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# Radiation polymerization and crosslinking of (N-isopropylacrylamide) in solution and in solid state

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## Summary

N-isopropylacrylamide (NIPAAm) hydrogels were synthesized by means of gamma irradiation, with three different methods: (a) irradiation of NIPAAm aqueous solutions; (b) irradiation of NIPAAm aqueous solution in presence of crosslinking agent N, N´-methylenebisacrylamide (BIS); and (c) in solid state, in form of disks compacted at different pressures prior to irradiation. Hydrogels of different crosslinking morphology were generated under different conditions.

The hydrogels were characterized with regard to their gel content, swelling behavior in dependence on the temperature, and network properties. Morphology of the samples was characterized by SEM.

## Introduction

Hydrogels are three dimensional networks of crosslinked hydrophilic polymers swollen in water. The hydrophilic gels based on both natural and synthetic polymers have continued to be of interest for encapsulation of cells and most recently such hydrogels have been attractive to the new field of "tissue engineering" as matrices for repairing and regenerating a wide variety of tissues and organs [1], and in a variety of industrial applications, such as bio-medical devices [2, 3]. Radiation methods are specially attractive to synthesize such gels because no additives are needed, the process is easily controlled and the economy is competitive when compared to other conventional methods [2, 4-8]. Gel formation of different polymers in solid state [9], compacted at different pressures before irradiation; have been also studied to obtain the lower dose of incipient gel and higher radiochemical yields of crosslinking [10-14].
Recently, considerable research attention has been focused on hydrogels that are able to alter their volume and properties in response to environmental stimuli such as pH, temperature, ionic strength and others [5, 15, 16], this phenomenon provides stimuli-sensitive hydrogels "smart hydrogels" suitable for applications in medical [17], agricultural, electrical, and many other industry field [18]. Thermoresponsive hydrogels undergo discontinuous volume phase transition behavior, they are in a highly swollen state at temperatures below a critical temperature, and above this

temperature they are in a shrunken state. The volume phase transition should be there near the lower critical solution temperature (LCST) of the corresponding polymers. Poly(N-isopropylacrylamide) (PNIPAAm), one of the best studied environmentally responsive polymers, undergoes a phase transition in aqueous solution at its lower critical solution temperature of ~ 32 °C [19-21].

PNIPAAm hydrogel is usually synthesized at room temperature from an aqueous solution of monogel by using a redox initiator composed of ammonium persulfate and N,N,N´,N´-tetramethylethylenediamine (TEMED) in presence of N,N´-methylene bisacrylamide (BIS), as a crosslinker [22-24]. Nagaoka [4] applied a gamma radiation induced polymerization and crosslinking method for the synthesis of PNIPAAm hydrogels in 10% w/w aqueous solutions, radiation doses between 20 and 200 kGy, and found a dose for incipient gel (Dg) of 71 Gy, gels with insufficient mechanical strength at doses less than 20 kGy, and a maximum thermosensitivity of 60 (defined as a ratio of the swelling at temperature after and before the LCST), at 20 kGy. Safrany [25] obtained macroporous gels of PNIPAAm by e-beam irradiation of aqueous solutions 20% of the polymer above the LCST; in that paper she synthesized first the polymer by some method and then crosslinked by ionizing radiation.

The aim of this work was to study and compare the properties of NIPAAm gel prepared by three different methods using radiation. The gels were prepared by irradiation aqueous solution of NIPAAm in presence and absence of crosslinking agent and by compacting NIPAAm at different pressures prior to irradiation.

## Experimental

N-Isopropylacrylamide from Aldrich, was purified by recrystallization from toluene/n-hexane, N, N-methylenebisacrylamide (BIS) also from Aldrich, was used as received.

In the first method (radiation method), 5.35 and 10% w/w aqueous solutions of NIPAAm were placed in glass ampoules with 4 mm inner diameters, purged of air by bubbling argon and then sealing them. Then the ampoules were irradiated at room temperature with a $Co^{60}$ source (Gamma Beam 651 PT of Nordion Co.), at different radiation doses up to 200 kGy at a dose rate of 3.85 kGy/h. In the second method (irradiation in the presence of crosslinking agent) the irradiation of the NIPAAm aqueous solutions (10% w/w) was realized in the presence of the N, N´-methylenebisacrylamide as crosslinking agent (0.3% w/w), and irradiated in the same conditions than in the first method. In the last method a powder of NIPAAm was compacted to disks of 1 cm diameter and about 0.1 cm thickness with a hydraulic press from Beckman, the pressure was determined by the force per unit area of sample, at pressures from 2 to 12 ton/$cm^2$. After the polymerization and crosslinking, the gels were removed from the tubes and washed in distilled water for 48 hours to eliminate the non-crosslinked polymer, cut in 1 cm long pieces and vacuum dried; the disks of PNIPAAm compacted at different pressures and irradiated, were washed in water for 48 h and vacuum dried.

