Synthesis, Characterization, and Drug Release Properties of Poly(*N*-isopropylacrylamide) Gels Prepared in Methanol–Water Cononsolvent Medium

Chandra Sekhar Biswas, Vijay Kumar Patel, Niraj Kumar Vishwakarma, Avnish Kumar Mishra, Rajasekhar Bhimireddi, RamaNand Rai, Biswajit Ray

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India

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ABSTRACT: Poly(*N*-isopropylacrylamide) (PNIPAM) hydrogels were simply prepared by free radical polymerization in different methanol–water mixture. A scanning electron microscopy study revealed that the freeze-dried hydrogels were macroporous. The swelling ratios in water at 20°C of the resulting hydrogels followed the order: $X_{0.43}>X_{0.21}>X_{0.76} \approx X_{0.57}>X_{0.31}>X_{0.13}>X_{0.06}>X_0$, where X_m denotes a gel prepared in a methanol–water mixture with *m* mole fraction of methanol (x_m). Below the lower critical solution temperature, the swelling ratio values of all of the hydrogels gradually decreased with the increase in the temperature. The complete collapse of the PNIPAM chain of all the gels occurred at about 38°C, whereas the same was observed at about 35°C for the conventional gel prepared in water. The swelling ratio values of all the PNIPAM gels in the methanol–water mixtures with different x_m values at 20°C passed through a minimum in the cononsolvency zone. The deswelling rates of the hydrogels decreased in the following order: $X_{0.43}> X_{0.31}> X_{0.21}> X_{0.57}> X_{0.76} \approx X_{0.13}> X_{0.06}> X_0$. The reswelling rates of these hydrogels decreased in the following order: $X_0> X_{0.31}> X_{0.06} \approx X_{0.13} > X_{0.76}> X_{0.57}> X_{0.21}> X_{0.43}$. The release rates of the Tramadol Hydrochloride drug at 37°C from the drug-loaded hydrogels were almost same for all of the hydrogels. © 2012 Wiley Periodicals, Inc. J Appl Polym Sci 125: 2000–2009, 2012

Key words: poly(*N*-isopropylacrylamide) hydrogel; cononsolvency; methanol–water mixture; morphology; swelling ratio; deswelling kinetics; reswelling kinetics; drug delivery; Tramadol Hydrochloride

INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNIPAM) homopolymer or its cross-linked gel undergoes volume phase transition in water at around 33°C.[1] This temperature is known as its lower critical solution temperature (LCST). PNIPAM also undergoes volume phase transition below its LCST due to the variation of the composition of water in water-miscible good organic solvents of PNIPAM like methanol,[2–4] ethanol,[5] tetrahydrofuran (THF),[6,7] dimethylsulphoxide,[1,7] and *N*,*N*-dimethylformamide (DMF),[8,9] etc. This is due to the cononsolvency phenomenon,[10–12] where the mixtures of two good solvents behave as a poor solvent for a linear polymer or its cross-linked gel.

As for example, below its LCST, PNIPAM homopolymer shows the gradual collapse of the coiled chain in changing the methanol content (x_m) of the methanol–water mixture from 0.0 to 0.2. This is due to the onset of cononsolvency, wherein the stronger interaction between water and methanol gradually predominates over that of their interactions with PNIPAM.[10,11,13,14] The globular state of PNIPAM in methanol–-water mixture is observed in the cononsolvency zone of around $x_m = 0.2$–0.4, wherein the stronger interaction between methanol and water predominates over that of their interactions with PNIPAM.[10,11,13,14] Here, PNIPAM is still in slightly swollen state, which contains almost around 80% solvent in its hydrodynamic volume.[14] With the increase of the x_m value in the range of 0.2–0.4, this globular state of PNIPAM swells slightly due to cononsolvency.[14] On further increase of the x_m value in the range of 0.4–0.5, the globular state starts redissolving in around $x_m = 0.4$ and becomes completely dissolve around $x_m = 0.5$.[14] On further increase of the methanol content ($x_m > 0.5$), solvency remains almost constant.[14]

The synthesis of porous PNIPAM hydrogels were reported in different cononsolvent mixtures, e.g., water–DMF mixture,[15–17] water–ethanol mixture,[18] water–acetone mixture,[18–20] water–THF mixture,[6]

Correspondence to: B. Ray (biswajitray2003@yahoo.co.in).
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TABLE I
Synthesis of Poly(*N*-isopropylacrylamide) Gels in the Presence of Different Composition of Methanol–Water Mixture[a]

	Run ID							
	X_0	$X_{0.06}$	$X_{0.13}$	$X_{0.21}$	$X_{0.31}$	$X_{0.43}$	$X_{0.57}$	$X_{0.76}$
MeOH (mL)	–	0.25	0.5	0.75	1.0	0.75	1.0	1.25
Water (mL)	1.25	1.0	0.75	0.5	0.25	0.5	0.25	–
Solution of TEMED (107 mmol/dm^3) in water (mL)	0.5	0.5	0.5	0.5	0.5	–	–	–
Solution of TEMED (107 mmol/dm^3) in methanol (mL)	–	–	–	–	–	0.5	0.5	0.5
Conversion (%)[b]	95	95	90	88	72	85	95	84
Appearance	Transparent	Opaque	Opaque	Opaque	Opaque	Opaque	Transparent	Transparent
Swelling ratio (W_s/W_d) at 20°C[c]	11.4	15.0	16.3	26.2	16.7	28.4	19.9	20.5
Swelling ratio (W_s/W_d) at 40°C[c]	1.8	1.6	1.6	1.7	1.8	1.5	1.4	1.9

[a] NIPAM = 160 mg, BIS = 8 mg, APS = 0.25 mL aqueous solutio of concentration 84 mmol/dm^3, polymerization temperature = 5°C, polymerization time = 12 h.
[b] Determined gravimetrically after drying under vacuum at 50°C for 72 h after dialysis.
[c] W_s = Weight of the swelled gel at a specified temperature after 24 h swelling, W_d = weight of the dry gel.

