Available online at www.sciencedirect.com
SCIENCE DIRECT
Polymer 47 (2006) 148–155
polymer
www.elsevier.com/locate/polymer

Copolymer hydrogels based on *N*-isopropylacrylamide and itaconic acid

Melina Kalagasidis Krušić *, Jovanka Filipović

Faculty of Technology and Metallurgy, Karnegijeva 4, 11 000 Belgrade, Serbia and Montenegro

Received 27 June 2005; received in revised form 20 October 2005; accepted 1 November 2005
Available online 21 November 2005

Abstract

In this study, the swelling behaviour of copolymer hydrogels of *N*-isopropylacrylamide (NIPAM) and itaconic acid (IA) in response to temperature and pH value of the external media was studied. The equilibrium degree of swelling for PNIPAM and PNIPAM/IA copolymers was greater at 25 °C than at 37 °C. The degree of swelling was low at low pH values. As the degree of ionization increased above the nominal pK_a values of IA, the increased hydrophilicity resulted in larger degrees of swelling. At 37 °C, the PNIPAM hydrogel and some copolymers show anomalous swelling behaviour, i.e. the overshooting effect, in buffered solutions of certain pH values. A swelling–deswelling study showed that the deswelling process of the hydrogels was faster then the swelling process. According to dynamic swelling studies, the diffusion exponent and the diffusion coefficient both increase with increasing content of IA.

Keywords: *N*-isopropylacrylamide; Itaconic acid; 'Overshooting' effect

1. Introduction

Stimuli sensitive or 'intelligent' gels go through reversible phase transitions, accompanied with excessive volume changes, in response to physical or chemical stimuli. These gels have a great potential for application in pharmaceutical and biotechnological fields. *N*-isopropylacrylamide (NIPAM) gels have been one of the most commonly studied thermo-reversible systems, with a low critical solution temperature (LCST) in water of 34 °C [1]. They swell below and collapse above the LCST. Hydrogels based on NIPAM and its copolymers have been used in order to develop reversible temperature-controlled drug release systems.

On the other hand, the presence of ionic components may provide pH sensitivity to the non-ionic PNIPAM, which would be very useful for the delivery of drugs to a specific site in the gastrointestinal tract (GI) [2]. Anionic residues shift the LCST to higher temperatures, which should be lower than the physiological temperature of 37 °C for in vivo applications, and may determine the resiliency of a polymer under physiological conditions. Erbil et al. [3] investigated the effect of type and concentration of ionizable comonomers, acrylic, itaconic and maleic acid, on the collapse behavior of PNIPAM gels in water.

The release of a drug from a hydrogel network depends on the degree of swelling of the gels, which can be precisely controlled by a combination of pH- and temperature sensitive gels for a given structure and degree of crosslinking. Tasdelen et al. investigated the influence of comonomer concentration and irradiation dose on the equilibrium swelling behaviour, as well as the swelling in water and model drug solutions of poly(*N*-isopropylacrylamide-*co*-itaconic acid) hydrogels [4].

The present work reports on the swelling properties of copolymer hydrogels based on *N*-isopropylacrylamide (NIPAM) and itaconic acid (IA), with various amounts of IA and *N*,*N*′-methylenebisacrylamide (MBA), as the crosslinker, in response to the temperature and pH value of the external media. Copolymers have similar behaviour to the homopolymer with some new characteristics, which are due to interaction between the monomers. The IA sequences contribute to the sensitivity of the copolymer to the environmental pH changes and NIPAM, as a temperature sensitive polymer, to its thermoresponsivity. The formation of hydrophobic complexes between IA and NIPAM through hydrogen bonds has been detected [5]. These complexes are stable in acidic media, where they suppress the swelling of the gel. At higher pH values, above the pK_a of itaconic acid, due to PIA ionization, the complexes desintegrate and the swelling becomes enormously higher. The ionization of the diprotic itaconic acid carboxylic groups occurs at different pH values and,

* Corresponding author. Tel.: +381 11 3303 730; fax: +381 11 3370 387.
E-mail address: meli@tmf.bg.ac.yu (M.K. Krušić).

0032-3861/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.polymer.2005.11.002

accordingly, the degree of swelling of the copolymer increases gradually with increasing pH.

Since the poly(*N*-isopropylacrylamide-*co*-itaconic acid) hydrogels contain nonionic units (NIPAM residues), which can become hydrophobic with a change of temperature, and hydrophilic units (IA residues), they could be classified as amphiphilic polymer networks at temperatures above their LCST. Amphiphilic hydrogels swell less than hydrophilic polymer networks and have some specific properties: they can also swell in organic solvents. When swollen in water, amphiphilic hydrogels can adsorb significant amounts of hydrophobic substances, e.g. drugs, hence they can be applied as drug delivery systems [6].

Anomalous swelling behaviour is characteristic for PNIPAM hydrogels and some copolymers, depending on their chemical composition. At the beginning of the swelling process, the swelling curves exhibit a maximum in the water uptake, after which the swelling gradually decreases to an equilibrium value at longer times. This is described in the literature as the overshooting effect [7].

