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Synthesis and characterization of thermoresponsive *N*-isopropylacrylamide/methacrylated pullulan hydrogels

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Abstract

Thermosensitive hydrogels were prepared by free radical polymerization starting from a methacrylated pullulan derivative (acting as the cross-linker) and using *N*-isopropylacrylamide (NIPAAM) as the monomer. Several hydrogels were obtained by changing the monomer to cross-linker ratio. A significant thermosensitivity was observed only when the molar amount of NIPAAM incorporated in the network was at least eight times higher that of methacrylate groups on pullulan. The hydrogel with high amount of NIPAAM deswells more than 80% after the *T*-jump. The lower critical solution temperature of thermosensitive hydrogels decreases with increasing amount of NIPAAM. The mechanical properties of the hydrogels are strongly affected by the percentage of incorporated NIPAAM and by the temperature. © 2002 Published by Elsevier Science Ltd.

Keywords: Temperature-responsive; Poly(*N*-isopropylacrylamide); Methacrylated pullulan

1. Introduction

Hydrogels are hydrophilic polymer networks capable of absorbing large amount of water [1,2]. Temperature-sensitive hydrogels are, in addition, able to give rise to a phase transition in a narrow temperature range accompanied by a discontinuous volume change [3–7]. The latter are interesting materials that can be used in a variety of applications, e.g. controlled drug delivery [8,9], immobilization of enzymes and cells [10,11], separation processes [12].

Hydrogels made of cross-linked poly(*N*-isopropylacrylamide) (polyNIPAAM) are among the most widely studied thermoresponsive materials as they undergo a sharp volume transition at a temperature close to 32 °C which corresponds to the lower critical solution temperature (LCST) of the linear polymer chains in water [3–5,13,14].

Many different NIPAAM hydrogel architectures have been prepared. The simplest material can be obtained by the polymerization of NIPAAM in the presence of a multifunctional vinyl monomer (for instance *N*,*N*′-methylenebisacrylamide). More versatile gels have been obtained by copolymerization with other vinyl monomers [15,16] or by the formation of interpenetrated polymer networks (IPN) [17] or semi-IPN [18–20]. In this way, hydrogels having improved characteristics such as better mechanical strength and additional pH-sensitivity can be prepared.

Ju et al. [20] synthesized pH/temperature-responsive semi-IPN and comb-type graft hydrogels by using a polysaccharide (alginate) and polyNIPAAM.

Polysaccharides are often used for hydrogels synthesis as they are generally inexpensive, biocompatible and have a great structural variety [2,21]. Among the methods normally employed to synthesize chemically cross-linked polysaccharide hydrogels, a two-step synthesis can be used where the polysaccharide is first functionalized with reactive double bonds and then cross-linked by free radical polymerization in water [22]. Starting from a similarly functionalized dextran derivative, pH-sensitive hydrogels have been prepared by copolymerization with acrylic acid [23].

In this study, we prepared thermosensitive hydrogels using a methacrylated pullulan (PULMA) derivative which was copolymerized with NIPAAM. Different gels were obtained by varying the amount of incorporated NIPAAM. The effect of chemical composition on equilibrium swelling, swelling–deswelling kinetics and on mechanical properties was investigated.

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2. Experimental section

2.1. Materials

Pullulan (PF-20 by Hayascibara Co. Ltd, Japan) had a viscosity average molecular weight $M_v = 1.7 \times 10^5$. *N*-isopropylacrylamide (NIPAAM) was obtained from Aldrich (Milan, Italy) and was purified by recrystallization from *n*-hexane. Dimethyl sulfoxide (DMSO), glycidyl methacrylate (GMA), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), potassium persulfate (KPS) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) were obtained from Fluka (Milan, Italy) and used without further purification.

2.2. Synthesis of glycidyl methacrylate derivatized pullulan

PULMA was synthesized by the same procedure described for dextran by van Dijk-Wolthuis et al. [22]. Briefly, GMA and DMAP were added to a solution of pullulan in DMSO. The solution was stirred at room temperature for 48 h and the reaction was stopped by adding HCl. The product was exhaustively dialyzed against distilled water and finally collected by lyophilization. The actual degree of substitution (DS, the percentage of methacrylate groups with respect to monosaccharide units of pullulan) was calculated by the ^{1}H NMR spectrum of PULMA as $(A/B) \times 100$, where A is the average of the integrated areas of double bond proton peaks at about 5.80 and 6.25 ppm while B is the integrated area of anomeric protons in the range 4.9–5.6 ppm. DS was about 10%.