The gel fraction was calculated from the weight ratio of the insoluble fraction and the weight of the monomer.

$$\text{Gel}\ (\%) = (W / W_0)\ \text{x}100. \qquad (\mathbf{1})$$

Where W and $W_0$ are the weights of crosslinked dried samples and initial monomer, respectively. The sol fraction (S) was calculated by subtraction the gel fraction from 1. The gel dose (Dg) (dose for incipient gel formation) was determined by plotting the sol fraction ($S+S^{1/2}$) as a function of the 1/D, where D is the radiation dose of the sample; and extrapolating to $S+S^{1/2}$ equal to 2, and the inverse of the dose of incipient gel was obtained.

The values of the radiation crosslinking (Gc) and degradation yields (Gd) for polymers, in which these two processes take place simultaneously, can be determined by means of the Charlesby- Pinner equation [26]:

$$S+S^{1/2} = (50\ N_A / (Mn_o GcD) + (Gd/Gc) \qquad (\mathbf{2})$$

Where S is the sol content, Gd/Gc is the relation of radiochemical yield of crosslinking and scission reaction, D is the irradiation dose in Mrads, and $Mn_o$ is the molecular weight number average of the initial polymer. In this paper we don't have polymers initially, then, we only determined the relation Gd/Gc by extrapolation of the line of the dependence, to the intersection with the ordinate.

The limit swelling of the samples were determined gravimetrically, they were immersed into distilled water at room temperature at different reaction times; after each time, the excess of solution on the surface was wiped, and the swelled cylinders or disks weighed, this procedure was repeated until the sample attained constant weight. The samples swelling percentage were calculated as follows:

$$\text{Swelling (\%)} = [(W_f - W_i)\ 100] / W_i \qquad (\mathbf{3})$$

Where $W_f$ and $W_i$ are the weights of the swelled and initial samples respectively. LCST was determined with the same procedure that for the time of the limit swelling, but in this case, the measurements of weight were realized at different temperatures in the limit swelling time and this temperature was calculated of the inflection point of the plot of swelling percentage as a function of temperature.

Thermosensitivity was defined as the ratio of the swelling samples at 10 and 40 °C, below and above the LCST of NIPAAm.

Differential scanning calorimetry (DSC) studies were realized on TA Instruments 2010; glass transition ($T_g$) determinations were carried out under nitrogen atmosphere (flow rate of 60 ml/min) and a rate of heating of 10 °C/min, in a range of temperature from 50 to 200 °C, and to confirm the LCST of the gels, the samples were immersed in distilled water at room temperature and allowed to swell during 24 h. DSC studies of the swelled gels, were carried out from 20 to 45 °C under nitrogen atmosphere, with a heating rate of 2 °C/min.

The surface morphology of the hydrogels was studied using a scanning electron microscope (SEM) Jeol LV 5600, low vacuum; the samples were first equilibrated in distilled water at room temperature, frozen in liquid nitrogen and cryogenically fractured in the transverse direction. A thing gold layer was deposited on the fractured area to reduce charging of the SEM.

## Results and Discussions

Figure 1 shows the crosslinking percentage as a function of radiation dose for the three methods studied, at doses from 5 to 200 kGy; in these conditions, a maximum crosslinking of 95% was obtained in aqueous solutions without any additive, and 98% in aqueous solutions with crosslinking agent BIS; it is known that addition of the crosslinking agent enhance the crosslinking and also the crosslinking density with small pores in the network; and a maximum crosslinking percentage of 76% was obtained in samples irradiated in solid disks with a pressure of 8 ton/cm$^2$.

