449.
4. Inomata, H.; Nagahama, K.; Saito, S. Macromolecules 1994, 27, 6459.
5. Hibayama, M.; Morimoto, M.; Nomura, S. Macromolecules 1994, 27, 5060.
6. Hirotsu, S.; Hirokawa, Y.; Tanaka, T. J Chem Phys 1987, 87, 1392.
7. Shibayama, M.; Tanaka, T. Adv Polym Sci 1993, 109, 1.
8. Shibayama, M.; Mizutani S.; Nomura, S. Macromolecules 1996, 29, 2019.
9. Erbil, C.; Aras, S.; Uyanir, N. J Polym Sci Part A: Polym Chem 1999, 17, 1847.
10. Attorbett, T.; Ratner, B. D.; Kost, J. In Recent Advances in Drug delivery Systems; Anderson, J. M., Kim, S.W., Eds.; Plenum Press: New York, 1984; p 209.
11. Vakkalanka, S. K.; Pepas, N. A. Polym Bull 1996, 36, 221.
12. Bell, C. L.; Peppas, N. J Control Release 1996, 39, 201.
13. Brannon, L.; Peppas N. Med Plast Biomater Magazine 1997, Nov 1–17.
14. Mears, S. J.; Deng, Y.; Cosgrove, T.; Pelton, R. Langmuir 1997, 13, 1901.
15. Kawasaki, H.; Sasaki, S.; Maeda, H. J Phys Chem B 1997, 101, 5089.
16. Blanco, M. D.; García, O.; Olmo, R.; Teijón, J. M.; Katime, I. Biomaterials 1996, 17, 1061.
17. Blanco, M. D.; García, O.; Olmo, R.; Teijón, J. M.; Katime, I. J Chromatogr B Biomed Appl 1996, 680, 243.
18. Yi, Y. D.; Bae, Y. C. J Appl Polym Sci 1998, 67, 2087.
19. Yi, Y. D.; Oh, K. S.; Baer, Y. C. Polymer 1997, 38, 3471.
20. Katime, I.; Quintana, J. R.; Valderruten, N.; Cesteros, L. C. Macromol Chem Phys 2006, 207, 2121.