# SYNTHESIS AND COMPARATIVE STUDY OF *N*-ISOPROPYLACRYLAMIDE (NIPAAm) HYDROGEL AND *N*-ISOPROPYLACRYLAMIDE-METHYL-METHACRYLATE (NIPAAm-MMA) GEL

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The purpose of this study was to investigate the behavior of the *N*-isopropylacrylamide (NIPAAm) hydrogel and *N*-isopropylacrylamide-methyl-methacrylate (NIPAAm-MMA) gel in a range of temperature close to that of the human body for potential soft tissue repair. The preparation of NIPAAm hydrogel and NIPAAm-MMA gel was done through the free radical polymerization technique. A change in the swelling of the NIPAAm hydrogel as a function of the temperature with the time, was observed, but not in the NIPAAm-MMA gel. The samples were tested at 22 $^{o}$C, 29 $^{o}$C, 35 $^{o}$C, 36 $^{o}$C, and 37 $^{o}$C, and characterized using FT-IR. Thermal stability of all the samples was studied by means of thermogravimetric analysis and the surface morphology of the NIPAAM hydrogel is compared with that of the copolymer of NIPAAm-MMA gel by atomic force microscopy (AFM).

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## 1. Introduction

Sensitive gels change their volume depending on the properties of the environment they are in, though most are liquid. This volume change is reversible and can be continuous or discontinuous, depending on the chemical structure of the sensitive hydrogel. Tanaka brought these materials to worldwide attention through his pioneering work on the temperature sensitive *N*-Isopropylacrylamide (NIPAAm) polymers and copolymers, and on solvent sensitive acrylamide polymers [1-2]. Hydrogels having nanoside dimensions could have many applications because of their size. As it is well known, many reported hydrogels possess stimuli responsive behavior such as thermo- and pH-sensitivity just as macrogels [3]. Because many recent review papers describe the interest in hydrogels for biomedical applications, we do not aim to give a complete overview here; we only shortly highlight the advantages of hydrogels with a few appealing examples related to potential soft tissue repair and delivery [4-7]. Hydrogels are sub-micron-size water-swollen particles composed of a three-dimensional network of hydrophilic polymer chains linked by

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permanent covalent bonds. Since their size and shape resemble single linear macromolecules in a coiled conformation, hydrogels can be regarded as internally cross-linked individual polymer chains. This combination of structure and size give them a unique and interesting distinctiveness for polymer physicists and chemists, and allows them to be incorporated as a new item in the usual classification of polymer architectures besides macromolecules that are branched, star-like, dendritic [8-9]. The consistent common way to synthesize hydrogels is polymerization with cross-linking agents, usually in emulsion or microemulsion. Hydrogels may also be obtained by the chemical intrachain cross-linking within single macromolecules [10]. Recently, an alternative method has been proposed based on intramolecular cross-linking induced by ionizing radiation [11]. In this method, a dilute aqueous solution of a polymer, free of any additives, is exposed to a high-dose pulse of fast electrons from an accelerator. As a result, the radicals are generated almost instantaneously (typically within a microsecond) on each polymer chain. Since the distance between the chains is relatively high and their mutual diffusion is slow, most of the generated radicals undergo recombination with their neighbours within the same macromolecule, this method has been tested on a number of hydrophilic polymers [12-16]. Studies with NIPAAm microgels with different size and swelling behavior have been obtained with different crosslinkers. The influence of the hydrophilic/hydrophobic characteristics of the crosslinkers can be related to the performance of these microgels [17-18]. In this work we prepared three polymers: the linear polymer of NIPAAm, the NIPAAm hydrogel which is a crosslinked polymer, and the crosslinked copolymer of NIPAAm-MMA gel, by free radical polymerization. We characterized them and did a comparison among their properties. To follow the change in the functionality, all the samples were characterized using fourier transform infrared (FT-IR). The changes of sweelling was studied at different temperatures, 22 $^{o}$C, 29 $^{o}$C, 35 $^{o}$C, 36 $^{o}$C, and 37 $^{o}$C, close to that of the human body. The thermal stability of all the samples was studied by means of thermogravimetric analysis (TGA) and the surface morphology of the crosslinked polymers was observed by atomic force microscopy (AFM).

## 2. Experimental

### 2.1. Materials

All chemical and solvents used in the synthesis were obtained from Aldrich Chemical and were used as received mainly *N*-isopropylacrylamide (NIPAAm), Methyl Methacrylate (MMA), Ethylene glycol dimethacrylate (EGDMA). The 2,2´-Azobisisobutyronitrile (AIBN) was purified by re-crystallization from methanol. Dry with tetrahydrofuran (THF) was acquired from Spectrum, HPLC-grade.