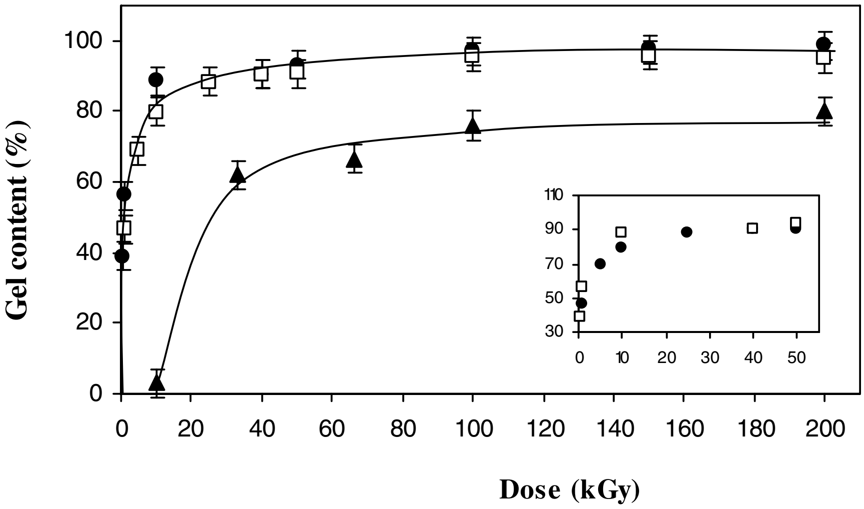

Figure 1. Crosslinking of NIPAAm by the three methods, (●) aq. solution (10%w/w) with BIS, (□) aq. solution (10%w/w) without BIS, (▲) disk of NIPAAm (solid).

The crosslinking percentage as a function of previous pressure was plot in Figure 2, when this monomer was irradiated at 100 kGy in compacted pellets, it was observed gel formation from a minimum pressure of about 4 ton/cm$^2$, this gel percentage increase at further pressures and almost no change from 8 ton/cm$^2$ and higher. We used a high dose for this experiment due to the small gel fraction obtained with lower dose.

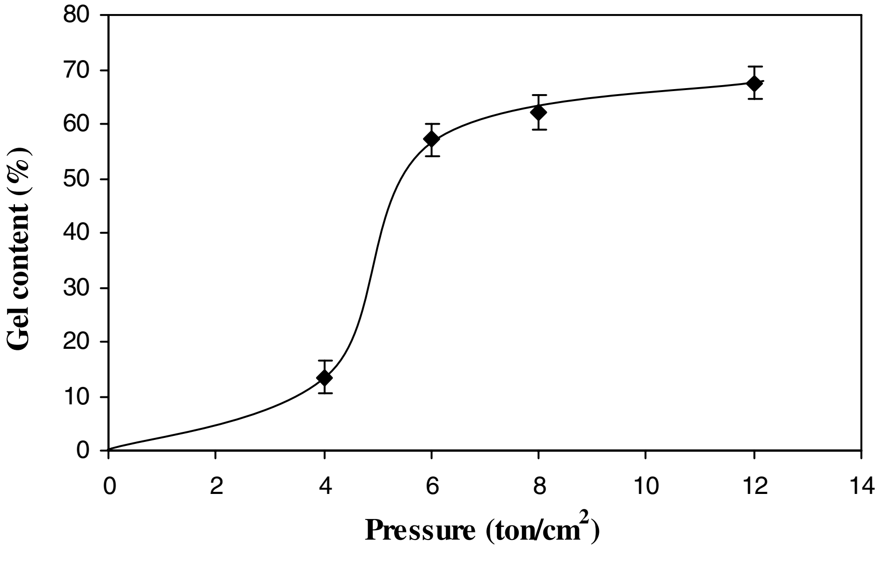

Figure 2. Effect of the pressure in the crosslinking of NIPAAm, the samples was irradiated with a dose 100 kGy.