2.3. Preparation of PULMA–NIPAAM hydrogels

Five hydrogels (NP0, NP2, NP4, NP8 and NP26) having different molar ratio of NIPAAM to methacrylate groups on pullulan (0, 1.6, 4.0, 8.0, 26.0, respectively) were prepared as follows. A stock solution (3%, w/v) of PULMA (DS = 10%) in water was prepared by dissolving 0.300 g of PULMA in 10 ml double distilled water and stirring for 20 h. The solution was degassed by bubbling argon for 30 min. Then, 2 ml of this solution were added to the appropriate amount of NIPAAM under argon. After the monomer dissolved, 0.050 ml of an aqueous solution (16 mg/ml) of KPS (initiator) and 0.008 ml of TEMED (used as an accelerator) were added. All the gels were prepared in cylindrical polyethylene vials (internal diameter 1.8 cm) and the reaction carried out for 4 h at room temperature. The gels were then immersed in 50 ml of water at room temperature and the water was changed three times a day for 5 days to reach equilibrium swelling.

2.4. Methods

Solution NMR. Spectra were recorded in D_2O with a Bruker AMX 600 spectrometer dissolving approximately 30 mg of PULMA in 0.8 ml of D_2O.

^{13}C CP-MAS NMR. Samples were finely cut and packed into 4 mm zirconia rotors that were sealed with Kel-F caps. Solid state ^{13}C CP-MAS NMR spectra were performed at 50.13 MHz on a Bruker AMX-200 spectrometer. The spin rate was 8 kHz; the $\pi/2$ pulse width was 4 μs, the recycling time was 3 s. Spectra were obtained using 1024 data points in the time domain, zero filled and Fourier transformed to a size of 1024 data points. The chemical shift was externally referred to tetramethylsilane. The cross-polarization was performed applying the variable spin-lock sequence known as Ramp-CP-MAS [24,25]. Experiments performed in the cross-polarization with a simultaneous phase inversion (SPI) [26,27] were used to selectively observe the different types of carbons. The contact time for the cross-polarization was 1 ms while the length of the pulse for the phase inversion was 26 μs.

FTIR spectra of the lyophilized material were recorded with a Shimadzu 8300 FTIR spectrometer (Shimadzu, Tokyo, Japan) equipped with an ATR Golden Gate accessory (Specac Inc., USA).

SEC. Molecular weight determination was performed using a LabFlow 4000 HPLC pump (LabService Analytica, Bologna, Italy) equipped with a Varian RI-4 refractive index detector (Varian Associates, Palo Alto, CA, USA) and three TSK-Gel GMPW columns (TosoHaas, Montgomeryville, PA). Eluent was 0.1 M NaCl at 1 ml/min.

2.5. Swelling experiments

Equilibrium swelling. Gels were weighed at different temperatures ranging from 25.0 to 48.0 °C (± 0.1 °C) using a thermostated bath. Hydrogels were equilibrated in water at each fixed temperature for approximately 12 h. Excess water was wiped off from the surface with moistened filter paper and the hydrogels were weighed. The swelling ratio was determined as the ratio of the weight of the swollen to the dried gel.

Kinetics of swelling and deswelling. The kinetics of gel swelling was studied after a *T*-jump from 25 to 48 °C. The hydrogels were equilibrated in water at room temperature (25.0 °C) and then immersed in a thermostatic chamber filled with distilled water at a temperature of 48.0 ± 0.1 °C. The hydrogels were removed from water at fixed time intervals, water wiped off from the surface with moistened filter paper and the hydrogels weighed. Percentage deswelling was calculated as the ratio of the loss in weight at time t after the *T*-jump to the difference in weight of the gel equilibrated at 25 and 48 °C, respectively (total weight loss).

The kinetics of gel reswelling was studied in the same way of gel deswelling after a *T*-jump from 48 to 25 °C. Percentage reswelling was calculated as the ratio of the increase in weight at time t after the *T*-jump to the difference in weight of the gel equilibrated at 25 and 48 °C, respectively.

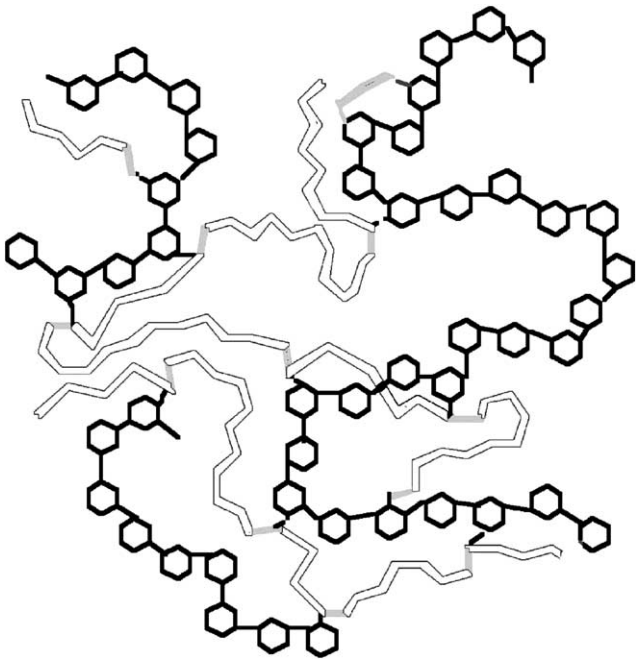

Fig. 1. Schematic representation of the structure of PULMA–NIPAAM hydrogels. (⬡–⬡–⬡) pullulan chain, (▒) methacrylate group, (▭) polyNIPAAM chain.