An attempt was made to simulate the pH changes of the gastric fluids in vitro and according to the residence time in the GI tract, hence the swelling of the samples was monitored in pH 2.2 (the pH value of the gastric fluid) and in 6.8 (average pH values of the intestine). The same experiment was conducted for different copolymer compositions and degrees of crosslinking.

Diffusion in the gels was studied in order to obtain better knowledge on the polymer morphology, transport phenomena and controlled release of drugs from polymer carriers.

The kinetics of water uptake, the kinetic order and the rate constants for the copolymer were calculated from the data of the kinetics of the swelling.

2. Experimental

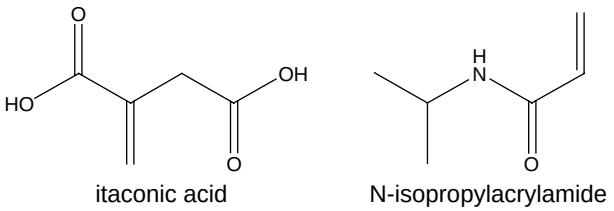
2.1. Materials

The monomers used in this study, itaconic acid (IA) and *N*-isopropylacrylamide (NIPAM) were obtained from Fluka (Switzerland) and Acros (Belgium), respectively. The crosslinking agent *N*,*N*′-methylenebisacrylamide (MBA) was obtained from Serva (Germany). Potassium persulphate (PPS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), the initiator and accelerator, respectively, were purchased from Merck (Germany) and Acros, respectively.

N-isopropylacrylamide was recrystalized from benzene/*n*-hexane (35/75) before use. Other materials were used as received, without purification (Scheme 1).

Aqueous media with different pH values were prepared using hydrochloric acid (La Chema, Czech Republic), potassium chloride (Alkaloid, Macedonia), potassium dihydrogenphosphate (La Chema, Czech Republic) and sodium hydroxide (Zorka Pharma, Serbia).

Distilled water was used for all copolymerizations and the preparation of the buffer solutions.



Scheme 1. The molecular structures of the monomers.

2.2. Preparation of copolymer hydrogels

The copolymer hydrogels of NIPAM and IA were obtained by radical crosslinking copolymerization at 25 °C under a N_2 atmosphere for a week. The weight ratios of NIPAM/IA monomer in the initial mixture were: 99:1, 95:5 and 90:10. The monomers were dissolved in water with the redox couple PPS and TEMED (both 1.0 wt% with respect to the monomers). The concentration of the crosslinking agent MBA was usually 2.0 wt%. The exception being the sample 95/5/3 where it was 3.0 wt% with respect to the other monomers. The reaction mixture was placed between two glass plates ($20\times5\times0.4$) cm sealed with a rubber spacer (2 mm thick). After completion of the reaction, the gels were cut into discs and immersed in water for a week to remove unreacted monomers. The water was changed daily. The discs were dried at room temperature to xerogels (1 mm thick and 5 mm in diameter).

The PNIPAM hydrogel was synthesized under the same conditions as were used for the copolymers, the concentration of MBA being 2.0 wt%.

The samples were named as PNIPAM/IA 99/1/2, 95/5/2, 95/5/3 and 90/10/2, where the first and second number correspond to the weight ratios of NIPAM and IA, and the third one corresponds to the concentration of the crosslinking agent.

3. Characterization

3.1. Equilibrium swelling studies

The swelling behaviour of the PNIPAM/IA copolymers (99/1/2, 95/5/2, 95/5/3 and 90/10/2) and the PNIPAM hydrogel was studied as a function of pH at 25 and at 37 °C. Three aqueous media with different pH values were used, namely: USP (The United States Pharmacopeia) hydrochloric acid buffer (pH 2.2), 0.05 M KH_2PO_4 (pH 4.5) and USP phosphate buffer (pH 6.8). A buffer of pH = 4.5, which is above the pK_{a1} value of IA ($pK_{a1} = 3.85$ [8]), was chosen in order to investigate how ionization of the first COOH group of the itaconic acid residues affects the degree of swelling.

The xerogels discs were immersed in buffer solutions and left to obtain equilibrium swelling at 25 and 37 °C. The progress of the swelling process was monitored gravimetrically and the degree of swelling was calculated using the equation:

$$q = \frac{W_t}{W_0} \tag{1}$$

where W_0 is the weight of the xerogel at time 0 and W_t is the weight of the swollen hydrogel at time t [9].

3.2. Oscillatory swelling studies

It is important that the structure and mechanical strength of a sample should be maintained during the process of drug release. In order to investigate the stability of the gels, the swelling–deswelling behaviour was studied. A sample was placed into a pH 6.8 buffer solution. After reaching equilibrium, the sample was transfered to a pH 2.2 buffer to shrink. The swelling-deswelling measurements were repeated three times.

3.3. Simulation of the conditions in the GI tract

All the copolymer samples were treated in the following way: the sample was immersed in a pH 2.2 buffer and left to swell for 2 h. The same gel was then transffered to a pH 6.8 buffer for 12 h, according to the mean residence times in the stomach and intestinal tract.