Table 1 shows the dose of incipient gel (Dg) and the relation of radiochemical yield of scission (Gd) and crosslinking (Gc) obtained for the crosslinked samples under different conditions from the plot of $S+S^{1/2}$ as a function of 1/D (Charlesby-Pinner equation). The lowest dose of incipient gel (0.18 kGy), was found in samples crosslinked in the presence of the crosslinking agent BIS, while in aqueous solution without BIS was a little greater (0.73 kGy). It is known that the crosslinking is the join between polymer chains by intermolecular covalent bonding, it can be generated by effect of the radiation but the crosslinking agent is a substance that promotes intermolecular bonding, linking them together to create a more rigid structure, the longitude and crosslinking density depend of the control in the crosslinking process. With the use of this substance, we helped to enhance the crosslinking and diminished the radiation dose necessary to form the network. The highest Dg was found in samples irradiated in solid disks under previous pressure of 8 ton/cm$^2$ (9.4 kGy), the combination of two radicals to crosslink is difficult in solid state because of lack of mobility, in spite of irradiated samples under previous pressure, Millinchuk [14] and Burillo [10-12] found an optimum pressure where the yield of crosslinking increase considerably in polymers like poly(vinylalcohol), poly(vinylchloride) and others, it is because of decrease in free volume and increase in radical termination probability, it was not the case for NIPAAm monomer. This big difference on Dg between PNIPAAm crosslinked in solid state and aqueous solution is due to the role played by the reactive intermediates formed in the radiolysis of water, $e^-_{aq}$, $H^\bullet$ and $OH^\bullet$. The mechanism of radiation-induced solid-state polymerization and crosslinking can be ionic, free radical or combination of both; however the principal effect which distinguishes solid phase reaction from homogeneous liquid reaction is the diffusion phenomena. Such necessary diffusion of reactants (ions or free radicals) is several orders of magnitude slower in the solid phase than in liquid phase; the crosslinking mechanism involves the production of polymer radicals at neighboring sites on adjacent chains, accompanied by the loss of molecular hydrogen [26].

Table 1. Dose of incipient gel, and radiochemical yield ratio (Gd/Gc), under different conditions of radiation crosslinking.

| *State of crosslinking* | *NIPAAm concentration (%)* | *BIS concentration (%)* | *Water (%)* | *Gd/Gc* | *Dg dose of incipient gel (kGy)* |
|---|---|---|---|---|---|
| Aqueous solution | 5.35 | 0.00 | 94.65 | 0.43 | 0.73 |
| Aqueous solution | 10.00 | 0.30 | 89.70 | 0.43 | 0.18 |
| Solid (disk) | 100.00 | 0.00 | 0.00 | 0.65 | 9.40 |

Swelling and deswelling process of the hydrogels at 20 °C were studied. A typical swelling behavior, fast at the beginning, then slower and slower until the gels reached their maximum, at about 3 h was found in all samples studied. The kinetics of hydrogels deswelling (Figure 3) was also fast at the beginning and then slow. Deswelling of gels synthesized in form of compacted disks is much faster (3 h) than the conventional gel synthesized in aqueous solutions (12 h).

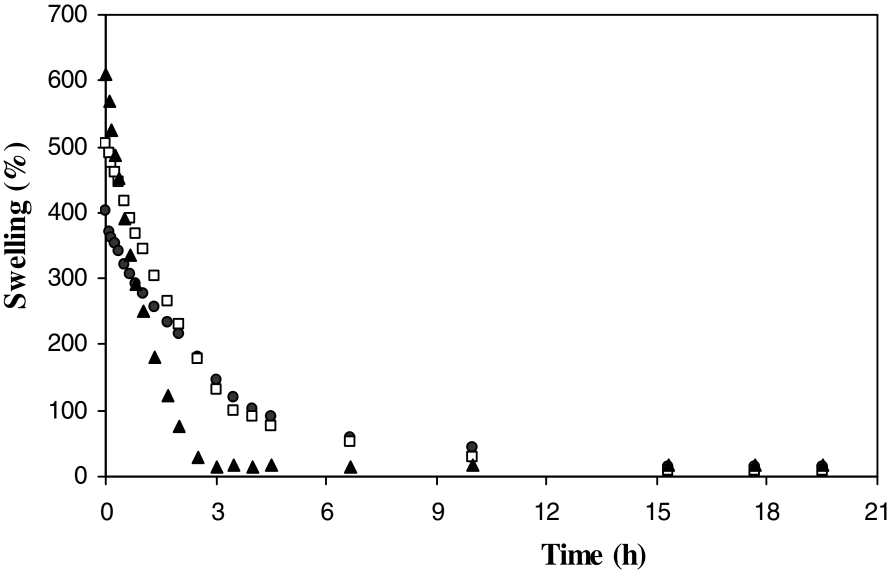

Figure 3. Deswelling behavior of PNIPAAm hydrogels synthesized at 100 kGy, (▲) compacted disk (8 ton/cm$^2$), (□) PNIPAAm without BIS, (●) PNIPAAm with BIS.