2.6. Rheological characterization

Rheological experiments were carried out with a Bohlin CS10 stress controlled rheometer (Cirencester, UK) using a PP20 plate–plate geometry (top plate diameter 2 cm). Sandpaper was stuck to both plates to avoid slippage of the gel. The measuring geometry was adapted in order to have the gel immersed in water during the measurements. A thermocouple was used to monitor the temperature of the water bath surrounding the gel. Preliminary stress-sweep experiments were done on each gel in order to select a strain value in the range of linear viscoelasticity. Creep tests were also done in order to ascertain the absence of any slip effect. Storage and loss moduli, G' and G'', were determined as a function of the applied frequency in the range 0.01–10 Hz at different temperatures (25–48 °C, ±0.1 °C) with a nominal strain of 5×10^{-3}.

3. Results and discussion

3.1. Synthesis of PULMA and PULMA–NIPAAM gels

In this study, thermoresponsive pullulan hydrogels were prepared by free radical cross-linking of NIPAAM using a pullulan derivative carrying multiple vinyl groups as the cross-linker. A schematic representation of the structure of PULMA–NIPAAM hydrogels is shown in Fig. 1. The PULMA derivative was obtained by the reaction of pullulan with GMA in DMSO at room temperature.

The transesterification of GMA with the hydroxyl groups

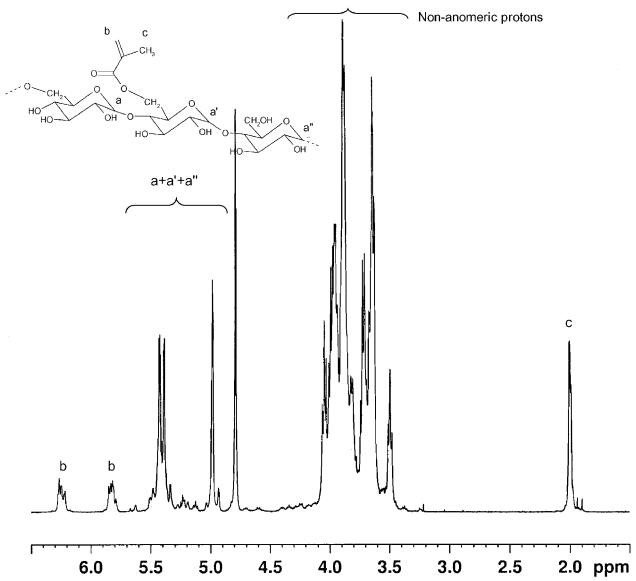

Fig. 2. ^{1}H NMR spectrum of PULMA with DS 10%.

of the glucopyranose residues allowed to obtain direct attachment of methacryloyl groups to pullulan chains. The ^{1}H NMR spectrum of PULMA (Fig. 2) shows signals at δ 5.80 and 6.25 ppm and at δ 2.0 ppm that can be assigned to the double bond and methyl protons of the methacryloyl group. These peaks are multiplets probably due to the different positional isomers that can be formed by esterification of different OH groups [22,28]. The signals in the regions 4.9–5.6 and 3.3–4.1 ppm were assigned, respectively, to anomeric and non-anomeric protons of pullulan. The degree of substitution (DS) calculated by the ^{1}H NMR spectrum of PULMA was about 10% with respect to the theoretical DS of 20% calculated on the basis of the molar ratio of reagents.

GPC elution profiles of pullulan and PULMA (data not shown) were essentially identical indicating that no degradation occurred.

PULMA hydrogels with different amounts of NIPAAM as comonomer were prepared by free radical polymerization in water. Five different gels, having a nominal molar ratio of NIPAAM to pullulan methacrylate groups varying from 0 to 26 (NP0, NP2, NP4, NP8 and NP26) were prepared. Gels were formed in about 15 min and turned progressively opaque. Gelation was followed by shrinking. The lower the content of NIPAAM, the higher was the decrease in gel size after reticulation.