etc. Very recently, we have reported the synthesis and the study of the swelling properties and morphology of PNIPAM hydrogels prepared in different ethanol–water cononsolvent mixtures.[21] In this context, the study of the polymerization (crosslinking) reaction of *N*-isopropylacrylamide (NIPAM) with the crosslinker *N*,*N*′-methylenebisacrylamide (BIS) in the different compositions of methanol–water mixtures will be very important in the understanding of its cononsolvency effect on the properties of the formed gel. Moreover, very recently, we have reported the synthesis and study of the swelling properties and morphology of the stereo-controlled PNIPAM gels prepared in the presence of different concentration of Lewis acid $Y(OTf)_3$ in 1 : 1(v/v) methanol–water binary solvent mixture.[22] To understand the effect the compositions of methanol–water mixtures as synthesis media in the presence of Lewis acid $Y(OTf)_3$ on the properties of stereo-controlled PNIPAM gels, it is important to explore the effect the compositions of methanol–water mixtures as synthesis media in the absence of Lewis acid $Y(OTf)_3$ on the properties of PNIPAM gels. Only Erbil et al.[20] reported the synthesis of one crosslinked PNIPAM gel sample in 60% (v/v) methanol–water mixture and studied only its temperature dependence of volume swelling ratios. So far, to our knowledge, there was no report of the synthesis of PNIPAM gels in the different compositions of methanol–water mixtures and the study of their morphology, swelling, deswelling, and reswelling properties. Here, we have reported the synthesis of a series of PNIPAM gels in the different compositions of methanol–water mixtures, their morphology studied by scanning electron microscopy (SEM), the variation of their swelling ratios in water at different temperatures, the variation of their swelling ratios in different composition of methanol–water mixture at 20°C, their deswelling and reswelling kinetics in water at 40°C and 20°C, respectively, and their drug release behavior at 37°C using the model drug Tramadol Hydrochloride.

EXPERIMENTAL

Materials

NIPAM (Aldrich, St. Louis, Missouri) was purified by recrystallization from *n*-hexane. *N*,*N*′-methylenebisacrylamide (BIS, Aldrich, St. Louis, Missouri), ammonium persulfate (APS, Loba Chemie, Mumbai, India), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED, Aldrich, St. Louis, Missouri), Tramadol Hydrochloride (Tramadol HCl) (Win Medicare Ltd, New Delhi, India) were used as received. Methanol (Loba Chemie, Mumbai, India) was dried and distilled over anhydrous calcium oxide. Deionized water was prepared by redistillation of the double distilled water in an all-glass distillation apparatus.

Synthesis of poly(NIPAM) hydrogels

Three stock solutions were prepared: (i) a solution of TEMED in water having concentration of 107 mmol/dm^3, (ii) a solution of TEMED in methanol having concentration of 107 mmol/ dm^3, and (iii) a solution of APS in water having concentration of 84 mmol/ dm^3. At first, the required amount (as specified in Table I) of NIPAM, BIS, TEMED solution, and solvents were taken in a small borosilicate glass tube (6 mm internal diameter × 100 mm length) fitted with rubber septum. Both the pregel mixture (NIPAM, BIS, and TEMED) and the APS stock solution in water were purged with N_2 gas for 30 min. These

two mixtures were dipped into an isothermal bath maintained at 5°C ± 0.1°C under N_2 atmosphere for 30 min. Then, the nitrogen-purged APS stock solution was added to the pregel mixture through rubber septum by a degassed syringe, mixed immediately by tilting the reaction tube up and down, and allowed to react at 5°C ± 0.1°C for 12 h. The prepared gels were cut into small disk type pieces of 3 mm thickness × 6 mm external diameter and dipped into the deionized water for dialysis to remove the unreacted chemicals, and water was changed twice in a day until the conductance of water used in dialysis became equal to the freshly distilled deionized water. After the dialysis, the gels were dried under vacuum at 50°C for 72 h. The conversion (%) was determined gravimetrically.

FTIR spectra of the dried gels

FTIR spectra of the freeze-dried hydrogel samples were taken in the 400–4000 cm^{-1} range by making the pellet with KBr.

Surface morphology

Gels were swollen in deionized water at 20°C for 24 h to reach the equilibrium swelling condition. These equilibrium-swollen gels were freeze-dried under vacuum to remove water completely. The surface morphology of the freeze-dried samples were analyzed with FEI-SEM Quanta 200F (Philips) at an accelerated voltage of 5 kV.

Swelling ratios at different temperatures

Swelling ratios of the different gels at 20°C, 22.5°C, 27.5°C, 30°C, 32.5°C, 35°C, 38°C, and 40°C temperatures were measured gravimetrically. The preweighed dried gels were immersed in deionized water for 24 h at the desired temperature in order to get the equilibrium-swollen gels. These equilibrium swollen gels were then taken out, the surface water was soaked with moistened filter paper, and their weights were taken. The swelling ratio (W_s/W_d) was calculated as the ratio of the weight of the equilibrium-swollen gel (W_s) to that of the dried gel (W_d).

Swelling ratios in different methanol–water mixtures at 20°C

Swelling ratios of the different gels in the methanol–water mixtures with the x_m values of 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.8, and 1.0 at 20°C temperature were measured gravimetrically using the method as described above.

Deswelling kinetics at 40°C

Deswelling kinetics in water at 40°C of the equilibrium-swollen gels obtained after immersing in water at 20°C for 24 h were measured gravimetrically. The preweighed equilibrium-swollen gels at 20°C were immersed quickly in the water at 40°C. At the definite time intervals, the gels were taken out, the surface water was soaked with moistened filter paper, their weights were taken, and then the gels were quickly immersed back in the water at 40°C. Water retention (%) was calculated as the weight percentage of the water retained ($W_t - W_d$) by the swollen gel (W_t) at any definite time interval (t) with respect to that (W_s-W_d) by the equilibrium-swollen hydrogel (W_s) at 20°C.

Reswelling kinetics at 20°C

Reswelling kinetics in water at 20°C of the equilibrium-swollen gels obtained after immersing in water at 40°C for 24 h were measured gravimetrically. The preweighed equilibrium swollen gels at 40°C were immersed quickly in the water at 20°C. At the definite time intervals, the gels were taken out, the surface water was soaked with moistened filter paper, their weights were taken, and then the gels were quickly immersed back in the water at 20°C. Water uptake (%) was calculated as the weight percentage of water absorbed by the swollen hydrogel at any definite time interval t (W_t -W_d) with respect to that by the equilibrium-swollen hydrogel ($W_s - W_d$) at 20°C.