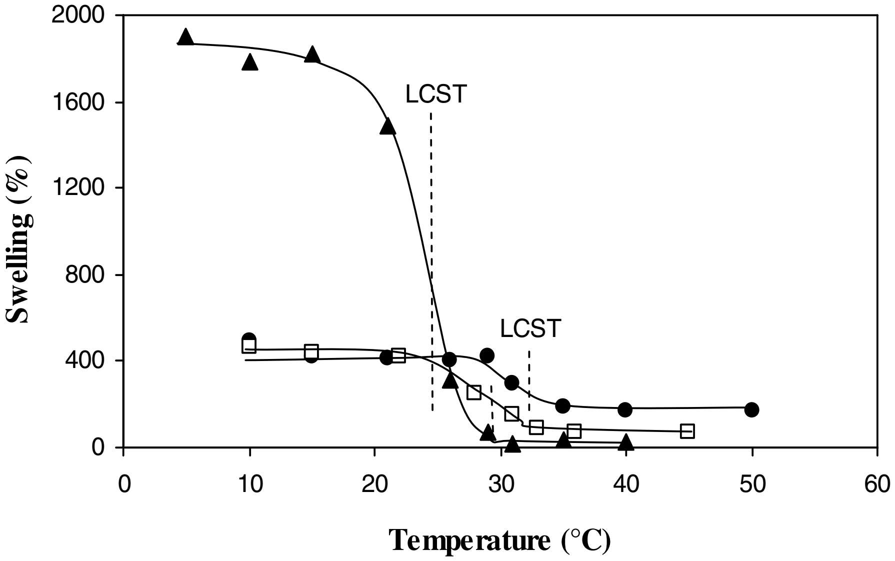

Figure 4. Determination of the lower critical solution temperature (LCST) of Poly(NIPAAm) gels, (▲) disk of NIPAAm (8 ton/cm$^2$, 200 kGy, 64%); (□) PNIPAAm without BIS (200 kGy, 95.2%); (●) PNIPAAm with BIS (200 kGy, 98.7%).

Figure 4 shows the swelling behavior as a funtion of temperature of one sample polymerized under pressure of 8 ton/cm$^2$, with 64% of crosslinking; and two samples synthesized without and with crosslinking agent (95.2% and 98.7%). We can observe the LCST of 29.7 °C for the aqueous solution without BIS while the LCST of 31.5 °C was found for the aqueous solution that contains BIS; there is not change with respect to the LCST of NIPAAm monomer or polymer [1].

Table 2 shows the thermosensitive swelling behavior, and the LCST of different hydrogels; we observed that the LCST were similar by the two methods, but it is easier to characterize by DSC than by swelling method, when the hydrogels are very weak. The LCST are similar with and without the addition of BIS, but it shifts considerably in the case of solid disks to 24-25 °C; Tg also shifts to lower temperature. It could be due to increment in the free volume in these last samples, when this happens, the polymer chains can slide between them more easily and they can move around at lower temperatures. This change in the free volume could be possible because of different mechanism of crosslinking without the presence of radiolysis of water products as $H^\bullet$, and $OH^\bullet$ and $e^-_{aq}$ and the applied pressure.

The thermosensitivity response (Table 2) of the hydrogel synthesized in aqueous solution with BIS was 2.9, and 5.11 for the hydrogel synthesized without BIS, lower than in case of hydrogel synthesized in solid disk of 72, because of lower crosslinking obtained in solid state (64%).

Table 2. LCST determined by swelling and DSC of swelled samples, Tg and thermosensitivity.

| *Samples* | *LCST (°C), by swelling* | *LCST (°C), by DSC* [a] | *Tg (°C) by DSC* [b] | *Thermosensitivity* |
|---|---|---|---|---|
| Solid disks at 8 ton/cm$^2$ (64% crosslinking) | 24.5 | 25.3 | 129.2 | 72.0 |
| Without BIS (95.2% crosslinking) | 29.7 | 29.7 | 144.8 | 5.1 |
| With BIS (98% crosslinking) | 31.5 | 31.8 | 143.9 | 2.9 |

[a] Measured at 2 °Cmin$^{-1}$, [b] Measured at 10 °Cmin$^{-1}$

Morphology of NIPAAm hydrogels synthesized by different methods was showed in Figure 5. We observed some differences like density of crosslinking, thickness of the walls and symmetry between the samples, because of the polymerization and crosslinking method and the use of additives. The most distinctive feature in Figure 5 is the different size of the voids between them; the morphology of the samples synthesized in aqueous solution (a), exhibit homogeneous porous architecture; and less homogeneous in samples synthesized with BIS (b), while the solid disks present a structure more irregular with a thin walls (c). So, the smallest voids are in the hydrogel that was synthesized with BIS, and the bigger are in the hydrogel formed under pressure.