PULMA–NIPAAM gel structures were characterized by FTIR spectroscopy (Fig. 3). Spectra reported in the main plot are normalized with respect to the intensity of the absorption at about 1005 cm^{-1}. In this range, polyNIPAAM FTIR spectrum does not show a significant absorption. This allows us to roughly evaluate the relative amount of NIPAAM incorporated, as the contribution of pullulan to the spectrum is kept constant. In the spectrum of the gel prepared without NIPAAM (Fig. 3, curve e), along with

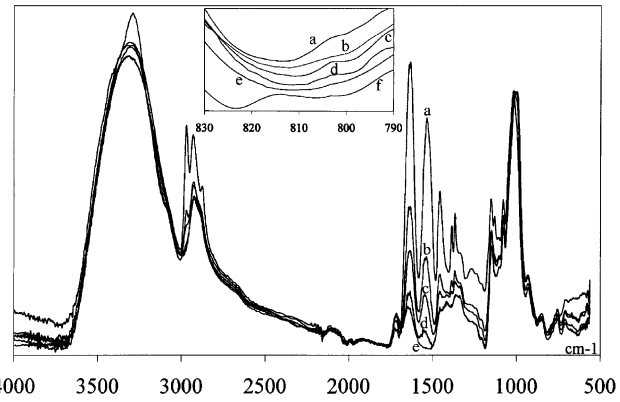

Fig. 3. FTIR spectra of PULMA–NIPAAM hydrogels. (a) NP26, (b) NP8 (c) NP4, (d) NP2, (e) NP0 and (f) PULMA.

absorption peaks attributed to pullulan, the typical peak at about 1720 cm^{-1} due to the carbonyl of polymerized methacrylate moieties is present. Spectra of gels prepared in the presence of the comonomer clearly show the appearance of characteristic absorption peaks due to polyNIPAAM (amide I and amide II peaks at 1642 and 1550 cm^{-1}, respectively). In particular the amide I peak is located in a region where no absorption is detectable for gels prepared without NIPAAM. The intensity of this peak demonstrates that an increasing amount of NIPAAM, more or less reflecting the molar ratios used during reaction, has been incorporated into the hydrogels. The spectral region where the absorption due to double bonds of PULMA is located is shown in Fig. 3. The carbon–carbon double bond peak is clearly observable in the spectrum of the unreacted PULMA derivative (Fig. 3, curve f) at about 813 cm^{-1} while it is completely absent in the hydrogels spectra. This means that all the PULMA methacrylate groups reacted during the free radical polymerization reaction.

A quantitative determination of NIPAAM/methacrylate molar ratio into the gels has been done by elemental analysis. The values obtained were 1.1, 2.8, 6.4 and 24 for NP2, NP4, NP8 and NP26, respectively. These results show that a reduced amount of comonomer has been incorporated into the hydrogels with respect to the theoretical value, especially for hydrogels with a lower NIPAAM content.

3.2. Solid state NMR

The ^{13}C CP-MAS NMR spectrum of the lyophilized NP8 hydrogel is shown in Fig. 4.

At 22.5 ppm the signal due to the methyl carbons C_l and $C_{l'}$ of polyNIPAAM chains is observed.

At about 35.3 ppm, the methylene carbon C_f signal of polyNIPAAM is present as a shoulder while the methine carbons C_i and C_g are observed at about 41.6 ppm. The carboxyl carbon C_h resonates at 175.4 ppm.

The broad resonance centered around 100 ppm is due to the anomeric carbons of pullulan (C_a, $C_{a'}$ and $C_{a''}$). The

