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# On the water swelling behaviour of poly(*N*-isopropylacrylamide) [P(*N*-iPAAm)], poly(methacrylic acid) [P(MAA)], their random copolymers and sequential interpenetrating polymer networks (IPNs)

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## Abstract

Thermo- and pH-responsive stimuli hydrogels based on *N*-isopropylacrylamide (*N*-iPAAm) and methacrylic acid (MAA) have been synthesized and their swelling behaviour studied as a function of composition, pH and temperature. Copolymers varying in composition have been obtained by copolymerizing these two monomers and interpenetrating polymer networks (IPNs) of P(MAA) and P(*N*-iPAAm) by the sequential method. Temperature and pH have been changed in the ranges from 25 to 40 °C and from 2 to 9, respectively. The swelling behaviour of the hydrogels depends on the nature of the polymer and the environmental conditions, namely pH and temperature. Copolymer gels under basic conditions exhibit higher degree of swelling than the homopolymer ones. The disruption of the complexes dominates the kinetic swelling of MAA enriched gels under basic conditions. The hydrogen bond formation between carboxyl and amide groups has been made clear through the dynamic swelling behaviour of copolymers under acidic conditions. IPNs reduce their ability to swell in water with increasing P(*N*-iPAAm) content because of the formation of hydrophobic interpolymer complexes through hydrogen bonding. Lower critical solution temperature occurs only in the enriched *N*-iPAAm copolymers under acidic conditions when the MAA carboxyl groups are unionized. © 2002 Elsevier Science Ltd. All rights reserved.

*Keywords:* *N*-isopropylacrylamide; Methacrylic acid; Swelling

## 1. Introduction

The synthesis of copolymer gels whose swelling behaviour responds to different external stimuli provide an unique opportunity to tailoring multifunctional materials for specific applications. The polymer network may be collapsed, i.e. a dramatic diminution of the network volume can be induced by changing stimuli such as temperature, solvent composition, pH, ionic strength and surfactants.

Many scientific works in recent years have been dealing with hydrogels incorporating *N*-isopropylacrylamide (*N*-iPAAm) monomer. The reason is the lower critical solution temperature (LCST) around 32 °C exhibited by P(*N*-iPAAm) water solutions and hydrogels [1]. This feature has been found interesting for some technological applications [2–6]. Among them, *N*-iPAAm based gels are being

used as drug delivery systems (DDS) [2,3] because its critical temperature is close to the human body temperature.

The pH of physiological media is very precisely controlled because of its crucial importance in all functions of the human body. One example is the change of pH through the gastrointestinal tract, from the acidic pH of the stomach, namely, pH from 2 to 4, increasing progressively in the small intestine to neutral or slightly basic pH. These non-arbitrary changes play an important role in the selective absorption of small molecules (i.e. drugs).

Hydrogels containing ionizable groups can take advantage of their ability to volume changes depending on the pH of the physiological medium. Poly(methacrylic acid) [P(MAA)] can respond to pH changes through the carboxyl groups. P(MAA) responds to changes on the pH in different manner than poly(acrylic acid) [P(AA)]. P(MAA) chains resist expansion before a critical charge density is attained. This fact has been interpreted as being due to a hypercoiled conformation of P(MAA) in the unionized state [7]. At present, the development of gels responding simultaneously

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to temperature and pH stimuli, seems to be a promising area of interest to find very specific drug carriers [8–17].

For the development of these systems, cross-linked copolymers of *N*-iPAAm and methacrylic acid (MAA) and their sequential interpenetrating networks have been synthesized. Apart from the hydrophobic and ionic interactions due to *N*-iPAAm and MAA moieties, these systems exhibit hydrogen bonding due to the amide (proton acceptors) and carboxylic groups (proton donors) [18–21]. The balance between hydrophobic, ionic and hydrogen bonding interactions, controls the swelling behaviour of these gels.

The scope of this work is therefore to study the differences of the thermal and pH dependence of the swelling behaviour of these copolymer and IPN hydrogels and to relate the swelling properties with the polymer–polymer and polymer–solvent interactions under different environmental changes.

## 2. Experimental

### 2.1. Materials

*N*-Isopropylacrylamide (*N*-iPAAm) (Acros Organics, New Jersey, USA) 99% purity, methacrylic acid (MAA) 98% purity, tetraethylene glycol dimethyl acrylate (TEGDMA), ammonium persulphate, *N,N,N',N'*-tetramethylethylenediamine, benzoyl peroxide, *N,N*-dimethyl-*p*-toluidine, 2,2-dimethoxy-2-benzophenone and potassium dihydrogen phosphate (Fluka-Chemie, A.G. Buchs, Switzerland), ethanol, methanol, disodium hydrogen phosphate anhydride and ortho phosphoric acid (Panreac Monplet & Esteban, SA, Barcelona, Spain). Deionized water from a Millipore Milli-U10 water purification facility was used where appropriate. Monomers and polymers were purified as described elsewhere [18].