3.4. SEM analysis

Scanning electron micrographs were taken on a JEOL JSM-T20 scanning electron microscope. In order to keep the pores of the xerogels intact for imaging, the xerogels were left in liquid nitrogen and then broken. Before SEM observation, specimens of the xerogels were fixed on stubs and the inner surface of xerogels were coated with gold/platinum alloys (15/85) under vacuum using JOEL JEE-SS vacuum evaporator.

4. Results and discussion

The swelling behaviour of the copolymer hydrogels differs from that of PNIPAM at 25 and at 37 °C. At 25 °C, the non-ionic PNIPAM gel is below its LCST and it swells, but there was not a big change in the equilibrium degree of swelling with pH, as was to be expected. In contrast, the swelling of the copolymer hydrogels PNIPAM/IA were strongly dependent on the pH value of the external medium. At low pH values the degree of swelling was low because the carboxylic groups in the side chains were not ionized and intermolecular complexation via hydrogen bonds occurs (physical crosslinking). As the degree of ionization increases above the nominal pK_a values of IA (3.85; 5.44 [8]), the increased hydrophilicity resulted in greater degrees of swelling.

The equilibrium degree of swelling for PNIPAM and the PNIPAM/IA copolymers at 25 and 37 °C are presented in Table 1. It can be seen that the corresponding swelling is greater at 25 °C than at 37 °C.

The q_e values for the copolymers at 25 °C and at a pH value of 2.2 decrease with increasing IA content, due to complexation via hydrogen bonds between the IA and NIPAM residues. At higher buffer pH values, the degree of swelling of the copolymer increases with increasing content of the hydrophilic component (IA).

Below the LCST value, which is at about 34 °C for PNIPAM gels, a hydration shell around the hydrophobic groups is formed by hydrogen bonds between the hydrophilic groups in the side chains and water, causing water uptake and swelling of the PNIPAM. The increase of the external temperature leads to the scission of the hydrogen bonds and hydrophobic interactions prevail. The LCST represents the temperature at which the hydrophobic forces (due to interaction of the $-NCH(CH_3)_2$ groups), which lead to insolubility in an aqueous environment, are balanced by H-bonding with water, which maintains a polymer in solution.

According to the results presented in Fig. 1, an anomalous swelling behaviour exists, i.e. the 'overshooting' effect, was evident at pH = 2.2 for all samples at 37 °C. The swelling curves exhibit a maximum in the water uptake for short swelling times, after which the swelling gradually decreases to an equilibrium value. Before the maximum is reached, the gels are transparent, while after the maximum, gels showed some opacity. The opacity of gels depended on the hydrogel composition: at lower itaconic acid contents the opacity was more pronounced. The pure PNIPAM hydrogel exhibited a more pronounced overshooting effect, than was the case with the copolymers. The equilibrium degree of swelling was higher for PNIPAM than for the copolymer samples at pH = 2.2 and 37 °C due to physical crosslinking which exist in acidic media. At the same temperature, the overshooting effect was observed only for the PNIPAM gel and the PNIPAM/IA 99/1/2 copolymer at pH values of 4.5 and 6.8.

At 37 °C and at pH values higher than the pK_a values of itaconic acid, the ionization of the carboxylic groups of the itaconic acid residues hinders the collapse of the PNIPAM chains, hence in the case of the PNIPAM/IA copolymers the anomalous swelling was not observed, and the swelling curves were sigmoidal, exept in the case of the copolymer with very low content of IA (Fig. 1).

A number of examples of the overshooting efect were presented and discussed by Diez-Pena et al. [7,10–16].

Table 1
Equilibrium degree of swelling for PNIPAM and the PNIPAM/IA copolymers at 25 and 37 °C

pH	T (°C)	q_e PNIPAM 100/0/2	q_e PNIPAM/IA 99/1/2	q_e PNIPAM/IA 95/5/2	q_e PNIPAM/IA 95/5/3	q_e PNIPAM/IA 90/10/2
2.2	25	13.04 ± 0.09	18.37 ± 0.01	16.28 ± 0.09	8.00 ± 0.03	14.42 ± 0.08
4.5		12.01 ± 0.06	18.49 ± 0.01	21.20 ± 0.12	13.05 ± 0.06	29.61 ± 0.02
6.8		11.15 ± 0.11	19.21 ± 0.01	22.27 ± 0.12	14.30 ± 0.11	36.68 ± 0.02
2.2	37	4.35 ± 0.10	3.63 ± 0.02	2.47 ± 0.04	2.06 ± 0.03	2.17 ± 0.01
4.5		3.66 ± 0.15	4.78 ± 0.01	10.72 ± 0.25	8.37 ± 0.13	23.40 ± 0.08
6.8		3.64 ± 0.02	4.13 ± 0.04	12.87 ± 0.18	9.67 ± 0.01	25.77 ± 0.03