Drug release experiments with model drug tramadol hydrochloride at 37°C

Dry gels were immersed in a 3 mL 10% (w/w) solution of Tramadol Hydrochloride in water for 48 h at 10°C to reach their equilibrium drug uptake capacity. Then, the gels were taken out and their surfaces were washed with deionized water carefully to remove the drugs attached on the surface. The drug-loaded gels were dried under vacuum at room temperature for 72 h to get the constant weight. The percentage (%) of drug loading was calculated by using the following equation:

$$\text{Drug Loading}(\%) = 100(W_l - W_d)/W_d$$

where W_l is the weight of the loaded gel and W_d is the weight of the dry gel. Drug release kinetics was monitored spectrophotometrically at 215 nm wavelength using UV-visible spectrophotometer (JASCO V, 670, Japan) by immersing the loaded gels in 1 L deionized water at 37°C. At the definite time intervals, 3 mL solution was taken out, placed in the

quartz cell to record the UV-vis spectrum to measure the drug release rate, and after measurement, returned back to the bulk solution to keep the total volume of the solution constant. The spectra were recorded at 15, 30, 60, 120, 180, 240, 360, and 480 min time intervals. A calibration curve was made by comparing the intensity of the peak at 215 nm of all of the spectra of a series of known different concentrations (10^{-4}–10^{-6} *M*) of the drug in water. The cumulative drug release (%) was analyzed by comparing the intensity of the peak of the drug at 215 nm at particular time with the calibration curve of the standards. By plotting the cumulative drug release (%) against the time, we got the relative rate of the drug release of the hydrogels.

RESULTS AND DISCUSSION

The synthesis conditions of PNIPAM hydrogels and their characterization data are included in Table I. The observed yields (%) are within 72–95%. The appearance of the as-prepared hydrogels changes from transparent (run X_0) to opaque (runs $X_{0.06}$, $X_{0.13}$, $X_{0.21}$, $X_{0.31}$, and $X_{0.43}$) and then changes back to transparent (runs $X_{0.57}$ and $X_{0.76}$). The observed transparency of the gels prepared at $x_m = 0$ (run X_0), 0.57 (run $X_{0.57}$), and 0.76 (run $X_{0.76}$) is due to the highly solvated coiled conformation of PNIPAM chain segment in the gel owing to the strong interaction of water/methanol–water mixtures with the PNIPAM chain segment. On the other hand, the observed opacity of the gels prepared at $x_m = 0.06$, 0.13, 0.21, 0.31, and 0.43 (runs $X_{0.06}$, $X_{0.13}$, $X_{0.21}$, $X_{0.31}$, and $X_{0.43}$, respectively) is due to the formation of less solvated aggregated globular PNIPAM chain segment owing to the cononsolvency of such methanol–water mixtures toward the PNIPAM chain segments of the gel.

The FTIR spectra of all of the freeze-dried hydrogel samples are shown in the Figure 1. All spectra are almost same. This confirms that all the gels are of same chemical composition.

The SEM images of all the freeze-dried hydrogels are shown in the Figure 2. The magnification of all the SEM images is 6000×. The gel prepared in water ($x_m = 0$) (run X_0) is macroscopically homogeneous [Fig. 2(a)] as evident from the absence of any apparently visible pores. Other gels have macroporous fibrillar type morphology. The porosity of the gels increases gradually with increase in the x_m value from 0 [Fig. 2(a), run X_0] to 0.06 [Fig. 2(b), run $X_{0.06}$] to 0.13 [Fig. 2(c), run $X_{0.13}$] in the synthesis solvent mixture. This is due to (i) the increase in the polymerization rate in the presence of methanol owing to the faster decomposition of ammonium persulfate initiator[23] and (ii) the gradual decrease in the solvency of the PNIPAM chain segment owing to the

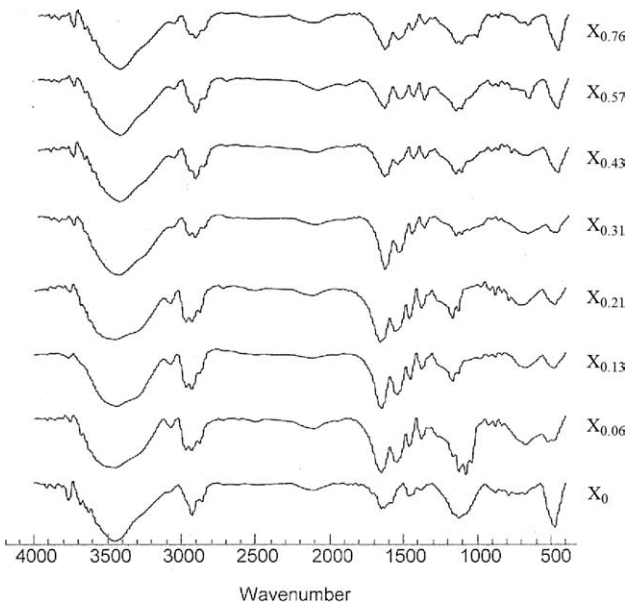

Figure 1 FTIR Spectra of the dried PNIPAM hydrogels synthesized in 0 (run X_0), 0.06 (run $X_{0.06}$), 0.13 (run $X_{0.13}$), 0.21 (run $X_{0.21}$), 0.31 (run $X_{0.31}$), 0.43 (run $X_{0.43}$), 0.57 (run $X_{0.57}$), and 0.76 (run $X_{0.76}$) mole fraction of methanol in water mixtures.

proximity of the cononsolvency. With a further increase of the x_m value to 0.21 (run $X_{0.21}$), there is a significant increase in the porosity of the gel [Fig. 2(d)]. This may have been due to the complete collapse of the PNIPAM chain segment into its globular state in the cononsolvency zone (x_m = 0.17–0.40).[13] With a further increase of x_m to 0.31 (run $X_{0.31}$), the resulting gel [Fig. 2(e)] showed a macroporous morphology with thick-walled cross-linked network structure with a smaller pore size. The higher viscosity of this methanol–water mixture[24] and the very weak interaction of the methanol–water complex toward the PNIPAM segments present in the gel owing to their strong interactions among themselves may have significant roles apart from its formation through the solid (swollen) phase polymerization at the almost middle of the cononsolvency zone. As a result, polymer–polymer chain interaction increases and eventually leads to the formation of a thick-walled cross-linked gel network. With a further increase of the x_m value to 0.43 (run $X_{0.43}$), the obtained gel is also macroporous with larger pore size having freely terminated PNIPM chains [Fig. 2(f)] owing to the solid (swollen) phase polymerization in the cononsolvency zone. With a further increase of the x_m value to 0.57 (run $X_{0.57}$), the resulting gel [Fig. 2(g)] shows a macroporous morphology with a smaller pore size. This may have been due to the increase in the solvency (redissolution) of the PNIPAM chain segment in the methanol-rich zone ($x_m \geq 0.50$). Thus, all these images confirm the formation of highly porous structures of the hydrogels