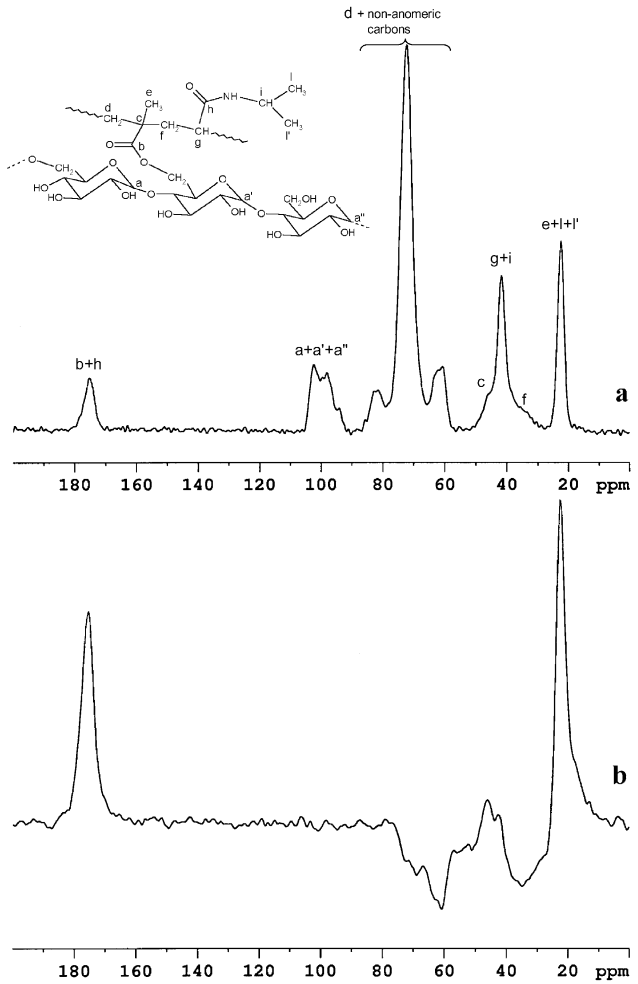

Fig. 4. (a) ^{13}C CP-MAS NMR spectrum of NP8 along with the resonances assignment. (b) ^{13}C CP-MAS NMR spectrum after applying the CP-SPI pulse sequence. Methine, methylene and methyl and quaternary carbons resonances are zeroed, inverted and positive, respectively.

signals in the range 55–85 ppm are due to all other carbons of pullulan.

As reported by other authors [29], CH_3, backbone quaternary carbon, backbone $-CH_2-$ and carbonyl carbon of poly(methyl methacrylate) gave resonance peaks at 17, 45, 57 and 177 ppm. In the NP8 spectrum all these peaks are not clearly visible as they are more or less coincident with signals due to the pullulan and polyNIPAAM moieties. A shoulder at about 45 ppm is visible and can be tentatively assigned to the backbone quaternary carbon. In order to confirm this assignment the CP-SPI sequence has been applied (Fig. 4(b)). It is worth to note that all resonances assigned to methine carbons are zeroed. Resonances assigned to methylene carbons are inverted; moreover, at 67.8 ppm another resonance due to the methylene C-6 of pullulan is observed. Resonances due to NIPAAM and methacrylate methyl carbons, 22.5 ppm, and carbonyl carbon, 175.4 ppm appear intense and positive. A small positive peak at about 45 ppm can be reasonably assigned to

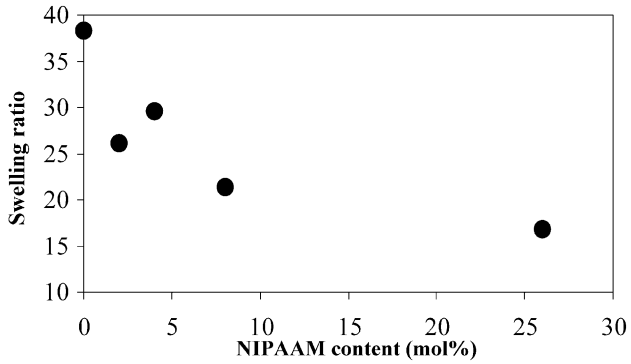

Fig. 5. Equilibrium swelling of PULMA–NIPAAM hydrogels at 25 °C in water as a function of NIPAAM content.

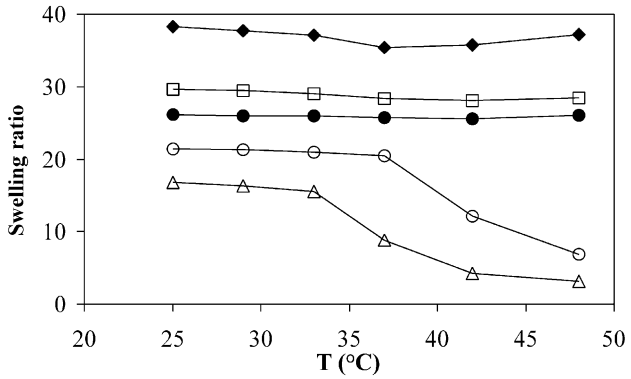

Fig. 6. Equilibrium swelling of PULMA–NIPAAM hydrogels with different NIPAAM content as a function of temperature. NP0 (◆), NP2 (●), NP4 (□), NP8 (○) and NP26 (△).

the backbone quaternary carbon of polymerized methacrylate groups.

The area of the resonance (22.5 ppm) due to methyl carbons of isopropylacrylamide and methacrylate and the resonance due to the anomeric carbons of pullulan (around 100 ppm) can be used for evaluating the molar ratio of the isopropylacrylamide to the repeat unit of pullulan. Before calculation, the contribution due to the methyl group of methacrylate (10% of the total anomeric carbon signals area) was subtracted from the 22.5 ppm signal area. The values obtained, corrected considering the cross-polarization dynamic process [30], allowed to calculate a NIPAAM/methacrylate molar ratio for the NP8 of about 6.5. This is in fair agreement with the value obtained from elemental analysis.