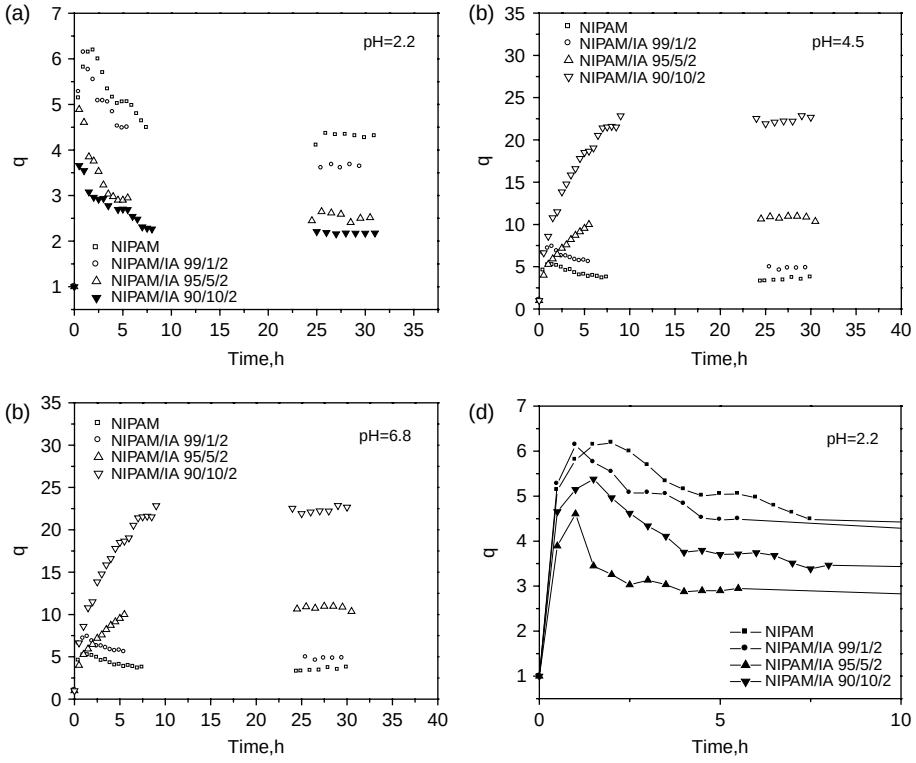


Fig. 1. The swelling curves of PNIPAM and copolymer hydrogels PNIPAM/IA at different pH values at 37 °C: (a) pH = 2.2; (b) pH = 4.5; (c) pH = 6.8; and (d) 'overshooting effect' at pH = 2.2.

According to these authors a generally applicable explanation of this phenomenon is not possible, because it is observed for the systems with very different chemical structures and depends on the large number of factors. The authors state that the explanations given for different systems are not essentially contradictory, but just treat the overshooting effect from different points of view. Diez-Pena et al. gave a kinetic model of the overshooting effect for the case of poly(*N*-isopropylacrylamide-*co*-methacrylic acid) hydrogels based on the assumption that the dynamic formation of hydrogen bonds in acidic solutions, promoted by the solvent under swelling, is the cause of the overshooting effect.

The poly(*N*-isopropylacrylamide-*co*-itaconic acid) hydrogel system, which was investigated in this study, is similar to the poly(*N*-isopropylacrylamide-*co*-methacrylic acid) system, except that itaconic acid has two carboxylic groups with different pK_a values, pK_{a1} = 3.85 and pK_{a2} = 5.44, so the ionisation of carboxylic groups with increasing pH occurs in two steps.

The following explanation of the overshooting effect for PNIPAM/IA gels is proposed. At the beginning of the swelling process in acidic solutions at 37 °C, the PNIPAM homopolymer and the PNIPAM/IA copolymers swell in the normal way until a critical amount of water has been sorbed. This critical amount of water corresponds to the maximum in the swelling curve. At this moment the network volume phase transition commences due to the phenomenum of polymer relaxation and the degree of swelling decreases to an equilibrium value.

The swelling process of a polymer network is determined by three free energy terms:

$$\Delta G = \Delta G_m + \Delta G_r + \Delta G_i \quad (2)$$

where ΔG_m is the free energy of mixing, ΔG_r the rubber elasticity term and ΔG_i term is an additional contribution to the total change in Gibbs free energy due to the ionic nature of polymer network. If the Flory–Rehner equation is applied, and using the mean field approximation, the Gibbs free energy of mixing of hydrogels of random Gaussian chain network is [17]:

$$\Delta G_m = kT[n \ln(1-\varphi) + \chi n\varphi] \quad (3)$$

where n is the number of solvent molecules in the gel, χ is the polymer–solvent interaction parameter, φ the volume fraction of the gel, k the Boltzmann constant, and T is the temperature.

The swelling of the PNIPAM gel at some temperature above the LCST value is considered by analyzing the equation for ΔG. The equilibrium swelling is determined by the competition of only two free energy terms, the free energy of mixing and the rubber elasticity term, because PNIPAM gel has no ionisable groups.

At the beginning of the swelling process, the number of solvent molecules in the gel, n, is small, and their contribution to ΔG_m is significant as a driving force for swelling, hence the gel first swells normally. As the swelling proceeds, the number of solvent molecules in the gel becomes greater and the ΔG_m value rises making the swelling process due to mixing less probable. At the certain point, when the number of solvent molecules reaches a critical value, ΔG_m tends to zero, the

swelling stops and commences to decrease to some equilibrium value, which is determined by the ΔG_r term. The overshooting effect is due to polymer relaxation phenomena because the diffusion of solvent into the hydrogel is faster than the relaxation of polymer chains, so it gets initially more water than the equilibrium value. Later, when the polymer relaxes to the equilibrium conformation, some water is expelled.