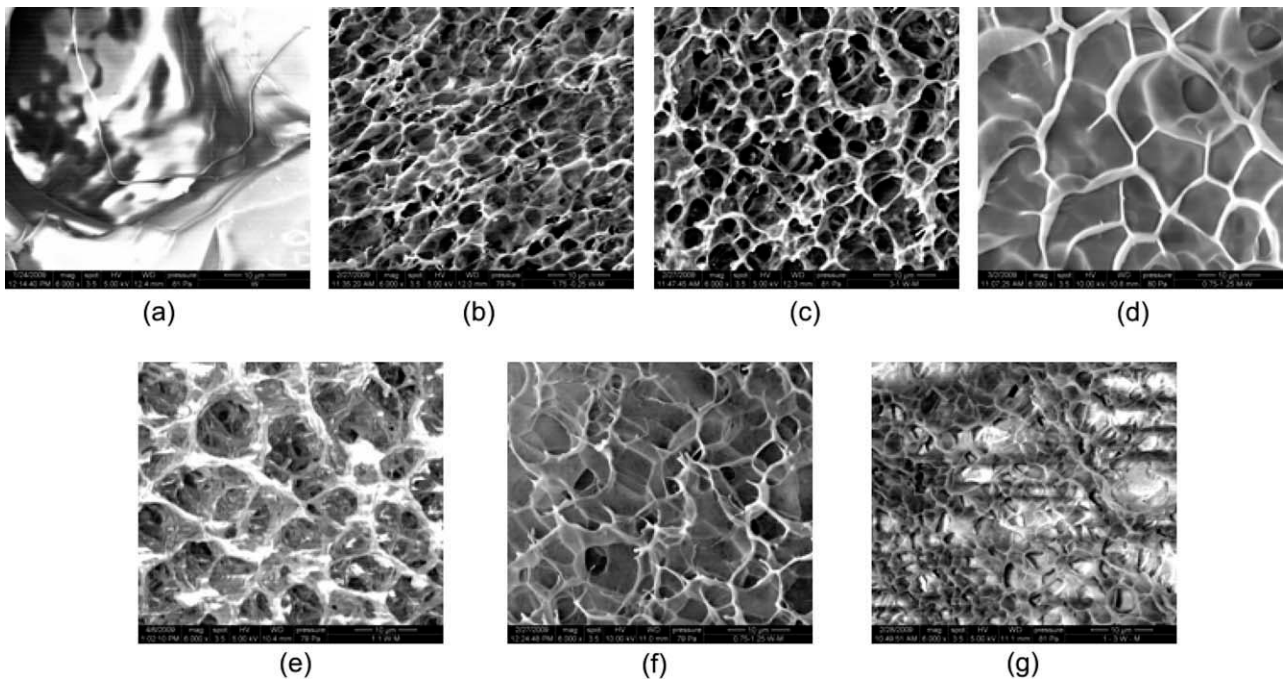

Figure 2 SEM images of the hydrogels synthesized in (a) 0, (b) 0.06, (c) 0.13, (d) 0.21, (e) 0.31, (f) 0.43, and (g) 0.57 mole fraction of methanol in methanol-water mixtures.

prepared in methanol–water mixtures. Moreover, the pore-sizes of the gel become maximum in the cononsolvency zone (at $x_m = 0.21$, 0.31, and 0.43) (runs $X_{0.21}$, $X_{0.31}$, and $X_{0.43}$, respectively).

The swelling ratios in water at different temperatures of all the hydrogels prepared in the different methanol–water mixtures are shown in the Figure 3. Below the volume phase transition, the equilibrium swelling ratios of the gel prepared in water ($x_m = 0$, run X_0) are smaller than those of all of the other gels prepared in different methanol–water mixtures (Table I). This is due to the formation of a macroporous cross-linked gel in methanol–water mixture as per discussion in the Morphology Study section; this eventually leads to an increase in the porosity and a water uptake tendency in the gel. The plot of the swelling ratio of the hydrogels in water at 20°C against the x_m value of the synthesis solvent (vide Table I) is shown in the Figure 4. The equilibrium swelling ratio of the hydrogels in water at 20°C increases gradually from 11.4 through 15.0 to 16.3 with the increase in the x_m value of the synthesis solvent from 0 (run X_0) through 0.06 (run $X_{0.06}$) to 0.13 (run $X_{0.13}$), respectively, because of the gradual

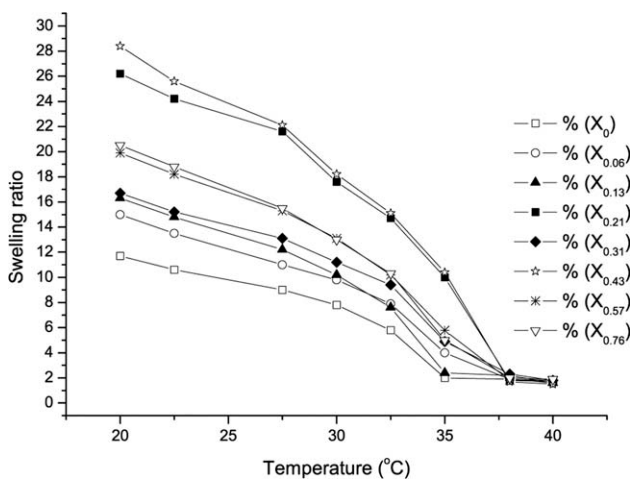

Figure 3 Equilibrium swelling ratios of all PNIPAM hydrogels in water at 20°C, 22.5°C, 27.5°C, 30°C, 32.5°C, 35°C, 38°C, and 40°C temperatures.

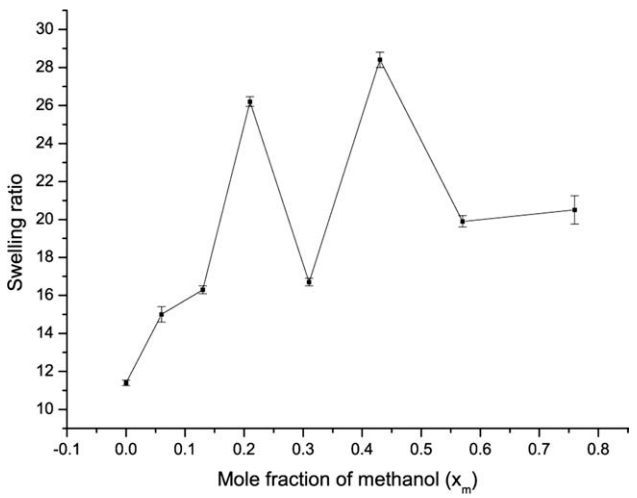

Figure 4 Plot of the Swelling ratio of the hydrogels in water at 20°C against the mole fraction of methanol (x_m) of the synthesis solvent.

