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Thermoreversible hydrogel based on radiation induced copolymerisation of poly(*N*-isopropyl acrylamide) and poly(ethylene oxide)†

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Thermoreversible copolymer hydrogel based on poly(ethylene oxide) and poly(*N*-isopropyl acrylamide) has been prepared by γ-radiation technique. The utility of ^{13}C n.m.r. spectroscopy in elucidating the structure and copolymer composition has been demonstrated. The volume transition as a function of temperature in these copolymers has been studied by swelling ratio measurements. Unlike poly(ethylene oxide) homopolymer gel, the copolymer gels show first order volume transition in the temperature range of 35–40°C. These gels are easy to synthesise in any shape and size and are found to be having good mechanical strength even in the fully swollen state. They can have potential applications in controlled drug delivery, bioseparations and biomedical fields.

(Keywords: hydrogel; thermoreversible; γ-radiation)

INTRODUCTION

There is a renewed interest in radiation induced polymerisation and cross-linking in polymeric hydrogels. The advantages of radiation methods are that they are relatively simple and do not require addition of any extra materials for polymerisation and cross-linking. Moreover, the degree of cross-linking, which strongly determines the extent of swelling in hydrogels can be controlled easily by varying the dose rates. Therefore, these methods are found to be very useful in preparing hydrogels for medical applications, where even a small contamination is undesirable. For example, fast responding thermoreversible gels based on poly(vinyl methyl ether) (PVME) have been prepared by γ-radiation and are used in controlled release applications[1]. Uenoyama and Hoffman have grafted poly(*N*-isopropyl acrylamide) (PNIPAm) onto silicone rubber substrate for model implants[2]. Recently, Nagaoka *et al.* have reported for the first time the synthesis of PNIPAm hydrogel by γ-radiation technique[3]. Radiation cross-linked poly(ethylene oxide) gels[4] have also been used as highly active phase transfer catalysts in alkylation reactions. Non-ionic flocculants, specifically for the applications in pulp manufacturing have been synthesised by γ-radiation of mixtures of poly(acrylamide) and poly(ethylene oxide)[5].

Modification of polymers by copolymerising with functional polymer chains has been a subject of fundamental and practical importance. We report here on the synthesis of thermoreversible hydrogel based on the radiation induced copolymerisation of poly(*N*-isopropyl acrylamide) and poly(ethylene oxide). Recently, Yoshioka *et al.* have reported on the synthesis of block-copolymers of PNIPAm-*co*-(*n*-butyl methacrylate) (BMA) and poly(ethylene glycols)[6]. However, these copolymers were prepared by the reaction between diamino-PEG and activated copolymer [PNIPAm-*co*-*N*-aryloxysuccinimide (NASI)-*co*-BMA] and not by using the γ-radiation technique. Moreover, these polymers were not truly covalently cross-linked gels but exhibited reversible cross-linking during sol–gel transition as a result of cooling and heating cycles. Gelation was believed to occur mainly due to the formation of thermoreversible cross-linkages between intermolecular poly(NIPAm-*co*-*n*-butyl methacrylate) blocks by hydrophobic interactions. Interestingly, the same authors also showed the effect of sequence length of PNIPAm on the Lower Critical Solution Temperature (LCST) of the block copolymer. For example, in their DSC study[7] the block copolymer, PNIPAm-*co*-PEG showed an endothermic peak at 38°C, whereas the random copolymer based on PNIPAm-*co*-PAm showed no endothermic peak. LCST type thermoreversible phase transitions are observed in many polymeric systems[8]. The cross-linked gels obtained from the thermoreversible polymers undergo a swelling–collapse transition at the LCST. A large number of theoretical models[9,10], which take into consideration either the hydrogen bonding interactions or the hydrophobic interactions alone are reported in the literature to explain the LCST phenomenon in gels. Recently, Lele *et al.* proposed an extended Lattice–Fluid Hydrogen Bond (LFHB) theory[11] which predicts that both hydrogen bonding interactions and hydrophobic interactions are essential to cause the LCST behaviour. The critical balance of the hydrophobic and hydrophilic groups in the polymer structure strongly determines the LCST.