In the case of NIPAM/IA copolymers the situation is more complicated. Due to the presence of ionisable groups in the IA residue, the third term in the Eq. (2) becomes operative. The occurrence of the overshooting effect depends on the magnitude of the ΔG_i term. This term is closely related to the IA content in the sample and the pH of the solution. In the swelling curves for NIPAM/IA 95/5/2 and NIPAM/IA 90/10/2 copolymers at pH values of 4.5 and 6.8 the overshooting effect is not present.

The human body temperature (37 °C) is above the LCST of PNIPAM, hence at 37 °C the equilibrium degrees of swelling for PNIPAM and all the copolymer samples are lower than at 25 °C. PNIPAM/IA 99/1/2 and PNIPAM swell very little at 37 °C and pH dependent swelling is observed. The copolymers PNIPAM/IA 95/5/2, PNIPAM/IA 95/5/3 and PNIPAM/IA 90/10/2 follow the same pattern at 37 °C as at 25 °C, i.e. the q_e values increase with increasing IA content and pH. However, there is a substantial increase of q_e for PNIPAM/IA 95/5/2 and PNIPAM/IA 90/10/2 at pH values of 4.5 and 6.8, because the IA content in these samples is higher and produces more pronounced electrostatic repulsion of the negatively charged ions, which has a pronounced effect on their swelling.

Increasing the degree of crosslinking leads to a decrease in the free volume and chain flexibility, hence the q_e values also decrease. The influence of the degree of crosslinking can be seen when q_e values at 25 °C and pH 2.2 for PNIPAM/IA 95/5/3 and PNIPAM/IA 95/5/2 are compared.

A series of poly(*N*-isopropylacrylamide-*co*-itaconic acid) hydrogels was investigated to determine the composition that exhibits appropriate pH sensitive swelling for the drug delivery in the small and large intestine. The pH values in the physiological medium change from the highly acidic conditions in the stomach (pH 1–3) to the almost neutral pH values in the small and large intestine, in the range of 6.63–7.49 and 6.37–7.04, respectively [18]. Acidic gels have a low degree of swelling in the acidic gastric fluid, but as they pass through the gastrointestinal tract (GI), the degree of swelling increases due to the increase of pH. In this way, the drug is protected from the acidity of the gastric fluid, but it is released at the higher pH values in the lower part of the GI tract. For this reason, the swelling behaviour in an acidic medium (pH 2.2) and in a buffer of pH 6.8 was investigated.

In order to simulate the conditions in the GI tract, dry copolymer samples were immersed in pH 2.2 buffer and left to swell for 2 h. The same gels were then transfered to a pH 6.8 buffer for 12 h, according to the mean residence times in the stomach and intestinal tract.

The degree of swelling vs. time dependences of the hydrogels at 37 °C are presented in Fig. 2. Although for copolymers with IA content of 5 and 10% a well pronounced

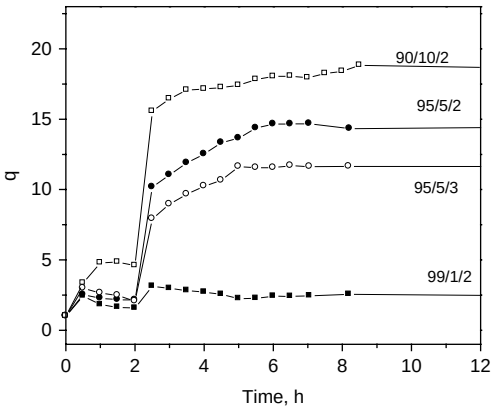


Fig. 2. The degrees of swelling vs. time at 37 °C: the gels were first immersed in a pH 2.2 buffer for 2 h, then transferred to a pH 6.8 and left to swell for 12 h.

dependance of the swelling on the pH was found, the hydrogel PNIPAM/IA 95/5/2 is more suitable for use for controlled drug release in the small and large intestine—it exhibits low swelling at pH of 2.2, but a high degree of swelling at pH 6.8, which is important for intestine-targeted drug release.

The swelling–deswelling behaviour, i.e. the effect of pH cycling of the 90/10/2 copolymer hydrogel and the PNIPAM gel, is presented in Fig. 3. The equilibrium degree of swelling of the copolymer gel is the highest for the first cycle, with a tendency to slightly decrease, in the subsequent two cycles. On the contrary, during the shrinking process the sample showed good reproducibility for all three cycles. The same equilibrium degree of swelling was obtained at the end of every cycle, which is in accordance with the results of Kit Li and D'Emanuele [19]. It can be seen from Fig. 3 that the deswelling process is faster then the swelling process of the hydrogel, which may be explained by the different mechanisms of these two processes. On the other hand, the degree of swelling of PNIPAM gel showed only small fluctuations and after the first swelling remained almost constant, irrespective of the pH of the buffers, i. e. as expected, it was pH insensitive.