increase in the porosity as per discussion in the Morphology Study section. The swelling ratio again increases significantly to around 26 for the gel prepared at $x_m = 0.21$ (run $X_{0.21}$). This is due to the formation of a very less cross-linked (i.e., larger pore size) gel through the solid (swollen)-phase polymerization owing to the complete collapse of the PNIPAM chain segment into its globular state within the cononsolvency zone ($x_m = 0.17$–0.40).[10,11,13] However, the swelling ratio decreases significantly to 16.7 for the gel prepared at $x_m = 0.31$ (run $X_{0.31}$). This may have been due to the formation of the phase-separated aggregates of macroporous gels through very fast and highly solid-(swollen) phase polymerization. The very weaker interaction of the methanol–water complex structure with the PNIPAM chain segments owing to their very strong interactions among themselves may have significant role here.[14] The high viscosity of the methanol–water mixture[24] may also have some role. It is to be mentioned here that a very weak gel is also formed at $x_m = 0.25$ and the resulted gel also shows the low swelling ratio value of 16.4 (result is not included) like the gel prepared at $x_m = 0.31$ (run $X_{0.31}$). The swelling ratio again increases significantly to 28.4 for the gel prepared at $x_m = 0.43$ (run $X_{0.43}$). This is due to the formation of a very less cross-linked (i.e., large pore size) gel through the solid (swollen)-phase polymerization like run $X_{0.21}$ owing to the same reason. Then, the swelling ratio decreases significantly to 20 for the gel prepared at $x_m = 0.57$ (run $X_{0.57}$). This is due to the formation macroporous gel with a smaller pore size as discussed in the Morphology Study section. The swelling ratio remains almost constant with a further increase to $x_m = 0.76$ (run $X_{0.76}$) owing to the formation of similar solvated coiled state of the PNIPAM chain segment, as is observed for the gel prepared at $x_m = 0.57$ (run $X_{0.57}$). In general, the equilibrium swelling ratio in water at 20°C of all of the PNIPAM gels varies in the following order: $X_{0.43} > X_{0.21} > X_{0.76} \approx X_{0.57} > X_{0.31} > X_{0.13} > X_{0.06} > X_0$. The swelling ratio in water at 40°C for all of the gels is more or less close to 2 (see Table I and Fig. 3). This is due to the complete collapse of the coiled conformation of the PNIPAM chain segment into its slightly solvated globular form at this temperature. In general, below LCST, the swelling ratio values gradually decreases with increasing temperature because of the release of water due to the gradual collapse of PNIPAM chain segment in the gel. Similar types of results have also been reported in the literature for mixtures of water and other water-miscible solvent systems.[6,9,20,21,25–28] Moreover, the swelling ratio values of all of the gels except the one prepared in water (run X_0) are observed at a minimum (~ 2) at about 38°C, whereas the same for the gel prepared in water (run X_0) is observed at around 35°C. This is due to the formation of macroporous cross-linked gel in the methanol–water mixtures. This eventually leads to the higher retention power of water within the gel matrices. Therefore, higher temperature is required to release most of the water molecules out of the gel matrices.

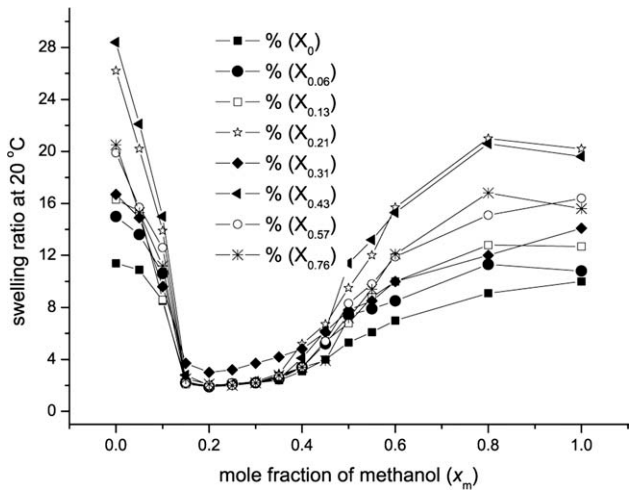

Figure 5 Equilibrium swelling ratios of all PNIPAM hydrogels in 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.8, and 1.0 mole fractions of methanol in water mixtures at 20°C.

The changes in the swelling ratio values of all of the PNIPAM gels in the methanol–water mixtures having different x_m values at 20°C are shown in Figure 5. With the increase of the x_m value from 0 to 0.2, the swelling ratio values of all of the hydrogels decreases sharply because of the onset of the cononsolvency and becomes almost equal to the minimum value of about 2 at around $x_m = 0.2$. After this point, the swelling ratio values of all gels, except the one prepared at $x_m = 0.31$ (run $X_{0.31}$), increases slightly with increasing x_m value from 0.2 to around 0.35, and the observed swelling ratio values are almost same for all of the hydrogels in these solvent compositions. This indicates that the PNIPAM chain segments of the collapsed gels in the cononsolvency region are in the same molecular conformational state. Their swelling ratio values increase very slowly because of the very slow redissolution of the aggregated PNIPAM chain segment with increasing methanol content within the cononsolvency zone. Moreover, this behavior is only due to the molecular interaction of the solvent and the polymer, not to other factors, such as cross-linking density, extent of aggregation of PNIPAM chain segments, or extent of formation of free PNIPAM chain segment, etc. With the further increase in the x_m value from 0.35 to 1, the swelling ratio values of all of the hydrogels gradually increase, and this reswelling trend is almost like the deswelling trend observed in the x_m region of 0–0.2. Finally, the observed swelling ratio

values of all of the hydrogels in methanol are lower than that in water. This is due to the lower density or larger molecular volume of the methanol with respect to that of water. In this regard, PNIPAM hydrogels prepared at $x_m = 0.31$ (run $X_{0.31}$) showed slightly higher swelling ratio values than the other hydrogels in the cononsolvency zone. This again confirms that the chain conformation of this gel is slightly different than other gels, as mentioned during the discussion of morphology and swelling ratio values in water at 20°C. Thus, the swelling ratio values of all of the PNIPAM gels in the different x_m values at 20°C pass through a minimum in the cononsolvency zone. Similar type of results have also been observed in ethanol–water mixture for the PNIPAM gels prepared in different ethanol–water mixtures.[16]