Although PNIPAm LCST hydrogels have been extensively studied and demonstrated to be promising materials, their commercial exploitation has been limited due to the extremely high cost of NIPAm monomer. Therefore, the combination of NIPAm monomer with other cheaper materials (such as PEO) while retaining the crucial properties of products such as thermoreversibility is a challenging

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task. Besides its cost, we have chosen poly(ethylene oxide) mainly due to its excellent biocornpatibility and good aqueous swelling characteristics. Although poly(ethylene oxide) gel falls under the class of thermoreversible hydrogels, it does not exhibit a well defined first order volume phase transition as a function of temperature. In this work, we have synthesised copolymers based on poly(ethylene oxide) and poly(*N*-isopropyl acrylamide) by γ-radiation technique. We believe that our synthesis results in grafting of PNIPAm onto PEO chains. The structure and copolymer compositions have been quantitatively determined by ^{13}C n.m.r. spectroscopy. We show that the copolymers exhibit a discontinuous thermoreversible volume transition as studied by swelling ratio measurements.

MECHANISM OF RADIATION POLYMERISATION AND CROSS-LINKING

The mechanism of radiation cross-linking in PEO and PNIPAm has been independently investigated by many research groups. When aqueous solutions of PEO are subjected to γ-ray irradiation, they yield cross-linked gels. This is possible however, only when certain minimum concentration and molecular weight of PEO is used for the γ-ray irradiation. The mechanism involves the radical formation of the polymer chain either by a direct action of the high energy radiation on the polymer chain, or by indirect attack on the polymer chain by solvent derived radicals. Earlier, Charlesby and Kopp[12] reported that the cross-linking and subsequent gelation in PEO solutions due to γ-radiation arises mainly from the direct effect, i.e. the energy absorbed directly by the polymer molecule is solely responsible for the radical formation and cross-linking. Based on their e.s.r. study, Ferloni *et al.*[13] have indicated that γ-ray radiation on the PEO chains leads to the localisation of positive charges on the PEO oxygen atoms as shown below

$$-(-CH_2-CH_2-\ddot{O}-)- \xrightarrow{\gamma-ray} -(CH_2-CH_2-\overset{+\cdot}{O}:-)- + e^-$$

The positive polymer radicals then undergo α and β scissions resulting in three types of radicals

$$-CH_2\dot{C}H-O-,\quad -O-\dot{C}H_2- \text{ and } -CH_2-\dot{O}-$$

Finally, the combination of these radicals can lead to cross-linking in PEO structure. However, later reports indicated that the indirect effect definitely plays a dominant role in generating free radical and subsequent reaction.

In the case of indirect effect, radiolysis of water can lead to $\dot{H}$ and $\dot{O}H$ radicals as an intermediates which can react with polymer to give polyradicals. Two such polyradicals combine together resulting in covalent bond formation leading to cross-linking. The fact that radiolysis of water indeed contributes significantly for generating polyradicals and which eventually gives cross-linked gels was further supported by other workers[14,15].

In a separate study, Nagaoka *et al.*[3] have reported the radiation polymerisation and cross-linking of *N*-isopropyl acrylamide monomer. The formation of the monomer radical was reported via both the direct effect of radiation and also indirect effect based on the reaction of products of water radiolysis with the monomer. They have reported the formation of radical on the isopropyl group of the monomer along with the formation of carboxyl alkyl radical. However, the radical on the isopropyl group being more stable than the other is unlikely to take part in the polymerisation and cross-linking reaction. Therefore, considering all the above discussions the possible mechanism of copolymerisation of NIPAm onto PEO can be proposed as follows,

(a) Formation of radicals on both PEO and NIPAm by direct and indirect effect as follows

$$-(-CH_2-CH_2-O)_n \xrightarrow{\gamma-ray} -(-CH_2-CH_2-\overset{+\cdot}{O}-)_n-$$

$$\rightarrow -(-CH_2-\dot{C}H-O-)_n-$$

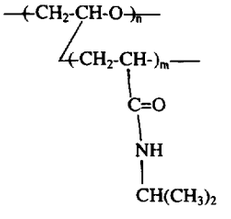
$$CH_2=CH-CO-NH-CH-(CH_3)_2$$

$$\xrightarrow{\gamma-ray} CH_3-\dot{C}H-CO-NH-CH-(CH_3)_2$$

and

$$CH_2=CH-CO-NH-\dot{C}-(CH_3)_2$$

(b) The combination of the above radicals gives rise to cross-linked copolymers of PEO and PNIPAm with the following structure



EXPERIMENTAL

Materials

PEO (M_w = 6000 and 100 000) polymers and NIPAm monomer were obtained from Polysciences, Inc., USA and used as such. The purities of these materials have been checked by m.p. and ^1H n.m.r. spectroscopy. Distilled ethanol and deionised water have been used for all the experiments.