3.3. Equilibrium swelling

Swelling behavior of hydrogels is strongly influenced by the incorporation of NIPAAM even at room temperature (Fig. 5). Equilibrium swelling of the hydrogels at 25 °C decreases with increasing NIPAAM content ranging from 38 for the pure PULMA hydrogel to 17 for the gel with the higher content of NIPAAM. Other authors observed a similar behavior with dextran methacrylated hydrogels prepared in the presence of increasing amount of un-ionized acrylic acid [23]. This can be interpreted as a result of several contributions. The increasing amount of NIPAAM would increase the equilibrium swelling because of the resulting lower degree of cross-linking. On the other hand, increasing amounts of NIPAAM will enhance the physical entanglement of polymer chains and the hydrophobicity of the polymer matrix leading to a decrease in gel hydration. The effect of hydrophobicity is probably enhanced by the coordination of water around the hydrophilic pullulan moiety, which can increase the tendency to phase separation of polyNIPAAM chains.

The temperature dependent swelling curves of the PULMA–NIPAAM hydrogels are shown in Fig. 6. Significant temperature dependence of the swelling ratio was clearly detectable only for NP8 and NP26 hydrogels. The higher the NIPAAM/PULMA ratio in the sample, the larger the loss in weight after the temperature jump. Sample NP26 shrinks to lose 81% of its weight at 25 °C while sample NP8 loses 68% of its weight. Swelling ratio decreases less than 10% in the case of NP2 and NP4 hydrogels probably because the composition in NIPAAM is too low. A similar behavior was observed by Dong and Hoffmann preparing thermosensitive hydrogels by copolymerization of acrylic acid and NIPAAM [31]. They found a significant loss of thermosensitivity when the acrylic acid component of the copolymeric network was higher than 10 mol%.

A slight decrease in swelling with increasing temperature was also observed in the case of NP0, although the NIPAAM comonomer is not present in this sample. This small temperature dependence can be ascribed to the presence of hydrophobic polymethacrylic chains that cause a small shrinking of the polymer network with increasing temperature. The transition temperatures of NP8 and NP26 are about 36 and 40 °C, respectively. Thus, the LCST of PULMA–NIPAAM hydrogels approaches that of pure polyNIPAAM (about 32 °C) as the NIPAAM content increases. This is in agreement with the results obtained by other authors with graft copolymers of dextran and poly(NIPAAM-*co*-DMAAM) which showed that the presence of a more hydrophilic moiety shifts the LCST to higher temperatures [32]. In this context, it must be underlined that even in the NP26 sample, despite the high molar ratio of NIPAAM to methacrylate groups, the weight percent of the pullulan moiety is significant (46% from elemental analysis data).

It is worthwhile mentioning that by increasing the temperature the NP26 hydrogel turned progressively less opaque during the deswelling experiment and became completely transparent when the equilibrium condition at 48 °C was reached. This phenomenon was completely reversible. Allowing the gel to equilibrate at 25 °C, it turned progressively more opaque as water re-swelled the network. Heating again above the LCST resulted in a transparent gel. The NP8 sample never became completely transparent,

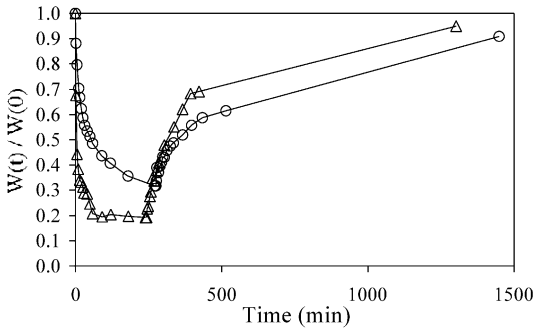

Fig. 7. Swelling–deswelling kinetics between 25 and 48 °C for equilibrium swelled PULMA–NIPAAM hydrogels. NP8 (○) and NP26 (△). $W(t)/W(0)$ is the ratio of wet weight of the gel at time t to the weight of the swollen gel at time zero (equilibrated at 25 °C).

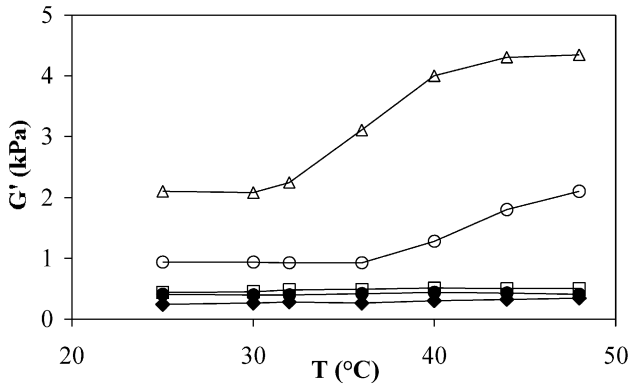

Fig. 8. Elastic modulus of PULMA–NIPAAM hydrogels with different NIPAAM content as a function of temperature. NP0 (◆), NP2 (●), NP4 (□), NP8 (○) and NP26 (△).