### 2.2. Synthesis of hydrogels

The synthesis of P(MAA), P(*N*-iPAAm), their random P(*N*-iPAAm-*co*-MAA) copolymers and sequential P(MAA)/P(*N*-iPAAm) interpenetrating polymer networks (IPNs), cross-linked with a 0.25 wt% of TEGDMA has been described in detail elsewhere [18].

To obtain sheet shaped gels, the next general procedure was employed. The reaction mixture was cast on a glass plate ( $13 \times 13 \times 3 \text{ mm}^3$ ) enclosed by a rubber spacer with a thickness of around 1 mm and sealed off with other glass plate in order to avoid air entering during the reaction. The polymerization dispositive was left to stand at room temperature for 12 h. Then the gel sheets were immersed in deionized (Milli Q grade) water for 2 days to remove the unreacted chemicals, during this time the water was replaced a few times for fresh deionized water.

Table 1

Molar composition of cross-linked samples as determined by elemental analysis

Sample	P( <i>N</i> -iPAAm) (mol%)	P(MAA) (mol%)
P( <i>N</i> -iPAAm- <i>co</i> -MAA) 85/15	82.6	17.4
P( <i>N</i> -iPAAm- <i>co</i> -MAA) 70/30	66.7	33.3
P( <i>N</i> -iPAAm- <i>co</i> -MAA) 50/50	50.5	49.5
P( <i>N</i> -iPAAm- <i>co</i> -MAA) 30/70	32.4	67.6
P( <i>N</i> -iPAAm- <i>co</i> -MAA) 15/85	15.4	84.6
IPN5	30.2	69.8
IPN4	28.3	71.7
IPN3	15.4	84.6
IPN2	1.7	98.3

### 2.3. Elemental analysis

The elemental analysis was carried out using a CHN EA 1108-Elemental Analyzer (Carlo Erba Instruments, Italy). The copolymer and polymer compositions estimated by elemental analysis are given in Table 1.

### 2.4. Swelling experiments

For swelling measurements cylindrical disk-shaped hydrogels were used. Because the dried samples are very rigid, it was necessary to cut them in the swollen state. The next procedure was followed in order to have samples with very similar dimensions and weights, since dissimilarities may cause differences in the results. Dried sheet shaped samples were immersed in distilled water (1:6 polymer/H<sub>2</sub>O w/w) and left overnight to equilibrate, and then cut into thin disks of 15 mm diameter and dried. This simple procedure allows us to establish very precise initial conditions.

Samples for pH and temperature dependence experiments were left to stand in buffer solutions ranging in pH from 2 to 9 at temperatures in between 25 and 40 °C.

Buffer solutions were prepared by mixing known amounts of *ortho*-phosphoric acid, disodium hydrogen phosphate and potassium dihydrogen phosphate in order to vary the pH and keeping the ionic strength constant. For some pH and samples, the equilibrium was reached after 24 h. Temperature dependence experiments were done for each composition and pH. Once the equilibrium was reached at 25 °C, the temperature was increased and the gel left to equilibrate for 24 h at a given temperature.

From time to time, samples were withdrawn from the buffer solution and weighed after removal of surface water by lightly blotting with a filter paper.

The swelling ratio is defined as  $Q = (W_t - W_i)/W_i$ , where  $W_i$  is the initial weight of the dried disk, and  $W_t$  is the weight after a swelling time  $t$ .

### 3. Results and discussion

#### 3.1. pH sensitivity at 25 °C of cross-linked P(*N*-iPAAm), P(MAA) and their copolymers P(*N*-iPAAm-co-MAA)

In Figs. 1 and 2, the swelling ratio  $Q$  at 25 °C in the pH range from 7 to 2 of cross-linked P(*N*-iPAAm), P(MAA) and their copolymers, is presented as a function of time. As a general rule, from the analysis of these plots, it can be concluded that all the synthesized copolymer gels show strong swelling pH dependence due to the introduction of an ionizable comonomer. The effective charge density in the hydrogel depends on the amount of comonomer and pH, which determines the degree of dissociation.