The deswelling rates of all of the hydrogels in water at 40°C are shown in Figure 6. This rate is slowest with the hydrogel prepared in water ($x_m = 0$) (run X_0). It gradually increases for the hydrogels prepared in the synthesis solvent containing higher x_m values (0.06 and 0.13) (runs $X_{0.06}$, and $X_{0.13}$, respectively). With a further increase in the x_m value from 0.13 (run $X_{0.13}$) to 0.21 (run $X_{0.21}$), the deswelling rate of resulting hydrogel becomes drastically faster. With the further increase in the x_m values from 0.21 (run $X_{0.21}$) to 0.31 (run $X_{0.31}$) to 0.43 (run $X_{0.43}$), the deswelling rates of the resulting gels increase gradually and becomes fastest with the gel prepared at $x_m = 0.43$. After this, the deswelling rate of the hydrogel prepared at $x_m = 0.57$ (run $X_{0.57}$) significantly decreases and comes between those of the gels prepared with the x_m values of 0.13 and 0.21 (run $X_{0.13}$ and $X_{0.21}$, respectively). With a further increase in the x_m value to 0.76 (run $X_{0.76}$), the obtained hydrogel shows a slower deswelling rate than that prepared with a x_m value of 0.57 (run $X_{0.57}$), but faster than that prepared with a x_m value of 0.13 (run $X_{0.13}$). In general, the deswelling rate depends on the rate of the ejection of water from the polymer matrix. This ejection rate depends on the porosity, the extent of aggregation of PNIPAM chain segment in the gel, and so on. The larger the porosity is, the faster the deswelling rate is; the higher the extent of aggregation of PNIPAM chain segment is, the faster the deswelling rate is. The observed gradual faster deswelling rate with the gels prepared in the higher x_m values in the range of 0–0.13 (runs X_0, $X_{0.06}$, and $X_{0.13}$, respectively) is due to the formation of a larger pore-size cross-linked gel and also to the formation of more aggregated globular PNIPAM chains in the formed gel because of the gradual collapse of the PNIPAM chain segment due to the onset of the cononsolvency. The drastically faster deswelling rate of resulting hydrogel prepared at $x_m = 0.21$ (run $X_{0.21}$) is due to the formation of the macroporous cross-linked gel with a larger pore size

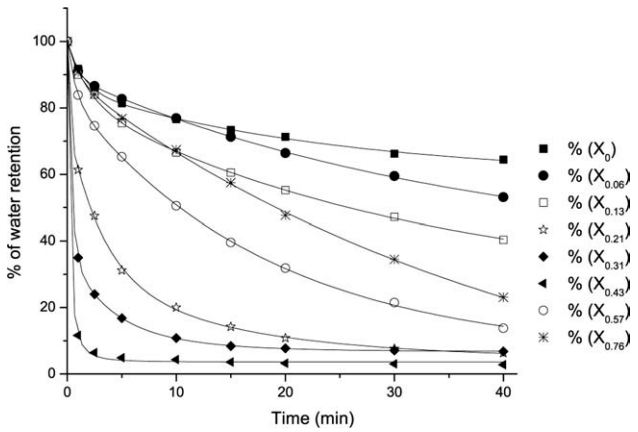

Figure 6 Deswelling kinetics of the PNIPAM hydrogels synthesized in 0 (run X_0), 0.06 (run $X_{0.06}$), 0.13 (run $X_{0.13}$), 0.21 (run $X_{0.21}$), 0.31 (run $X_{0.31}$), 0.43 (run $X_{0.43}$), 0.57 (run $X_{0.57}$), and 0.76 (run $X_{0.76}$) mole fractions of methanol in water mixtures.

and highly aggregated PNIPAM chain segment through the solid (swollen)-state polymerization because of the cononsolvency of the methanol–water mixtures. The observed gradual increase in the deswelling rate of the gels prepared at $x_m = 0.31$ and 0.43 (run $X_{0.31}$, and run $X_{0.43}$, respectively) within the proximity of the cononsolvency zone may have been due to the gradual increase of the both or either one of the same reasons as mentioned in case of the gel prepared at $x_m = 0.21$ (run $X_{0.21}$). The considerably slower deswelling rate of the gel prepared at $x_m = 0.57$ (run $X_{0.57}$) is due to the formation of relatively smaller pore size macroporous (cross-linked) gel morphology [Fig. 2(g)] containing less aggregated PNIPAM chain segments in the methanol rich region ($x_m \geq 0.50$) beyond the cononsolvency zone. The observed slower deswelling rate of the gel prepared at $x_m = 0.76$ (run $X_{0.76}$) with respect to the gel prepared at $x_m = 0.57$ (run $X_{0.57}$) is due to the formation of a gel containing relatively less aggregated PNIPAM chain segments in the higher methanol-rich region outside the cononsolvency zone. Thus, the deswelling rate of these hydrogels decreases in the following order: $X_{0.43} > X_{0.31} > X_{0.21} > X_{0.57} > X_{0.76} \approx X_{0.13} > X_{0.06} > X_0$. Similar type of observation has also been reported for the PNIPAM gels prepared in different ethanol-water mixtures.[21]

The reswelling rate of all the hydrogels at 20°C is shown in the Figure 7. This rate is fastest with the hydrogel prepared in water ($x_m = 0$, run X_0). This is followed by the hydrogel prepared at $x_m = 0.31$ (run $X_{0.31}$). The reswelling rate is slowest and almost comparable with the gels prepared at $x_m = 0.21$ and 0.43 (run X0.21, and X0.43, respectively). It increases slightly for the gel prepared at $x_m = 0.57$. It further increases significantly for the gel prepared at $x_m = 0.76$ (run $X_{0.76}$). It further increases slightly and

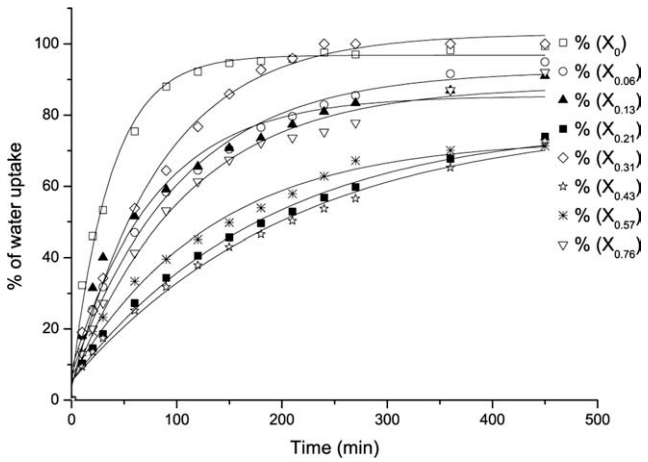

Figure 7 Reswelling kinetics of the PNIPAM hydrogels synthesized in 0 (run X_0), 0.06 (run $X_{0.06}$), 0.13 (run $X_{0.13}$), 0.21 (run $X_{0.21}$), 0.31 (run $X_{0.31}$), 0.43 (run $X_{0.43}$), 0.57 (run $X_{0.57}$), and 0.76 (run $X_{0.76}$) mole fractions of methanol in water mixtures.