Synthesis of PEO-co-PNIPAm gels

Aqueous solutions of PEO (1.5 wt%) were prepared in distilled water by gentle stirring of PEO powder and water. The dissolution took 10–15 hours to get homogeneous solutions. The concentration of NIPAm monomer was varied accordingly (*Table 1*) and dissolved in the PEO solution. The solutions were degassed by bubbling nitrogen gas continuously for 15 min. The solutions were sealed in glass tubes and samples were exposed to γ-radiation from a ^{60}Co source at a dose rate of 0.361 Mrad h^{-1} at room temperature for 15 hours. After the irradiation, the resulting gels were taken out and washed several times with distilled water and ethanol. The washed gels were dried in vacuum oven at 40–45°C until constant weight was obtained.

Swelling ratio measurements

The dried cylindrical gels (with known weight) were placed in pure water taken in glass tube with standard joints. The tubes were kept at different temperatures in a temperature controlled oven (with an accuracy of ±0.2°C)

Table 1 Feed compositions for the preparation of hydrogels

Sample	PEO (g)	NIPAm (g)	Water (g)
VE	0.6	–	40.0
VA-1	0.6	0.2	40.0
VA-2	0.6	0.4	40.0
VA-3	0.6	0.8	40.0
VA-4	0.6	1.0	40.0

and samples were allowed to equilibrate for 4–5 days. Cryostat bath was used for the low temperature swelling measurements. After attaining equilibrium, the swollen gels were taken out and weighed accurately to the fourth decimal point. The swelling ratios were expressed as the ratio of swollen weight to the dry weight (W_s/W_d).

^{13}C n.m.r. measurements

All the ^{13}C spectra were obtained on a Bruker MSL-300 FT-n.m.r. spectrometer operating at 75.47 MHz for carbon using a conventional high resolution 10 mm probe. Dry samples were swollen in H_2O/D_2O (90/10 vol%) mixture in 10 mm n.m.r. tube until equilibration. The samples were directly taken for ^{13}C n.m.r. measurements at room temperature (26°C). The quantitative ^{13}C spectra were obtained using inverse gated decoupling mode with 36° flip angle and 2 sec recycle delay. Ideally, determination of quantitative relative intensities requiring obtaining nuclear Overhauser enhancement (nOe) suppressed spectra with a recycle time in excess of five times the relaxation time. Freeman *et al.*[16] reported a gated decoupling technique in which the nOe's were eliminated by cycling the decoupler on only during signal acquisition. This results in completely decoupled spectra without nOe. In our case, we have used only 36° flip angle and hence do not require the recycle delay of $5T_1$. Moreover, we have roughly estimated the T_1's of the order of 300–400 msec. Typically, 15 000 accumulations were made to get highly resolved spectra for all the samples. Chemical shift positions were referred with respect to an external sample of dioxane in D_2O taken at 67.8 ppm. Integrated areas were used for the estimation of copolymer composition.

RESULTS AND DISCUSSION

Structure and composition of copolymers

Figure 1 shows the completely decoupled ^{13}C n.m.r. spectra of PEO and PNIPAm-*co*-PEO samples swollen in H_2O/D_2O mixture at room temperature. The spectra were obtained using high resolution probe. It may be noted at this point that the hydration levels achieved at the equilibrium swelling of the samples was sufficient to average the C–H dipolar interactions to a greater extent. Hence, a reasonably well resolved ^{13}C spectra could be obtained in the conventional high resolution mode with Broad-Band (BB) decoupling. More narrowing of ^{13}C peaks is certainly achievable by Magic Angle Sample Spinning (MASS) with dipolar decoupling. However, we find that the spectra obtained in the high resolution mode is good enough for the quantitative estimation of the copolymer composition.

It can be seen from *Figure 1a* that the pure PEO sample shows a single ^{13}C peak at 70.8 ppm, which is the backbone $-CH_2$ carbon. However, upon copolymerisation with PNIPAm, all the ^{13}C peaks of PNIPAm also appear in the spectra. The chemical shift assignments for all the carbons is made and summarised in *Table 2*. The possible structure of the copolymer along with carbon numbers is given in the inset of *Figure 1*.