As swelling behaviour above pH 5 shows similar trends depending on the copolymer composition, we only present in Fig. 1 dynamic swelling curves corresponding to pH 7. In the pH range investigated, all the copolymers (Fig. 1) swell more than their P(*N*-iPAAm) and P(MAA) parent homopolymers. A representation of  $Q$  at equilibrium ( $Q_{\infty}$ ) as a function of pH and copolymer composition is presented in Fig. 3(a) and (b), respectively. A surface map of  $Q_{\infty}$  as a function of both parameters is presented in Fig. 3(c). As it can be seen a certain synergic effect, i.e. the equilibrium of swelling does not follow a linear behaviour depending on composition. As it can be observed, the value of  $Q_{\infty}$  at pHs above 5 is higher for copolymers than for homopolymers and goes through a maximum for 70% *N*-iPAAm content and a relative maximum at 30% *N*-iPAAm leading to the two peaks of Fig. 3(c). In particular, copolymers having 70 mol% in *N*-iPAAm are the most water swellable for the pH ranging from 5 to 9. The 85 mol% *N*-iPAAm gel follows similar trends as the 70 mol% *N*-iPAAm, however, it does not reach so high values of  $Q$ . Hydrogels having a *N*-iPAAm content below 50% have a less remarkable swelling ability. They are located in the plots (Figs. 1 and 2) far away. The minimum in the swelling ratio corresponds to the equimolecular composition and the  $Q_{\infty}$  values appear as a valley in Fig. 3(c). This fact may be interpreted as a structural factor, leading to a lower interaction between *N*-iPAAm-MAA units and a higher interaction among *N*-iPAAm-*N*-iPAAm

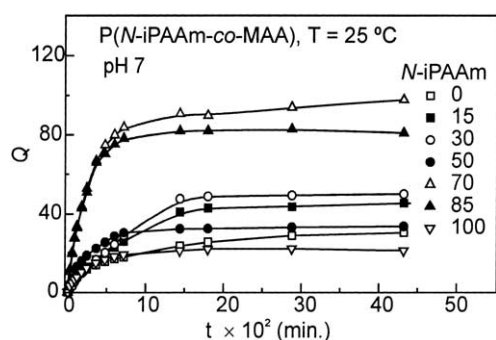


Fig. 1. Swelling ratio,  $Q$  as a function of time for cross-linked P(*N*-iPAAm), P(MAA) and a series of P(*N*-iPAAm-co-MAA) copolymers in phosphate buffers at pH 7.

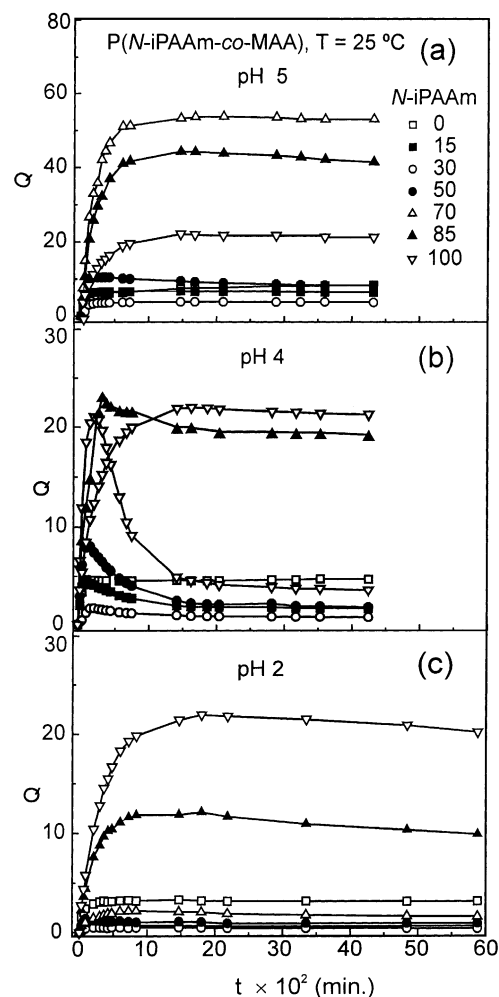


Fig. 2. Swelling ratio,  $Q$  as a function of time for cross-linked P(*N*-iPAAm), P(MAA) and a series of P(*N*-iPAAm-co-MAA) copolymers in phosphate buffers at 25 °C: (a) pH 5 (b) pH 4 (c) pH 2.

and MAA-MAA blocks. It produces a lower deviation from the behaviour of both homopolymers.