Dynamic swelling studies were undertaken in order to characterize the mechanism of buffer diffusion into the gels. Water transport into polymer networks, i.e. swelling–time curves, may be described by the following equation [20]:

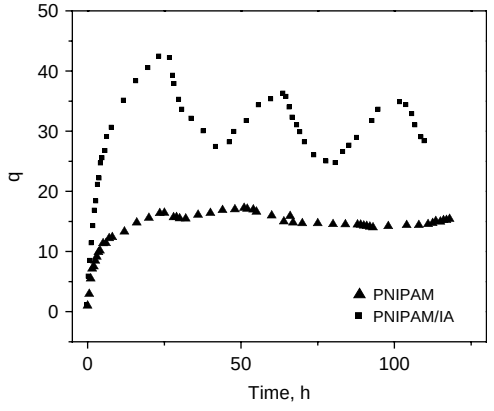


Fig. 3. The swelling–deswelling studies for PNIPAM and PNIPAM/IA 90/10/2.

Table 2
Kinetic parameters for PNIPAM and the PNIPAM/IA copolymers at 25 °C

sample	pH	$k\times10^5$ s^{-1}	n	R^2	$D\times10^7$ cm^2 s^{-1}
PNIPAM 100/0/2	2.2	10.3	0.55	0.994	3.38
	4.5	8.12	0.62	0.994	3.34
	6.8	10.8	0.58	0.997	4.47
PNIPAM/IA 99/1/2	2.2	7.90	0.52	0.996	2.12
	4.5	8.48	0.48	0.997	2.16
	6.8	7.29	0.47	0.987	3.15
PNIPAM/IA 95/5/2	2.2	8.20	0.58	0.999	2.92
	4.5	7.67	0.60	0.999	2.18
	6.8	8.06	0.63	0.997	3.00
PNIPAM/IA 95/5/3	2.2	8.08	0.54	0.993	2.65
	4.5	7.15	0.63	0.994	2.99
	6.8	9.72	0.58	0.999	3.80
PNIPAM/IA 90/10/2	2.2	8.64	0.58	0.999	2.13
	4.5	5.75	0.71	0.992	2.02
	6.8	6.33	0.72	0.999	3.43

$$\frac{M_t}{M_e} = kt^n \tag{4}$$

In this expression, k is a proportionality constant related to the structure of the network, n is the diffusion exponent, t is time, M_t and M_e are the amounts of buffer absorbed at time t and at equilibrium, respectively.

The logarithmic form of Eq. (4) was used to determine the values of n and k, from the slope and the intercept, respectively. If n is less than 0.5 the swelling process is controlled by the Fickian diffusion mechanism. On the contrary, if n varies between 0.5 and 1, diffusion and macromolecular relaxation control the swelling process.

The kinetic parameters for the investigated hydrogels at 25 and 37 °C are presented in Tables 2 and 3, respectively. For PNIPAM/IA 99/1/2 at all investigated pH values, the value of n is close to 0.5, so the diffusion can be considered as Fickian. The highest deviation from Fickian behaviour was observed for PNIPAM/IA 90/10/2.

Comparing the hydrogel with the same itaconic acid content, but with a different concentration of the crosslinking agent, it is obvious that the values of n decrease as the degree of crosslinking increases, as is to be expected.

The second Fick's law can be approached for one-dimensional diffusion into simple geometric shapes (e.g. discs, cylinders and spheres). Thus, the following equation holds [21]:

$$\frac{M_t}{M_e} = 2\left(\frac{Dt}{\pi l^2}\right)^{1/2} \tag{5}$$

where t is the time, D is the diffusion coefficient, M_t and M_e are the amount of buffer sorbed at time t and at equilibrium, respectively, and l is the thickness of a xerogel discs. From the slope of the W_t/W_e vs. $t^{1/2}$ dependence, the diffusion coefficient for each hydrogel sample was calculated.

The calculated values of the diffusion coefficients at 25 and 37 °C are presented in Tables 2 and 3, respectively.

Raising the temperature above the LCST value for PNIPAM leads to the contraction of the NIPAM component of the gel. Therefore, Fickian diffusion prevails and the diffusion exponent n decreases. With increasing IA content, the hydrophilicity of the copolymer increases. As a consequence, the diffusion of the buffer into the gel is easier and higher values of the diffusion coefficient are observed on going from a low to a high pH value of the surrounding media. The diffusion coefficient for PNIPAM are higher than those for the copolymer samples at all studied pH values.

A PNIPAM gel undergoes a temperature induced phase transition in water at 34 °C, and at 37 °C it is in its collapsed state. The LCST value of PNIPAM is slightly modified by copolymerization with itaconic acid, according to the results of Erbil et al., who found that three different ionizable components (acrylic acid, itaconic acid and maleic acid) had a different effect on the volume phase transition and swelling equilibrium of PNIPAM based gels in water [3].

The swelling data can be normalized to the mass of the initial xerogel. Thus, the normalized degree of swelling, Q_t, at time t is given by:

$$Q_t = \frac{m_t - m_0}{m_0} = \frac{W_t}{m_0} \tag{6}$$

m_0 is the initial mass of the dry disc, m_t is the mass of the swollen disc at time t and W_t is the mass of buffer taken up at time t.