Table 2 Chemical shift assignments for ^{13}C peaks in the copolymer

Type of carbon and number	Chemical shift (ppm)
1,2 $-CH_2$ (PEO)	70.8
3, $-CH_2$ (PNIPAm)	36.08
4,6 –CH (PNIPAm)	43.08
5, –C=O (PNIPAm)	176.54
7,8 $-CH_3$ (PNIPAm)	22.85

Table 3 Copolymer composition by ^{13}C n.m.r. spectroscopy (molar feed ratios are given in parentheses)

Sample	Mole ratios in copolymers	
	PEO	PNIPAm
VA-2	1.0 (1.0)	0.27 (0.26)
VA-3	1.0 (1.0)	0.54 (0.52)
VA-4	1.0 (1.0)	0.69 (0.65)

We have prepared PEO-*co*-PNIPAm copolymers with increasing amounts of PNIPAm. The feed compositions of the monomers is given in *Table 1*. It can be readily seen from *Figure 1* that with increasing PNIPAm content in the copolymer gel, the intensities of all the ^{13}C peaks of PNIPAm progressively increase with respect to the intensity of PEO peak at 70.8 ppm. Significant improvement in the resolution was also observed. The copolymer compositions were determined by measuring the integral areas of all the peaks. The experimental copolymer composition obtained by ^{13}C n.m.r. are given in *Table 3*. These values were compared with the feed composition. It can be seen that there is an excellent agreement with the values of the feed, indicating that the reaction proceeds to completion. Moreover, the yields of all the reaction products were quantitative, suggesting the completion of the reaction.

Swelling ratios of copolymer gels

Figure 2 shows the temperature dependent swelling ratios of PEO homopolymer gel (VE) compared with the swelling ratios of PEO-*co*-PNIPAm copolymer gels (VA-2 and VA-4). The PEO gel shows a continuous decrease in swelling ratio as a function of increasing temperature with no sharp volume transition. There are no reports as yet on the well defined LCST of PEO hydrogels. However, upon copolymerisation of PNIPAm and PEO, the resultant gels showed a discontinuous volume transition between 35 and 42°C, releasing almost 70–80% of the absorbed water above the transition temperature. The transition temperatures of the copolymer gels were found to be changing with the composition of the gel. *Figure 2* shows that the transition temperature is a non-monotonic function of the composition of the copolymer gel. It is also interesting to note that the equilibrium swelling ratios of PEO-*co*-PNIPAm copolymer gels at any temperature are found to be lower than the swelling ratios of the PEO gel. This could be due to the fact that copolymerisation of PNIPAm with PEO increases the hydrophobic content of the polymer, resulting in the lower swelling ratios of copolymer gels. While the hydrophobicity of the copolymer comes from the pendent isopropyl groups of the PNIPAm, the hydrophilicity is mainly contributed by the PEO chains in the structure. It is also expected that