becomes almost comparable with the gels prepared at $x_m = 0.13$ and 0.06 (runs $X_{0.13}$, and $X_{0.06}$, respectively). The reswelling rate generally controls by the rate of diffusion of water into the polymer matrix. Apart from porosity, the rate of diffusion depends on the state of the polymer chains in its matrix. The reswelling rate is faster when the polymer chains are in a loosely aggregated coiled structure. The rate is slower when the polymer chains are present in a highly aggregated globular structure. On gradual addition of methanol to water, because of the onset of the cononsolvency of methanol–water synthesis solvent mixture toward PNIPAM chain segment, the coil conformation of the PNIPAM chain segment gradually turns into an aggregated globular state up to around $x_m = 0.17$.[10,11,13] Therefore, the observed decrease in the reswelling rate with increasing methanol content from $x_m = 0$ to 0.06 to 0.13 (runs X_0, $X_{0.06}$, and $X_{0.13}$, respectively) is in conformity with the previous explanation. With a further increase of the methanol content (x_m) from 0.2 to 0.43 (in the cononsolvency zone), PNIPAM chain segment expectedly presents in the highly aggregated globular state. Therefore, the reswelling rate would be slowest with such gels prepared within the proximity of the cononsolvency zone. The observed slowest reswelling rate for the gels prepared at $x_m = 0.21$ and 0.43 (run $X_{0.21}$ and $X_{0.43}$, respectively) is in conformity with the previous explanation. The almost comparable reswelling rate of these two gels (run $X_{0.21}$ and $X_{0.43}$,) may have been due to similar and highly aggregated globular states of the polymer chains in the gel matrices. The observed faster reswelling rate for the gel prepared at $x_m = 0.31$ (run $X_{0.31}$) may have been due to its less cross-linked, thick-walled network type macroporous gel morphology. A slight increase in the reswelling rate for the gel prepared at $x_m = 0.57$ (run $X_{0.57}$) is due to relatively less aggregated PNIPAM chain in the gel formed at the higher methanol content ($x_m = 0.57$) medium outside the cononsolvency zone ($x_m = 0.2$–0.43) because of the higher solvency of the PNIPAM segment. The observed faster reswelling rate for the gel prepared at $x_m = 0.76$ (run $X_{0.76}$) is due to the formation of a loosely aggregated (highly solvated) coiled structure of the PNIPAM chain segment in the gel matrix. The almost comparable reswelling rate of this gel with that prepared at $x_m = 0.13$ (run $X_{0.13}$) may have been due to the similar loosely aggregated coiled structure of the polymer chain in the gel matrix. Thus, the reswelling rates of these hydrogels decreases in the following order: $X_0 > X_{0.31} > X_{0.06} \approx X_{0.13} > X_{0.76} > X_{0.57} > X_{0.21} \approx X_{0.43}$. Similar type of results has also been reported for the PNIPAM gels prepared in different ethanol–water mixtures.[21]

Drug release behavior has been investigated using a water-soluble drug Tramadol Hydrochloride. The plot of drug loading (%) of different gels against the mole fraction of methanol (x_m) of the methanol–water mixtures used for the synthesis of the corresponding gel is shown in the Figure 8. The trend of the drug loading is almost identical with the change of the swelling ratios in water at 20°C with the variation of the value of x_m (Fig. 4). All these results are in conformity with the discussion related to the swelling ratio values of different gels at 20°C in water. The rates of cumulative drug release (%) at 37°C against time are shown in Figure 9. It is clear from the figure that there is not much difference in the rates of cumulative drug release of all of the

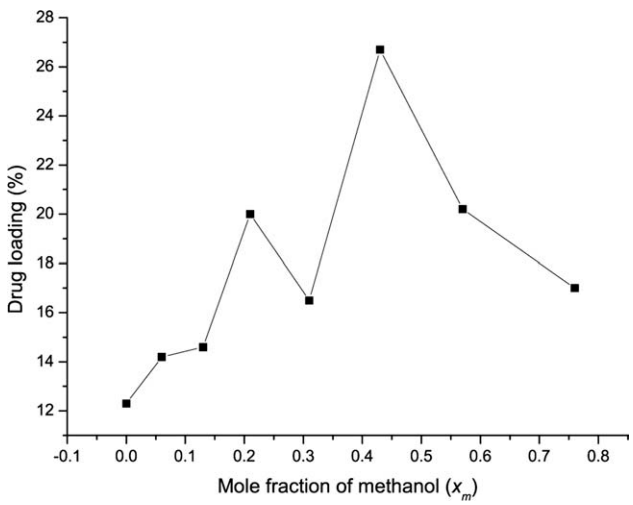

Figure 8 Drug loading percentage of the PNIPAM hydrogels synthesized in 0 (run X_0), 0.06 (run $X_{0.06}$), 0.13 (run $X_{0.13}$), 0.21 (run $X_{0.21}$), 0.31 (run $X_{0.31}$), 0.43 (run $X_{0.43}$), 0.57 (run $X_{0.57}$), and 0.76 (run $X_{0.76}$) mole fractions of methanol in water mixtures.

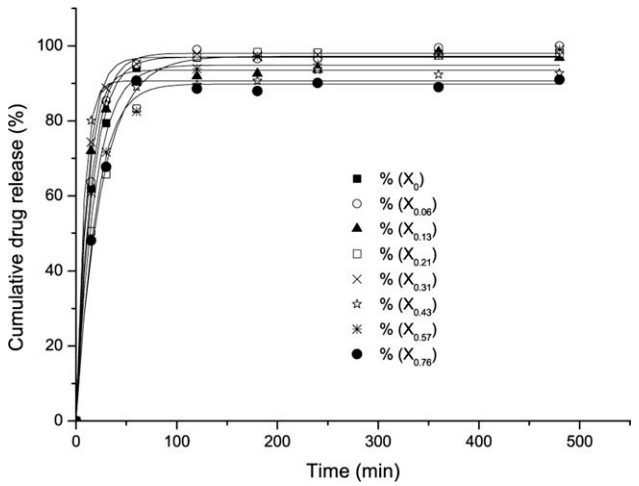

Figure 9 Drug release kinetics of the PNIPAM hydrogels synthesized in 0 (run X_0), 0.06 (run $X_{0.06}$), 0.13 (run $X_{0.13}$), 0.21 (run $X_{0.21}$), 0.31 (run $X_{0.31}$), 0.43 (run $X_{0.43}$), 0.57 (run $X_{0.57}$), and 0.76 (run $X_{0.76}$) mole fractions of methanol in water mixtures at 37°C.