In the low pH range which is displayed in Fig. 2, it is observed that the swelling ratio decreases considerably for all the copolymers as well as for P(MAA). This pH is below the  $pK_a$  of MAA, which can explain the reduction in the swelling ratio. For polyelectrolyte hydrogels a reduction of the pH of the aqueous solution, modifies the degree of ionization. Therefore, it reduces the net ion concentration difference (osmotic swelling pressure) which results in a dehydration of the gel (decrease in the volume due to polymer elasticity) to an extent where further compression is limited by the excluded volume of the polymer chains. It should be kept in mind that the hypercoiled structure of P(MAA) in the unionized state produces an abrupt volume shrinkage at a narrow acidic pH. As it was mentioned before, pure P(*N*-iPAAm) with no ionizable groups, does not exhibit any pH dependence.

As can be seen in Fig. 2(a), at pH 5 the swelling ratio is still the highest for the 70 mol% *N*-iPAAm copolymer and

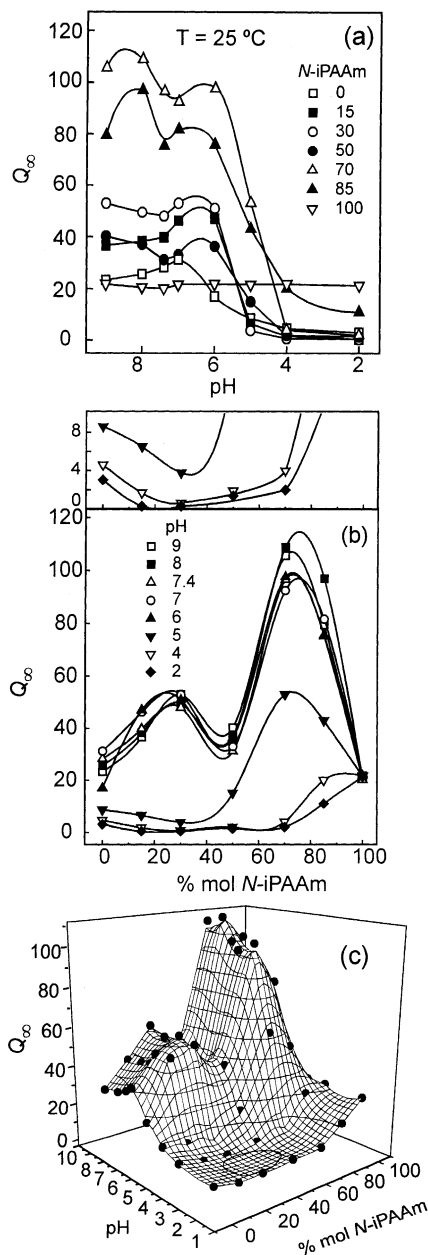


Fig. 3. Swelling ratio equilibrium  $Q_{\infty}$  for cross-linked P(*N*-iPAAm), P(MAA) and a series of P(*N*-iPAAm-*co*-MAA) copolymers in phosphate buffers at 25 °C: (a) as a function of pH; (b) as a function of polymer composition with a magnification of the region corresponding to MAA rich samples under acidic conditions; (c)  $Q_{\infty}$  as a function of both pH and polymer composition.

there is a minimum at 30 mol% *N*-iPAAm. It is interesting to note that for this particular pH,  $Q_{\infty}$  for the 50 mol% *N*-iPAAm hydrogels lies between those of the pure homopolymers, in agreement with a higher interaction among *N*-iPAAm–*N*-iPAAm and MAA–MAA blocks.

Fig. 2(b) displays the swelling behaviour at pH 4. The most remarkable feature of this particular pH is the anomalous swelling curve. Dynamic swelling curves exhibit an overshoot, its absolute value depending on copolymer composition. In the first step the samples increase their

swelling ratio, later on they reach a maximum and finally they deswell below the equilibrium value of P(MAA). We have attributed this feature to a lower degree of ionization of the acid that produces the formation of hydrogen bonds between both monomeric units. When the water uptake increases, the mobility also increases thus allowing the rearrangement of the polymer structure by means of the complementary binding group. Such comonomeric hydrogen bonding would be in competition with the hydrogen bonding of these units with solvent water molecules, so that the net process is the exchange of the hydrogen bonds. The highest level of dynamic hydrogen bond formation takes place in the 70 mol% *N*-iPAAm content copolymer because the shrinkage is also the highest. According to this argument Chen et al. [22] showed that the  $T_g$  of IPNs of P(AA) and poly(ethyl oxazoline) increases significantly after the material was immersed in water. They could not attribute this increase to the loss of polymer by extraction. They argued that swelling by water allows additional carboxyl and amide group to rearrange themselves with the desired juxtaposition for hydrogen bonding. It has been very recently reported [19] that hydrogen bond between amide and carboxylic groups are responsible for an increase in the glass transition value in 30 and 15% *N*-iPAAm content copolymers.