though less opaque areas were observed during the heating process. All the other gels were opaque or milky white in the whole temperature range examined. NP0 was slightly less opaque than other gels at 25 °C. Usually the opposite behavior is observed with NIPAAM containing hydrogels. The hydrogels are transparent at room temperature and become opaque after heating above the LCST [35]. This is usually attributed to the heterogeneity of the material generated by the formation of highly aggregated poly-NIPAAM domains. We think that a possible explanation of our finding with the NP26 hydrogel can be given considering a study of Takeshita et al. [33] on physical poly(vinyl alcohol) (PVA) hydrogels. They found that transparent or opaque hydrogels can be obtained by PVA physical gelation depending on the volume ratio of DMSO/water mixtures used as solvent. By using light scattering techniques, they found that spinodal decomposition precedes gel formation in the case of opaque hydrogels while phase separation is not observed in the case of transparent hydrogels. From their measurements, they conclude that the former hydrogels have a structure larger than that of the concentration fluctuations due to network structure, i.e. the mesh size of network. The appearance of opaqueness is attributed to the existence of some structure scattering light that may be in a spatial scale of submicrometer to micrometer. The last consideration can be applied to our NP26 hydrogel below the LCST. When the temperature is raised above the LCST the gel significantly shrinks (to 20% of its starting volume). This can reduce the size of the scattering structures below the value needed for visible scattering. At the same time, the size of the aggregated NIPAAM domains is probably not large enough to give scattering of visible light. This is reasonable as polyNIPAAM chains are chemically linked to and entangled with pullulan chains. These constraints could hamper the formation of extended aggregated NIPAAM domains. The phenomenon will be further investigated by scattering techniques.

3.4. Kinetics of swelling and deswelling

Swelling–deswelling kinetic plots after temperature jumps between 25 and 48 °C are shown in Fig. 7. The ratio of the weight at time t to the weight of the hydrogel equilibrated at 25 °C is plotted against time. We report only the data relative to the two strongly thermosensitive hydrogels, NP8 and NP26. In this case, the higher the NIPAAM/PULMA ratio in the sample, the faster the loss in weight after the temperature jump. Deswelling of sample NP26 is complete after 1 h while NP8 takes 3 h to reach the 90% of total deswelling. This can be possibly ascribed to the lower degree of cross-link of the NP26 hydrogel that will make both the diffusion of water and NIPAAM chain relaxation faster. These same statements are valid also in the reswelling kinetic. The NP26 hydrogel regains 66% of its original weight at 25 °C after 3 h, whereas sample NP8 regains only 50% of its weight after 4 h. Thus, as already found by other authors [34], reswelling takes longer time than deswelling. This is probably due to the very compact shrunken structure of hydrogels equilibrated at 48 °C. Diffusion of water through these structures during reswelling is more difficult than diffusion of water out of the swelled porous structure during the shrinking of the network. In fact, the onset of swelling from the periferic region of sample NP26 was clearly observed. Furthermore, the swelling kinetics can be strongly dependent also on polymer chain relaxation that can be significantly hindered in the deswelled hydrogel. Finally, as shown in Fig. 7, the response to the temperature change was reversible as hydrogels were able to regain their initial weight after the temperature changes.

3.5. Mechanical characterization of gels

The elastic modulus G' for all PULMA–NIPAAM hydrogels at several temperatures is shown in Fig. 8. At 25 °C, the elastic modulus increases from 0.24 to 2.1 kPa by increasing the relative amount of NIPAAM from 0 to 26. The same behavior has been reported by Muniz and Geuskens [35] in the case of semi-interpenetrated cross-linked polyacrylamide–polyNIPAAM hydrogels. The elastic modulus increase can be related to the results obtained with

the equilibrium swelling measurements. Higher elastic moduli correspond to a lower swelling ratio. This can be ascribed both to the high density of the network due to the presence of increasing amount of polyNIPAAM chains and to a partial collapse of polyNIPAAM due to the presence of the highly hydrophilic pullulan chains. The increase in modulus with the temperature for samples NP0, NP2 and NP4 is negligible and reflects the independence of the swelling ratio on temperature. Conversely, NP8 and NP26 networks become more rigid with increasing temperature, according to the decreased size of the shrunken gels and the increased density of polymer chains. Going from the completely relaxed to the completely collapsed structure the elastic modulus was more or less doubled (from 0.93 to 2.1 kPa for NP8 and from 2.1 to 4.35 kPa for NP26). As already stated for the equilibrium swelling data, the transition temperature approaches the polyNIPAAM LCST by increasing the NIPAAM/PULMA ratio.