gels. Almost 80–95% drugs are released from the corresponding drug-loaded gel within about 60 min. This behavior has similarity with "burst effect," where a large volume of drug quickly releases. This effect depends on several factors like cross-linking ratio of gel, drug loading concentration, aggregation state of gel, pore diffusion of the drug, surface desorption rate, etc. Here, the observed behavior may be due to the fact that the experimental temperature is well above the LCST value of PNIPAM and all the gels turns into a highly globular state at this temperature, and the interaction between the PNIPAM chain segment of all the gels and the incorporated drug are of similar type, and the molecular dimension of drug molecule is quite smaller than that of the pore size of all the gels, and there is a lack of a diffusion front barrier to regulate the diffusion process in all gels. As a result, the drug comes out with almost similar rate during the contraction of the polymer network. Thus, all the gels show almost identical drug release rate.

CONCLUSIONS

PNIPAM hydrogels have simply been prepared by free radical polymerization in different methanol–water mixtures. SEM study reveals that the resulting hydrogels are macroporous. The swelling ratios of the resulting hydrogels in water at 20°C follow the order: $X_{0.43} > X_{0.21} > X_{0.76} \approx X_{0.57} > X_{0.31} > X_{0.13} > X_{0.06} > X_0$. Below the LCST, the swelling ratio values gradually decrease with increasing temperature because of the release of water due to the gradual collapse of the PNIPAM chain segment in the gel. At 20°C, the swelling ratio values of all of the PNIPAM gels with different x_m values pass through a minimum in the cononsolvency zone. Moreover, the swelling ratios of all of the gels in pure water are higher than those observed in methanol. The deswelling rates of the hydrogels decrease in the following order: $X_{0.43} > X_{0.31} > X_{0.21} > X_{0.57} > X_{0.76} \approx X_{0.13} > X_{0.06} > X_0$. Thus, we have systematically varied the deswelling rate of the hydrogels by simply varying the composition of the methanol–water mixture used as synthesis solvent, and the fastest rate occurs at $x_m = 0.43$. The reswelling rates of these hydrogels decrease in the following the order: $X_0 > X_{0.31} > X_{0.06} \approx X_{0.13} > X_{0.76} > X_{0.57} > X_{0.21} > X_{0.43}$. All the gels show almost identical release rate of Tramadol Hydrochloride drug at 37°C. All of these swelling, deswelling, and reswelling, properties are explained on the basis of the variation of the cross-linking density (porosity), polymer chain and solvent interaction, and due to the cononsolvency behaviour of the methanol–water mixture toward the PNIPAM chain segment in the PNIPAM hydrogels and the extent of solution or solid (swollen)-phase polymerization with gradual changes in the composition of the methanol–water mixture.

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References

1. Hirokawa, Y.; Tanaka, T. J Chem Phys 1984, 81, 6379.
2. Amiya, T.; Hirokawa, Y.; Hiroshe, H.; Hirose, Y.; Li, Y.; Tanaka, T. J Chem Phys 1987, 86, 2375.
3. Asano, M.; Winnick, F. M.; Yamashita, T.; Horie, K. Macromolecules 1995, 28, 5861.
4. Saunders, B. R.; Crowther, H. M.; Vincent, B. Macromolecules 1997, 30, 482.
5. Zhu, P. W.; Napper, D. H. J Colloid Interface Sci 1996, 177, 343.
6. Zhang, X. Z.; Yang, Y. Y.; Chung, T. S. Langmuir 2002, 18, 2538.
7. Mukae, K.; Sakurai, M.; Sawamura, S.; Makino, K.; Kim, S. W.; Ueda, I.; Shirahama, K. Colloid Polym Sci 1994, 272, 655.
8. Zhu, P. W.; Napper, D. H. Chem Phys Lett 1996, 256, 51.
9. Tokuyama, H.; Ishihara, N.; Sakohara, S. Polym Bull 2008, 61, 399.
10. Winnik, F. M.; Ringsdorf, H.; Venzmer, J. Macromolecules 1990, 23, 2415.
11. Schild, H. G.; Muthukumar, M.; Tirrell, D. A. Macromolecules 1991, 24, 948.
12. Nandi, A. K.; Sen, U. K.; Bhattacharya, S. N.; Mandal, B. M. Eur Polym J 1983, 19, 283.
13. Zhang, G.; Wu, C. J Am Chem Soc 2001, 123, 1376.
14. Zhang, G.; Wu, C. Phys Rev Lett 2001, 86, 822.
15. Mukae, K.; Sakurai, M.; Sawamura, S.; Makino, K.; Kim, S. W.; Ueda, I.; Shirahama, K. J. Phys Chem 1993, 97, 737.
16. Asano, M.; Horie, K.; Yamashita, T. Polym Gels Networks 1995, 3, 282.
17. Ito, K.; Ujihara, Y.; Yamashita, T.; Horie, K. J Polym Sci Part B: Polym Phys 1998, 36, 1141.
18. Lee, W. F.; Yen, S. H. J Appl Polym Sci 2000, 78, 1604.

19. Zhang, X.-Z.; Zhuo, R.; Yang, Y. Biomaterials 2002, 23, 1313.
20. Erbil, C. Yildz, Y.; Uyanik, N. Polym Int 2000, 49, 795.
21. Biswas, C. S.; Patel, V. K.; Viswakarma, N. K.; Mishra, A. K.; Ray, B. J Appl Polym Sci 2011, 121, 2422.
22. Biswas, C. S.; Patel, V. K.; Vishwakarma, N. K.; Mishra, A. K.; Saha, S.; Ray, B. Langmuir 2010, 26, 6775
23. Ray, B.; Mandal, B. M. J Polym Sci Part A: Polym Chem 1999, 37, 493.
24. Chen, J. H.; Chen H. H.; Chang, Y. X.; Chuang, P. Y.; Hong, P. D. J Appl Polym Sci 2008, 107, 2732.
25. Asano, M.; Horie, K.; Yamashita, T. Polym Gels Networks 1995, 3, 281.
26. Ito, K.; Ujihara, Y.; Yamashita, T.; Horie, K. J Polym Sci Part B: Polym Phys 1998, 36, 1141.
27. Lee, W. F.; Yen, S. H. J Appl Polym Sci 2000, 78, 1604.
28. Zhang, X. Z.; Zhuo, R.; Yang, Y. Biomaterials 2002, 23, 1313.