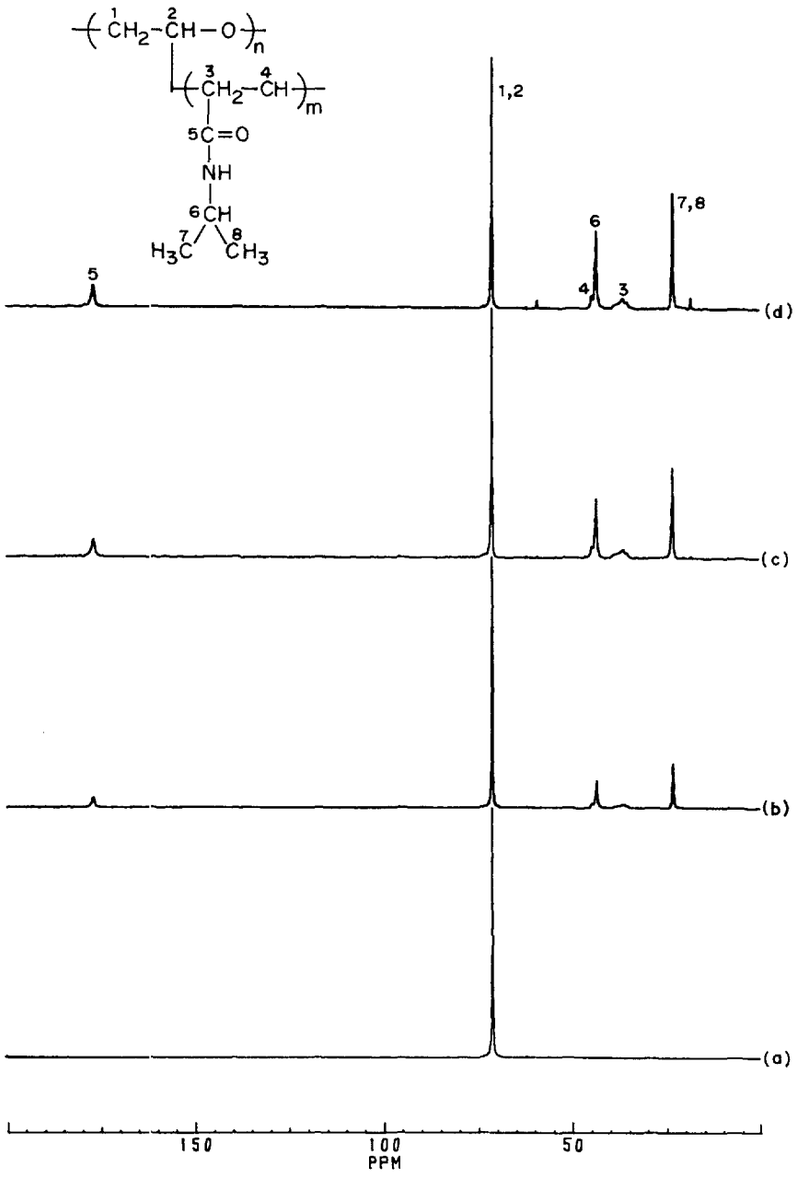


Figure 1 ^{13}C n.m.r. spectra of PEO homopolymer gels (VE) (a) and PEO–PNIPAm copolymer gels with mole ratios of 1:0.26 (VA-2) (b), 1:0.52 (VA-3) (c) and 1:0.65 (VA-4) (d)

copolymerisation of NIPAm monomer with PEO proceeds randomly and can lead to additional inter- and intra-molecular cross-linking in the copolymer structure. This additional cross-linking can also decrease the swelling capacity of the gels significantly.

Effect of molecular weight of PEO on the swelling ratios of copolymer gels

We have copolymerised NIPAm with PEO of molecular weights of 6000 and 100 000. *Figure 3* shows the swelling of these gels as a function of temperature. The gel prepared from 6000 molecular weight PEO shows a discontinuous volume transition and a higher swelling capacity at temperature below the transition temperature. In contrast, the gel prepared from 100 000 molecular weight PEO exhibits a continuous decrease in swelling capacity as a function of temperature and a lower swelling capacity at temperatures below the transition point. This behaviour could be attributed to the fact that higher molecular weight PEO gives a high degree of cross-linking during γ-radiation, resulting in lower swelling ratios of the copolymer gels. This is in agreement with the earlier report by Deng *et al.*[5]

We have also studied the thermoreversibility of the copolymer gel which is demonstrated in *Figure 4*. A disc-shaped gel of 0.7 cm diameter in dry state was immersed in water at 5°C until equilibrium swelling was attained. The diameter of the gel was increased to 2.5 cm in 75 hours, indicating an equilibrium swelling ratio (q) of 34.3. The gel was then transferred to a water bath maintained at 60°C for deswelling. The gel collapsed in 6 hours showing a swelling ratio of 6.2. However, upon reswelling the gel at 5°C the equilibrium swelling was reached at an earlier value of 34.3. This clearly indicates the thermoreversible nature of the gel.

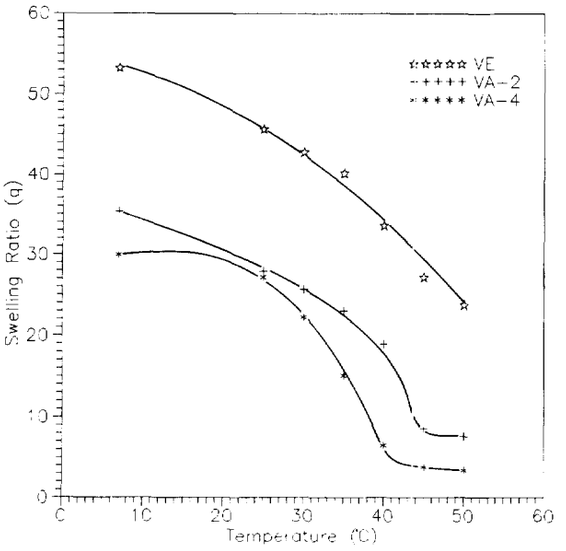


Figure 2 Swelling ratios of gels as a function of temperature. VE is a PEO homopolymer gel, VA-2 and VA-4 are copolymer gels with PEO–NIPAm mole ratio of 1:0.26 and 1:0.65, respectively