Fig. 2(c) shows the swelling behaviour at pH 2. Except for the 85% *N*-iPAAm copolymer, with a very high *N*-iPAAm content, all the copolymers show an equilibrium swelling ratio much lower than the pure P(MAA). As previously stated, the lowest swelling ratio for our copolymers can be attributed to the formation of complexes between both monomers. As can be seen in Figs. 2 and 3, the minimum of the swelling ratio occurs at 30 mol% *N*-iPAAm content copolymer.

From our results we can correlate the formation of these complexes with the pH and with the copolymer composition since for the higher MAA content copolymers, these complexes are formed at higher pH than for the lower MAA content copolymers. Therefore, enriched MAA copolymers carry with hydrogen bonding from the polymer synthesis, whereas copolymers with higher amount of *N*-iPAAm needed stronger acidic medium to promote hydrogen bonds.

In Fig. 4, the swelling ratio ( $Q$ ) at pH 7 for 50, 30, 15 and 0% *N*-iPAAm is presented as a function of  $\log t$  in order to appreciate the differences in the first stages of the swelling. It is observed that at the beginning, the water uptake is lower for 30 and 15% *N*-iPAAm gels than for P(MAA) and 50% *N*-iPAAm gel. However, the swelling ratio of these two samples increases overcoming the values reached by the other samples. This behaviour may be attributed to the inverse process that occurred under acidic pH, the hydrogen bond disruption above  $pK_a$  of the MAA.

A complete picture of these features are very well illustrated looking at the three-dimensional plot presented in Fig. 3(c), where it is easily seen that the swelling ratio is

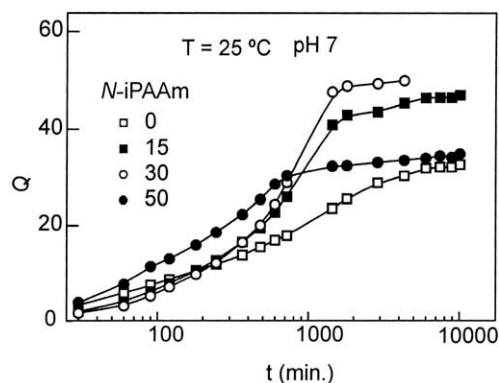


Fig. 4. Swelling ratio,  $Q$  as a function of  $\log(t)$  for 50, 30, 15, 0%  $N$ -iPAAm copolymers at pH 7.

much higher for copolymers slightly enriched in  $N$ -iPAAm at the medium and high pH region. Whereas samples enriched in MAA exhibit a lower swelling ratio than the other copolymers. The decreasing of the swelling ratio also occurs at higher pH for these samples. The minimum swelling degree occurs in the low MAA composition region and at low pH.

The swelling behaviour can be explained as a result of the balance between the osmotic pressure and the polymer elasticity, which sets the physical dimensions of the hydrogel. The elastic energy of the gel network is controlled by the degree of cross-linking in the polymer matrix and is set during the synthesis of the gel, but in this case we must also take into account the hydrophobic contributions and the additional physical cross-linking through hydrogen bonding.

It was observed by  $^1\text{H}$  MAS NMR measurements of slightly swollen samples in  $\text{D}_2\text{O}$  [18], that the 70%  $N$ -iPAAm hydrogel presents the sharpest lines indicating that its mobility is also the highest. The mobility of these samples enriched in MAA as by  $^1\text{H}$  MAS NMR was considerably lower than that of predominantly  $N$ -iPAAm copolymers. Under basic conditions, when there are not hydrogen bonding between comonomers, the incorporation of small amounts of MAA prevents the attractive hydrophobic interactions that are limiting the swelling of pure  $P(N$ -iPAAm) monomers and accommodates an additional osmotic contribution to the swelling. Otherwise the addition of  $N$ -iPAAm on the  $P(\text{MAA})$  backbone decreases the stiffness of the polymer chain and increases the ability of the network to expand on water.