### 2.2. Measurements and characterization

The Fourier Transform Infrared spectra (FTIR) were collected for Perkin Elmer Spectrum Model 400 by the technique of Attenuated Total Reflectance (ATR). The thermal stability was analyzed using a TA Instrument Thermogravimetric Analyzer (TGA) Model 2050 at a heating rate of 2 $^{o}$C/min under air. Atomic Force Microscopy (AFM) was carried out on an AFM XE-70 Park Systems at 25 $^{o}$C in no-contact mode using commercial silicon cantilevers covered with aluminum. Common laboratory glassware was used in this study. The temperature-sensitive and swelling experiments of gels used the following equations; where temperature is given in $^{o}$C, weight average in g (grams), diameter average in cm (centimeters), and the gel swelling was evaluated with the subsequent equation:

$$\%H = \frac{(W_s - W_d)}{W_d} \quad (1)$$

Where $W_s$ is the weight of the swollen gel and $W_d$ is the weight of the dry gel. The degree of crosslinking *Qv* was evaluated following the next equation:

$$Qv = \frac{V}{V_o} = \left(\frac{d}{d_o}\right)^3 \quad (2)$$

Where *V* is the volume gel swollen, *Vo* is volume of the dried gel, $d_0$ diameter of the dried gel and *d* diameter of gel swollen.

### 2.3. Synthesis of NIPAAm *polymer, NIPAAm hydrogen and NIPAAm-MMA gel*

#### *2.3.1. NIPAAm polymer*

As it was described in the literature, the preparation of the NIPAAm polymer from NIPAAm consisted in mixing an amount of NIPAAm monomer with the corresponding amount of AIBN, and then dissolving that in dry THF. The flask was degassed at 25 $^{o}$C and was purged with nitrogen at least 24 h. The solution was heated for 24 h at 65 $^{o}$C, allowing formation of a polymer. After cooling at room temperature, the residual solvent was allowed to evaporate for 48 h and finally in vacuum at room temperature for 24 h [17].

#### *2.3.2. NIPAAm hydrogel*

We followed an analogous route, as reported, to prepare the samples of NIPAAm hydrogel with some variations. A molar ratio of 10:0.15:0.08 of NIPAAm:EGDMA:AIBN was put in a round bottom flask, then that was dissolved in THF. The flask was degassed at 22 $^{o}$C and purged with nitrogen for at least 24 h. The solution was transferred using a syringe to system consisting of two silanized glass plates, separated by a silicone gasket and held together by metal clamps. The assembly was placed in the vertical position in an oven for 24 h at 65 $^{o}$C, allowing formation of a hydrogel. After cooling at room temperature, the glass plates were separated and the residual solvent was allowed to evaporate. From the hydrogel sheet obtained, discs of 0.7 cm diameter were cut. The gel-discs were washed with distilled water and allowed to dry in air for 48 h and finally in vacuum at room temperature for 24 h [18].

#### *2.3.3. Copolymer NIPAAm-MMA gel*

To prepare the NIPAAm-MMA gel a similar route of preparation to that of NIPAAm hydrogel, only the MMA was added to the solution. The sample obtained was a flexible film, different of the hydrogel alone. In Figure **1,** shown the scheme of the reaction, where the possible hydrogen-bonding interactions between polymers chains of NIPAAm hydrogel and NIPAAm-MMA gel.

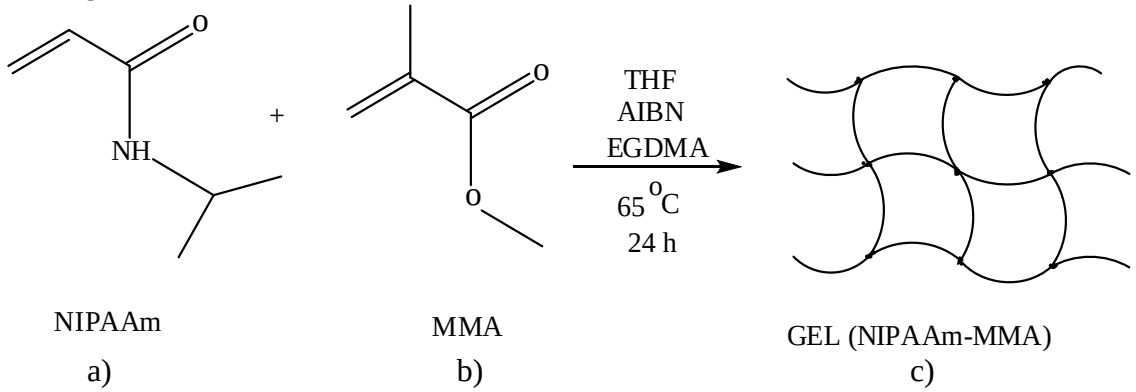


*Fig. 1. Scheme of the reaction of (NIPAAm-MMA) copolymer gels*

## 3. Results and Discussion

The Figure 2 shows the spectra of FT-IR for the NIPAAm polymer, NIPAAm hydrogel and (NIPAAm-MMA gel). It is possible to notice that the signals from their functional groups are very similar.