Similary, the normalized equilibrium degree of swelling is given by:

$$Q_e = \frac{m_e - m_0}{m_0} = \frac{W_e}{m_0} \tag{7}$$

Using the values of Q_t and Q_e it is possible to analyze the kinetic order of the swelling process [22].

Thus, if first-order kinetics are obeyed:

$$\frac{Q_t}{Q_e} = 1 - \exp(-Kt) \tag{8}$$

and a plot of $[\ln(Q_e - Q_t)/Q_e]$ vs. t should be linear with a slope of $-K$.

However, if second-order kinetics are obeyed:

$$\frac{t}{Q_t} = \frac{1}{KQ_e^2} + \frac{t}{Q_e} \tag{9}$$

Table 3
Kinetic parameters for PNIPAM and PNIPAM/IA copolymers at 37 °C

Sample	pH	$k\times10^4$ s^{-1}	n	R^2	$D\times10^7$ cm^2 s^{-1}
PNIPAM/IA 95/5/2	2.2	–	–	–	–
	4.5	1.07	0.43	0.995	4.29
	6.8	1.50	0.44	0.998	3.83
PNIPAM/IA 95/5/3	2.2	–	–	–	–
	4.5	1.04	0.37	0.991	4.44
	6.8	1.21	0.51	1.000	7.47
PNIPAM/IA 90/10/2	2.2	–	–	–	–
	4.5	0.92	0.50	0.989	2.94
	6.8	1.34	0.53	1.000	5.02

Table 4
First-order and second-order kinetic parameters for NIPAM and the copolymer hydrogels

Sample	T (°C)	pH	Q_e (exp)	First-order		Second-order	
				$K\times10^3$ (min^{-1})	Q_e (calc.)	$K\times10^3$ (min^{-1})	Q_e (calc.)
PNIPAM 100/0/2	25	2.2	12.1	6.29	11.8	0.85	12.5
		4.5	11.0	5.04	10.3	0.54	11.4
		6.8	10.2	6.92	9.69	1.00	10.4
PNIPAM//IA 99/1/2		2.2	18.4	4.15	17.3	0.37	18.5
		4.5	18.5	4.13	17.7	0.40	18.7
		6.8	19.2	3.35	17.8	0.24	19.7
PNIPAM//IA 95/5/2		2.2	15.3	5.40	13.8	0.42	16.2
		4.5	20.2	4.55	18.8	0.28	21.6
		6.8	21.3	5.30	19.6	0.32	22.5
PNIPAM//IA 95/5/3		2.2	6.96	4.05	7.16	0.88	7.51
		4.5	12.2	4.10	12.1	0.47	12.9
		6.8	13.3	5.82	13.7	0.85	13.9
PNIPAM//IA 90/10/2		2.2	13.5	4.26	14.4	0.64	14.3
		4.5	28.6	3.46	28.0	0.14	31.1
		6.8	35.7	3.89	34.7	0.14	38.3
PNIPAM	37	2.2	3.35	18.80	3.33	7.21	3.26
		4.5	2.66	13.70	3.13	10.6	2.43
		6.8	2.66	51.16	2.67	11.4	2.55
PNIPAM//IA 99/1/2		2.2	2.63	44.83	2.60	6.71	2.55
		4.5	4.19	30.74	3.66	5.96	3.65
		6.8	3.04	76.58	3.46	13.6	3.12
PNIPAM//IA 95/5/2		2.2	1.47	10.22	1.29	13.92	1.48
		4.5	9.74	7.14	9.75	1.20	10.2
		6.8	11.9	14.33	12.0	4.86	11.9
PNIPAM//IA 95/5/3		2.2	1.06	33.14	0.96	41.70	1.05
		4.5	7.37	6.80	7.36	1.55	7.76
		6.8	8.67	10.38	8.64	2.66	8.84
PNIPAM//IA 90/10/2		2.2	2.17	51.55	2.34	2.06	7.91
		4.5	23.7	6.15	21.2	0.39	23.7
		6.8	24.8	8.56	24.4	0.08	25.4

and a plot of t/Q_t vs. t should be a straight line with a slope of $1/Q_e$ and an intercept of $1/KQ_e^2$.

The values of normalized equilibrium degree of swelling (Q_e) and rate constants (K) were determined from the best fit of the experimental results, using the logarithmic forms of Eqs. (8) and (9) to analyse the experimental results. The results are presented in Table 4, as well as the experimental values of Q_e, for comparison.

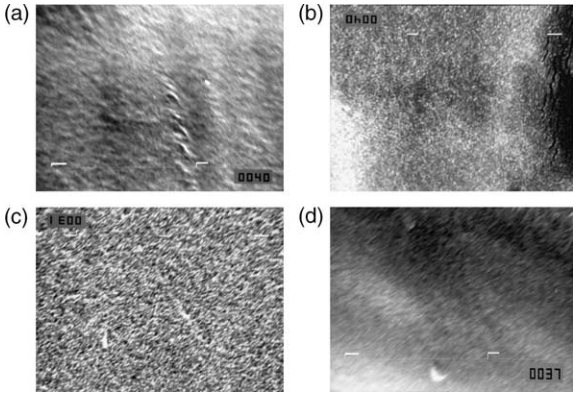


Fig. 4. SEM micrographs of the investigated hydrogels: (a) PNIPAM/IA 99/1/2; (b) PNIPAM/IA 95/5/2; (c) PNIPAM/IA 90/10/2; (d) PNIPAM. The bar indicates a length of 7 μm (7500×).