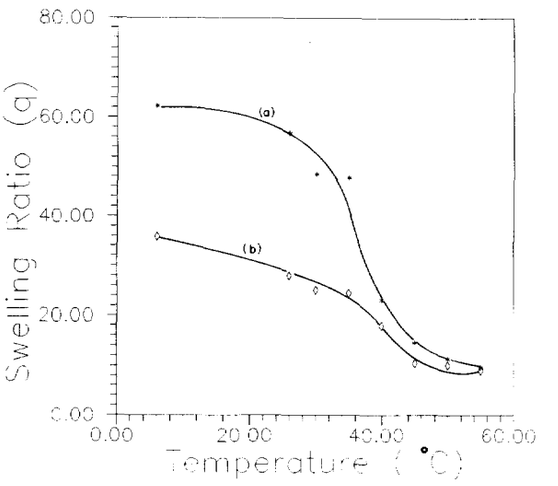


Figure 3 Temperature dependent swelling ratios of PEO–PNIPAm copolymer gels prepared from PEO of different molecular weights: (a) PEO $M_w = 6000$; (b) PEO $M_w = 100\,000$

Figure 4 shows the reversible swelling–deswelling kinetics of the copolymer gel.

CONCLUSIONS

In conclusion, we have synthesised thermoreversible PEO–PNIPAm copolymer gels using γ-radiation technique. The structure and composition of the copolymer gels have been studied by ^{13}C n.m.r. spectroscopy. The temperature dependent swelling ratio measurements of these gels in water showed that the PEO homopolymer does not exhibit a well defined first order transition even though PEO has been reported to be an LCST polymer. On the other hand, copolymer gels of PEO and PNIPAm showed clear LCST behaviour. The LCSTs of the gels were found to be dependent on the composition of the copolymers. Since these gels are synthesised by γ-radiation technique they are free from impurities and have potential biomedical applications.

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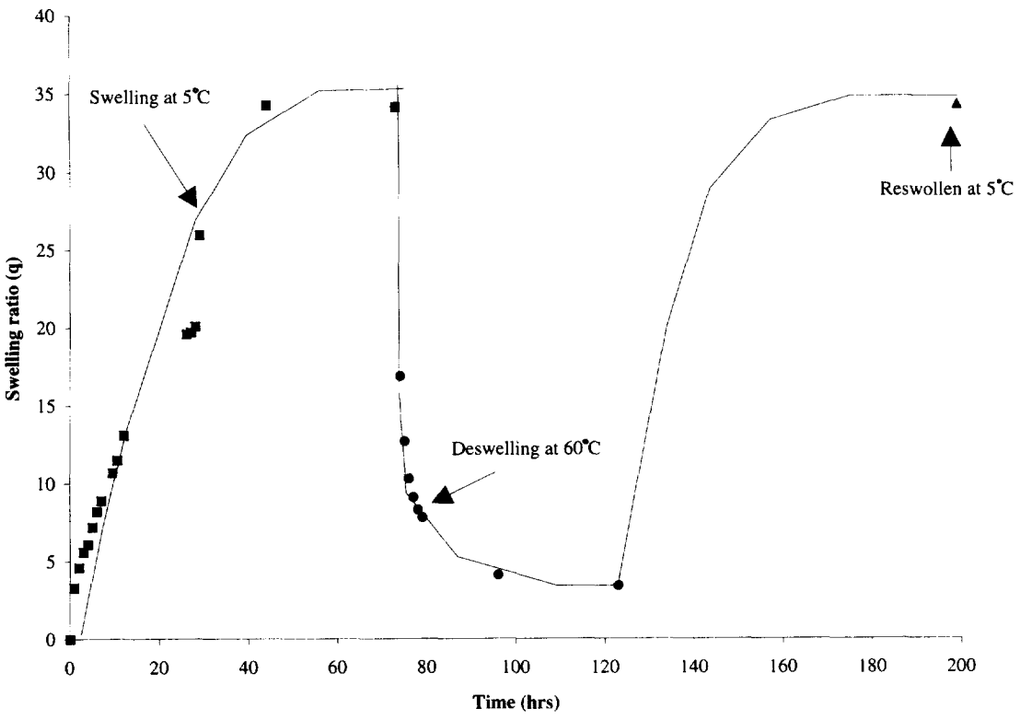

Figure 4 Kinetics of swelling–deswelling of PEO–PNIPAm copolymer gel

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