The existence of hydrophobic interpolymer complexes due to the formation of hydrogen bonding interactions between the MAA carboxyl group and the  $N$ -iPAAm amide group can only exist in the neutral form of the carboxylic moiety as it has been reported by Kratz et al. [23]. These complexes due to hydrogen bonding are strengthened due to the existence of hydrophobic interactions [24]. Koussathana et al. [24] have investigated the complex formed for  $P(N$ -iPAAm) and  $P(\text{AA})$ , and they demonstrated that this

complex has a hydrophobic character. This hydrophobic interaction is maximum at a  $P(\text{AA})$  weight fraction of 0.3 [24]. This is related to the particular composition of the hydrophobic aggregates. The hydrophobic isopropyl group of  $P(N$ -iPAAm) plays an important role not only in the hydrophobicity of the complex but also on its stoichiometry. Nonaka et al. [20] have also shown that in the case of  $\text{PMAA}$  the hydrophobic character of the interpolymer complex formed is increased, probably by the interactions with the methyl groups, leading to a strengthening of the complex. We have also observed that the copolymer with 30 mol%  $N$ -iPAAm content showed the lowest swelling ratio under acidic conditions. It is indicating that at this composition the interaction between amide and carboxyl groups is the highest one.

### 3.2. pH sensitivity at 25 °C of $P(\text{MAA})/P(N$ -iPAAm) IPNs

Figs. 5 and 6 display the swelling behaviour of MAA enriched IPNs. Pure  $P(\text{MAA})$  and 15%  $N$ -iPAAm copolymer are also plotted for comparative purposes.

As it has been shown in the experimental part, the IPNs synthesized in the present paper are mainly composed of MAA. It is necessary to mention that the IPN with 30 mol%  $N$ -iPAAm content, namely IPN5, does not swell under the mild basic conditions investigated in this paper but swells in methanol and under strong basic conditions [18,19]. The hydrophobic character of this IPN has been attributed to the hydrophobic complexes between  $P(N$ -iPAAm) and  $P(\text{MAA})$  through hydrogen bonding. The hydrogen bond is more effective in IPNs than in copolymers because in the copolymers not all the chains are complementary and in consequence there exist less co-operativity than in the case of IPNs.

Having a look on the swelling curves at pH 7, IPNs under basic pH are more water swellable than pure  $P(\text{MAA})$  as it happens with high MAA content copolymers. IPN2, with the lowest  $N$ -iPAAm content (namely 1.7 mol%), increases

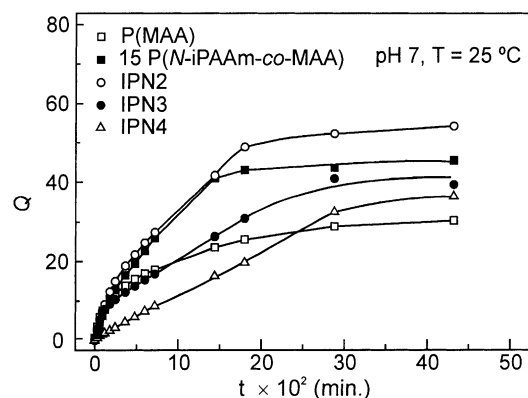


Fig. 5. Swelling ratio,  $Q$  as a function of time for cross-linked  $P(\text{MAA})$ , 15/85  $P(N$ -iPAAm-co-MAA) copolymer and IPNs in phosphate buffers at 25 °C at pH 7.

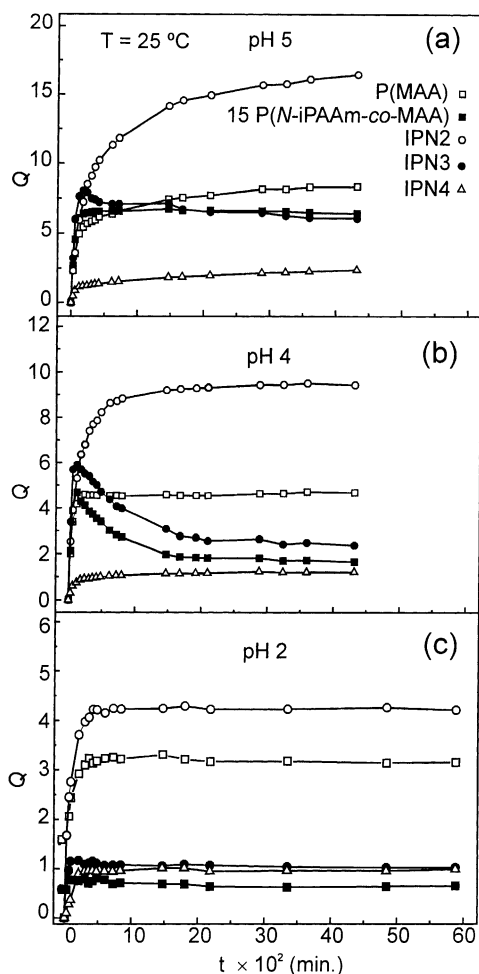


Fig. 6. Swelling ratio,  $Q$  as a function of time for cross-linked P(MAA), 15/85 P(*N*-iPAAm-*co*-MAA) copolymer and IPNs in phosphate buffers at 25 °C: (a) pH 5 (b) pH 4 (c) pH 2.