4. Conclusions

PULMA was used to prepare hydrogels by free radical polymerization using various amount of NIPAAM as comonomer. The effective amount of NIPAAM incorporated in the network, calculated as the molar ratio of NIPAAM to methacrylate group, was 1.1, 2.8, 6.4 and 24. Only the last two hydrogels showed a significant shrinking with increasing temperature indicating that at least 4–5 NIPAAM monomers per methacrylate monomer have to be incorporated in the polyvinylic chains to attain thermosensitivity. The LCST of thermosensitive hydrogels decreases by increasing the amount of NIPAAM going from more or less 40 to 36 °C approaching the value (32 °C) of pure polyNIPAAM. The hydrogel with the higher amount of NIPAAM showed a dramatic shrinking (more than 80% of their initial weight) after the *T*-jump. Mechanical properties of hydrogels are significantly improved by the introduction of NIPAAM as comonomer and by increasing the temperature.

PULMA–NIPAAM hydrogels could be useful as intelligent temperature-responsive drug delivery systems or in the biomedical field.

Acknowledgments

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References

[1] Kudela V. In: Mark HF, Bikales NM, Overberger CC, Menges G, editors. Hydrogels, 2nd ed. Encyclopedia of polymer science and engineering, vol. 7. New York: Wiley/Interscience; 1987. p. 783.
[2] Park K, Shalaby WSW, Park H. Chemical gels. Biodegradable hydrogels for drug delivery. Lancaster, PA: Technomic; 1993. p. 67.
[3] Shibayama M, Nagai K. Macromolecules 1999;32:7461.
[4] Wu C. Polymer 1998;39:4609.
[5] Tanaka T. Sci Am 1981;244(1):110.
[6] Dagani R. Chem Engng News 1997;75(23):26.
[7] Gao J, Wu C. Macromolecules 1997;30:6872.
[8] Wu MH, Bao BR, Chen J, Xy YJ, Zao SR, Ma ZJ. Radiat Phys Chem 1999;56:341.
[9] Dong LC, Hoffmann AS. J Controlled Release 1990;13:21.
[10] Park TG, Hoffmann AS. J Biomed Res 1990;24:21.
[11] Park TG, Hoffmann AS. Biotech Bioengng 1990;35:152.
[12] Freitas RFS, Cussler EL. Sep Sci Technol 1987;22:911.
[13] Advances in polymer science, vols. 109 and 110. Berlin: Springer; 1993.
[14] Schild HG. Prog Polym Sci 1992;17:163.
[15] Mukae K, Bae HY, Okano T, Kim SW. Polym J 1990;22:250.
[16] Yıldız B, Isık B, Kıs M. Polymer 2001;42:2521.
[17] Zhang J, Peppas NA. Macromolecules 2000;33(1):102.
[18] Shin BC, Jhon MS, Lee HB, Yuk SK. Eur Polym J 1998;34:1675.
[19] Muniz EC, Geuskens GJ. Membr Sci 2000;172:287.
[20] Ju HK, Kim SY, Lee YM. Polymer 2001;42:6851.
[21] Park H, Park K. In: Ottenbrite RM, Huang SJ, Park K, editors. Hydrogels in bioapplications. ACS Symposium Series 629, Washington, DC: ACS; 1996. p. 2.
[22] van Dijk-Wolthuis WNE, Franssen O, Talsma H, van Steenbergen MJ, Kettenes-van den Bosch JJ, Hennink WE. Macromolecules 1995; 28:6317.
[23] Chiu HC, Wu AT, Lin YF. Polymer 2001;42:1471.
[24] Metz G, Wu X, Smith SO. J Magn Reson 1994;A110:219.
[25] Cook RL, Langford HL, Yamdagni R, Preston CM. Anal Chem 1996; 68(22):3979.
[26] Wu X, Zilm KW. J Magn Reson 1993;A102:205.
[27] Wu X, Zilm KW. J Magn Reson 1993;A104:119.
[28] van Dijk-Wolthuis WNE, Kettenes-van den Bosch JJ, van der Kerk-van Hoof A, Hennink WE. Macromolecules 1997;30:3411.
[29] Hou SS, Kuo PL. Polymer 2001;42:9505.
[30] Stejskal EO, Memory JD. High resolution NMR in the solid state fundamentals of CP-MAS. New York: Oxford University Press; 1994. Chapter II E.
[31] Dong LC, Hoffman AS. J Controlled Release 1991;15(2):141.
[32] Huh KM, Hashi J, Ooya T, Yui N. Macromol Chem Phys 2000; 201(5):613.
[33] Takeshita H, Kanaya T, Nishida K, Kaji K. Macromolecules 1999;32: 7815.
[34] Gotoh T, Nakatani Y, Sakohara S. J Appl Polym Sci 1998;69:895.
[35] Muniz EC, Geuskens G. Macromolecules 2001;34(13):4480.