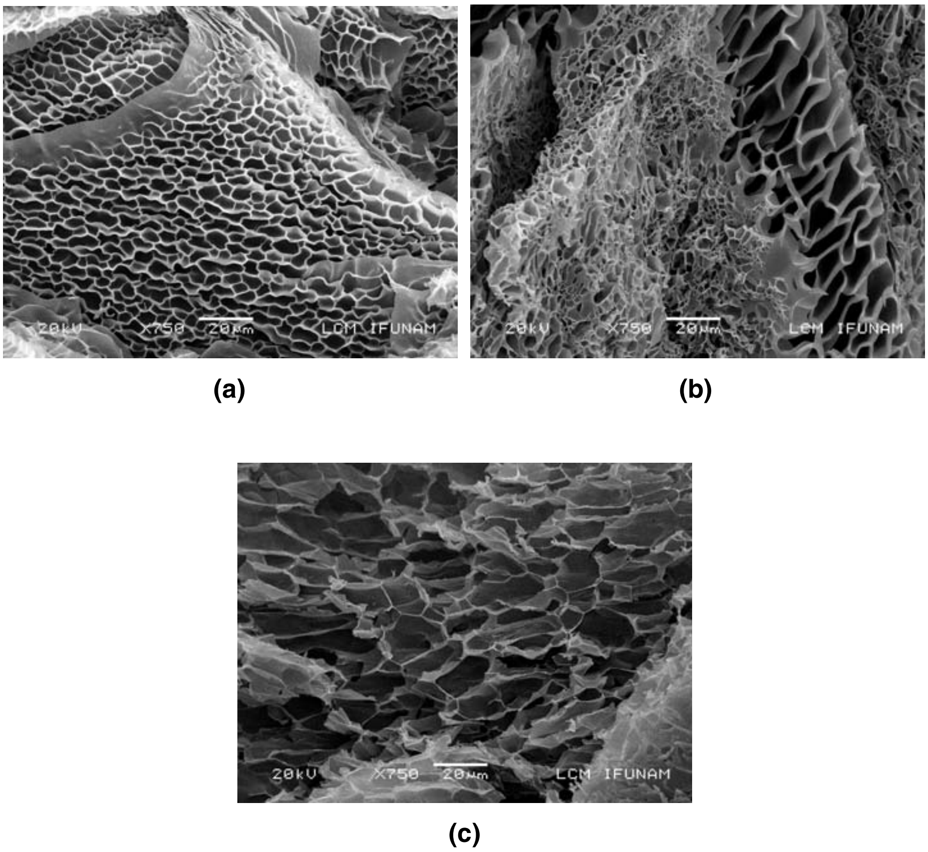

Figure 5. SEM micrographs of the PNIPAAm hydrogels obtained for the three methods, (a) NIPAAm polymerized and crosslinked without BIS (60 kGy, 91%), (b) NIPAAm polymerized and crosslinked with BIS (60 kGy, 93.5%), (c) disk of PNIPAAm under pressure (8 ton/cm$^2$, 100 kGy, 62.1%).

## Conclusions

γ polymerization and crosslinking of NIPAAm hydrogels by different methods, results in gels with different microstructures. Radiochemical yields ratio Gd/Gc, and LCST of hydrogels obtained in aqueous solution with and without crosslinking agent BIS were similar, but in compacted disk prior to irradiation, samples present higher Gd/Gc ratio, which means that radiochemical yield of degradation, is the predominant effect in the irradiation and crosslinking, in solid state. Thermosensitivity is very high in samples irradiated in solid state in comparison with hydrogels synthesized in aqueous solution, and also very weak with thinner walls. SEM micrographs show irregular structures with big pores in these last hydrogels.

Irradiation polymerization and crosslinking of NIPAAm in aqueous solution was the best method of synthesis; addition of the crosslinking agent BIS did not change any properties considerably, only on the dose of incipient gel 0.73 and 0.18 kGy, without and with crosslinking agent respectively. Moreover, the irradiation of NIPAAm in solid state, produce hydrogels with lower crosslinking percentages and weak mechanical properties.

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