its water content faster than the other samples. Other interesting feature is that the richest MAA IPN (IPN4 displayed as open triangles) in the earlier stages swells very slowly, the curve lies below those corresponding to the other gels. However, after a time, the swelling rate increases and the equilibrium values are higher than that of pure P(MAA). This behaviour can also be explained because of the disruption of hydrogen bonds between both networks, which were created during the synthesis of the IPN. Zhang and Peppas [17] have studied the swelling behaviour of a P(MAA)/P(*N*-iPAAm) IPN. They found that the DSC endotherm corresponding to the LCST of P(*N*-iPAAm) was detected as pH increases. They explained this behaviour on the basis of the change of P(MAA) mobility with pH. However, another plausible explanation may be the breaking of the acid–amide hydrogen bond under basic conditions.

For the lower pH regimes, IPN4 shows a very low swelling ratio, similar to the pH 2, 4 and 5. It can be due to the stability of the interpolymer complexes. IPN3 shows a

quite similar behaviour to the 15% *N*-iPAAm copolymer, which has the same composition. Both show an initial swelling followed by a deswelling, due to the formation of the complexes between carboxylic acid and amide group. IPN2 with a very low *N*-iPAAm content shows a similar behaviour to the pure MAA homopolymer with a slight increase in its swelling behaviour. No sign of interpolymer complexes formation can be detected for this composition. The low range of compositions studied for the IPNs does not allow further conclusions.

### 3.3. Thermal sensitivity of P(*N*-iPAAm-*co*-MAA) hydrogels

P(*N*-iPAAm) gels are known to undergo a temperature induced phase transition with a LCST. A lower critical phase separation is generally regarded as a phenomenon governed by the balance of hydrophilic and hydrophobic forces on the polymer chain and driven by a negative entropy of mixing [1]. Furthermore the temperature dependence of certain molecular interactions, such as hydrogen bonding and hydrophobic effects, contribute to these types of phase separations. At the LCST the hydrogen bonding between the polymer and water becomes unfavourable compared to the polymer–polymer and water–water interaction and therefore an abrupt transition occurs as the hydrated hydrophilic macromolecule quickly dehydrates and changes to a more hydrophobic structure [24].

Experimental results and theoretical considerations suggest that hydrophobic interactions play an important role in the swelling/deswelling process [23]. During the volume phase transition the hydrogel splits off a large amount of its pore water and becomes stiff and opaque. The transition temperature, as well as the physical nature of the volume phase transition can be modified by chemical interaction, e.g. copolymerization with charged monomers. In general, the addition of more hydrophilic comonomer to a P(*N*-iPAAm) hydrogel increases the LCST because the monomer hinders the dehydration of the polymer chains and acts to expand the collapsed structure [8,25–28].

The introduction of ionic monomers not only increases the critical temperature but has a more subtle effect on the mechanism of the volume phase transition. Stile et al. [25] showed that in addition to an elevated LCST, the P(*N*-iPAAm-*co*-Aac) hydrogel exhibited a broader transition than the P(*N*-iPAAm) hydrogel indicating a decreased swelling thermosensitivity.

Fig. 7 shows the swelling response of copolymer hydrogels as a function of temperature and pH. The LCST of P(*N*-iPAAm) is around 33 °C in agreement with the calorimetric measurements [18] and it is independent of the pH. On the contrary, the temperature sensitivity of the copolymers depends on the pH. As shown above, introduction of fixed ionic monomers accommodates an additional osmotic contribution to the swelling that competes with the attractive hydrophobic interaction of the *N*-iPAAm units. The balance between competing attractive hydrophobic and