The second order kinetics show a better fit for both temperatures. Table 4 shows that the values of the theoretical equilibirum degree of swelling are in good agreement with the experimental results of equilibirum swelling of the investigated hydrogels. From the values of the swelling rate constant K, it can be observed that the swelling rate is of the same order of magnitude for all the samples. The higher K values at 37 °C indicate faster swelling.

The morphology of the copolymer hydrogels has been studied by SEM. Fig. 4 shows the SEM micrographs of the PNIPAM/IA copolymers (Fig. 4(a)–(c)) and pure PNIPAM hydrogel (Fig. 4(d)). These images were taken at 7500× magnification. The bar indicates a length of 7 μm. As can be seen, the copolymer depicted in Fig. 4a was porous, but the degree of porosity was smaller than that of the copolymers shown in Fig. 4(b) and (c), which had a higher IA content.

5. Conclusion

The swelling properties of the PNIPAM/IA copolymer hydrogels, as well as of a PNIPAM hydrogel have been studied. It has been found that the swelling behaviour of a hydrogel depends on the copolymer composition, pH of the surounding medium and the temperature.

The q_e values of the investigated hydrogels increase with increasing IA content and pH value at 25 and 37 °C, but the equilibrium degree of swelling is greater at 25 °C than at 37 °C, owing to phase transition of PNIPAM above its LCST (34 °C).

The overshooting effect was present in the swelling curves of all samples at 37 °C and pH = 2.2. At pH values of 4.5 and 6.8 at 37 °C the overshooting effect was observed only for the PNIPAM gel and the PNIPAM/IA 99/1/2 copolymer.

Considering the n values at different temperatures, it was observed that diffusion and polymer relaxation control the overall rate of buffer uptake at 25 °C, but at 37 °C, the swelling is Fickian. With increasing IA content in the copolymers, the diffusion of buffer into the gel is easier and, hence, the values of the diffusion coefficient are higher.

According to the presented results, the PNIPAM/IA 95/5/2 hydrogel can be considered as the best for potential use as a drug carrier for targeted drug release in the lower part of gastrointestinal tract, i.e. it has a low degree of swelling at pH of 2.2, but a higher degree of swelling at pH 6.8.

Acknowledgements

The authors acknowledge funding from the Ministry of Sciences, Technologies and Development of the Republic of Serbia, Fundamental Science Project No. 1948, 'The Synthesis, Modification and Characterization of Synthetic and natural Polymeric Materials'.

References

[1] Schild HG. Prog Polym Sci 1992;17:163–249.
[2] Yhang J, Peppas NA. Macromolecules 2000;33:102–7.
[3] Erbil C, Aras S, Uyanik N. J Polym Sci, Part A: Polym Chem 1999;37: 1847–55.
[4] Tasdelen B, Kayaman-Apohan N, Guven O, Baysal B. Int J Pharm 2004; 278:343–51.
[5] Diez-Pena E, Uijada-Garrido I, Barrales-Rienda JM. Polym Bull 2002;48: 83–91.
[6] Patrickios CS, Georgiou TK. Curr Opin Colloid Interface Sci 2003;8: 76–85.
[7] Diez-Pena E. Macromolecules 2003;36:2475–83.
[8] Weast RC, editor. Handbook of chemistry and physics. 55th ed; 1975, 1975. p. 129 [Cleveland, OH].
[9] Peppas NA, Bures P, Leobandung W, Ichikawa H. Eur J Pharm Biopharm 2000;50:27–46.
[10] Diez-Pena E, Quijada-Garrido I, Frutos P, Barrales-Rienda JM. Polym Int 2003;52:956–65.
[11] Walker CM, Peppas NA. J Appl Polym Sci 1990;39:2043–54.
[12] Shieh LY, Peppas NA. J Appl Polym Sci 1991;42:1579–987.
[13] Lee WF, Chen CF. J Appl Polym Sci 1998;69:2021–34.
[14] Lee WF, Lin YH. J Appl Polym Sci 2001;81:1360–71.
[15] Lee WF, Chen YJ. J Appl Polym Sci 2001;81:2888–900.
[16] Diez-Pena E, Quijada-Garrido I, Barrales-Rienda JM. Macromolecules 2002;35:8882–8.
[17] Lee J, Macosko CW, Urry DW. Macromolecules 2001;34:4114–23.
[18] Ranjha de Modhary NM. PhD Thesis. These $N^0$2920. Universite de Geneve, Section de pharmacie; 1997.
[19] Kit Li S, D'Emanuele A. Int J Pharm 2003;267:27–34.
[20] Khare AR, Peppas NA. Biomaterials 1995;16:559–67.
[21] Blanco MD, Garcia O, Rosa RM, Teijon JM, Katime I. Biomaterials 1996;17:1061–7.
[22] Diez-Pena E, Quijada-Garrido I, Barrales-Rienda JM. Macromolecules 2002;35:8882–8.