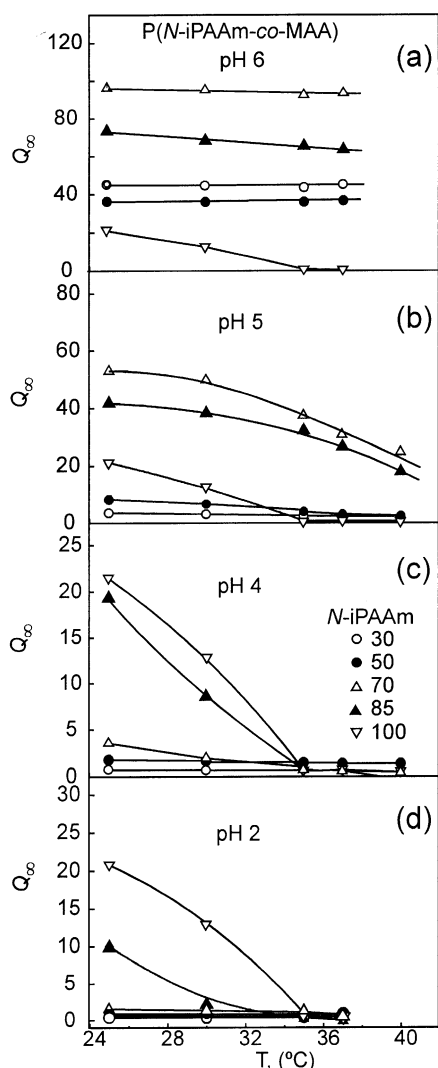


Fig. 7. Influence of the temperature on the swelling ratio as a function of pH for cross-linked P(*N*-iPAAm), P(MAA) and a series of P(*N*-iPAAm-co-MAA) copolymers in phosphate buffers: (a) pH 6 (b) pH 5 (c) pH 4 and (d) pH 2.

repulsive electrostatic interaction on the volume phase transition can be controlled through the amount of comonomer, the pH, which determines the degree of dissociation, and the ionic strength [23].

For pH above the  $pK_a$  of MAA, the LCST transition is suppressed for all the copolymers. At lower pH, where the hydrophilicity decreases, a decrease in  $Q$  for the higher *N*-iPAAm content copolymers can be noticed at the LCST. In Fig. 7, it is observed that for 50, 70 and 85% *N*-iPAAm copolymers at pH 5, the value of  $Q_{\infty}$  decreases slowly with increasing temperature. Their LCSTs raised that one of pure P(*N*-iPAAm) homopolymer. With decreasing pH, the swelling ratio decreases greatly and the behaviour of 85% *N*-iPAAm copolymer is similar to that of the P(*N*-iPAAm) due to an increase of the hydrophobicity for this copolymer.

#### 4. Conclusions

Copolymers based on *N*-iPAAm and MAA display a strong pH-sensitivity due to the presence of the carboxyl group and the additional complex formation between amide and carboxyl moieties. In the pH range above the  $pK_a$  of MAA, the swelling ratio is controlled by the balance between hydrophobic and ionic interactions. In this pH range, a synergy is observed between both comonomers, because the copolymers reach higher  $Q$  values at equilibrium than the P(*N*-iPAAm) and P(MAA) homopolymer hydrogels. However, a relative minimum at the 50% *N*-iPAAm copolymer is observed. It may be attributed to a higher interaction among similar functional groups, i.e. *N*-iPAAm–*N*-iPAAm or MAA–MAA blocks. In the low pH range all the copolymers exhibit a diminution of  $Q$ , particularly in those cases with a higher MAA content. Anomalous swelling curves are observed under pH 4. It may be tentatively interpreted as a swelling–deswelling process. This process is attributed to a reorganization of the own gel structure due to the hydrogen bond formation among the amide group of *N*-iPAAm and the carboxyl group of MAA. This fact which may be considered as an additional cross-linking, leads to water expelling during the dynamic swelling measurements. A minimum of the swelling ratio  $Q$  is observed for the 30% *N*-iPAAm copolymer which is indicative of a higher efficiency of the hydrogen bonding for this specific composition. The hydrogen bond disruption of this sample can also be evidenced by the dynamic behaviour of the swelling ratio  $Q$  in the high pH region.

The temperature-sensitivity of the copolymers is not so remarkable. Only copolymers with 70 and 85% *N*-iPAAm content show the LCST below the  $pK_a$  of the MAA. This fact is putting forward that only a slight introduction of hydrophilic MAA in the P(*N*-iPAAm) structure is sufficient to suppress the hydrophobic interaction within the P(*N*-iPAAm) which is responsible of the LCST.

In the interpenetrating polymer networks, hydrogen bonding among P(*N*-iPAAm) and P(MAA) chains, is the dominant force controlling the swelling. The efficiency of the hydrogen bonding in IPNs is higher than in copolymers. IPNs decrease their ability to swell in water with increasing *N*-iPAAm content, and for 30% of *N*-iPAAm, IPNs are not anymore swellaible under the experimental conditions. This composition is also the most favourable for hydrogen bonding in copolymers.

Changes of composition, pH or solvent may modify hydrogen bonding. The control of hydrogen bonding may allow us to obtain a great variety of different hydrogels which can be used to prepare DDS. The inter-polymer complexes through hydrogen bonding should also depend on temperature and this possibility is being currently explored.

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