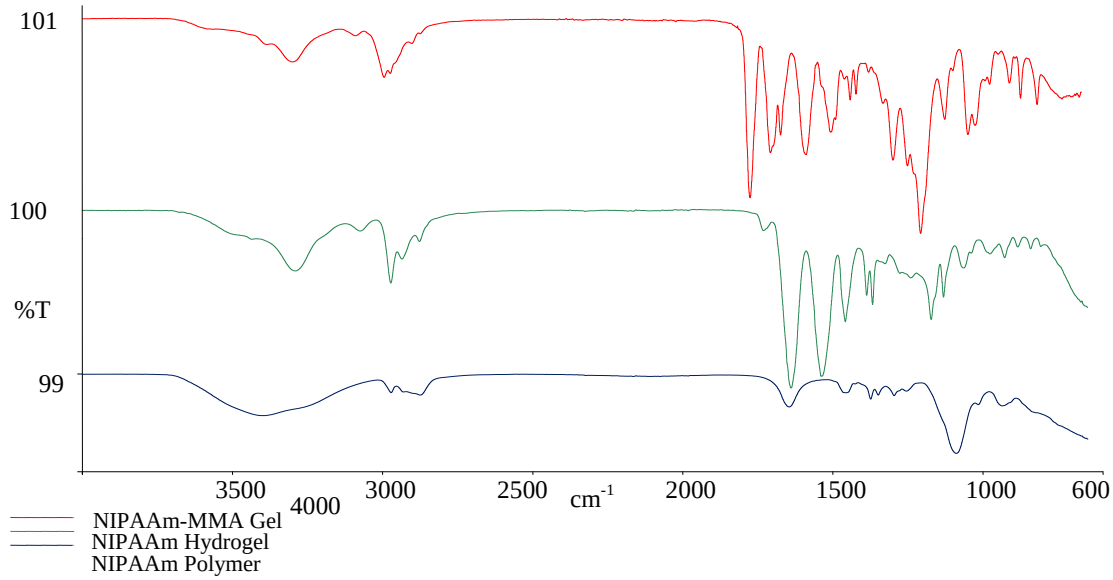


*Fig. 2. FT-IR of the polyNIPAAm, NIPAAm hydrogel and NIPAAm-MMA gel*

The table 1 shows the data of the signals from the spectra of FT-IR of the functional groups of the NIPAAm polymer, NIPAAm hydrogel and NIPAAm-MMA gel.

*Table 1 Spectral and yield data for the synthesized samples*

| Sample | Functional group | FT-IR ($cm^{-1}$) |
|---|---|---|
| NIPAAm polymer | N-H | 3400 |
| | C=O | 1650 |
| | C-H | 2900 |
| NIPAAm hydrogel | N-H | 3289 |
| | C=O | 1638 |
| | C-H | 2968 |
| NIPAAm-MMA gel | N-H | 3287 |
| | C=O | 1658, 1727* |
| | C-H | 2973 |

* There are two types of carbonyl group for (NIPAAm-MMA) gel corresponding to 1727 of ester and 1658 $cm^{-1}$ of amide

In Fig. 3 are shown the results of the changes of swelling of the NIPAAm hydrogel and (NIPAAm-MMA) gel samples versus time. Various runs were done by varying the temperature from 22 $^{o}$C, 29 $^{o}$C, 35 $^{o}$C, 36 $^{o}$C up to 37 $^{o}$C for all the samples. It was noticeable that the swelling was increasing with respect to the time up to stabilize at 72 h. The values of the degree of crosslinking Qv, and the percentage of moisture % H for NIPAAm hydrogel depended of the time. In the case of NIPAAm-MMA samples the swelling is almost linear with respect to the time without practically changes. Also there is no effect with the temperature in that range.

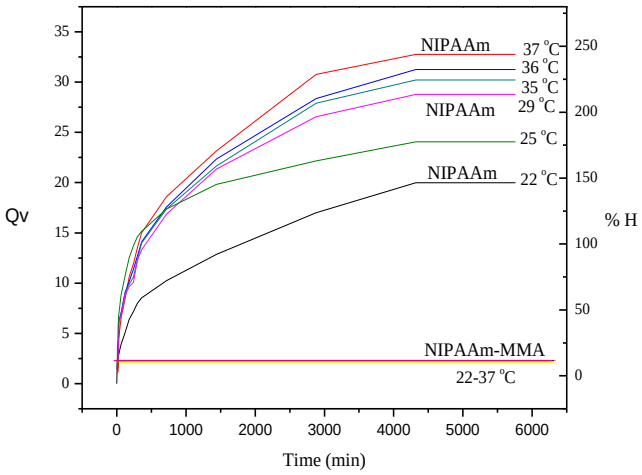


*Fig. 3. Behavior of the degree of crosslinking Qv, the percentage of moisture %H NIPAAm hydrogel and (NIPAAm-MMA) gel*

The results of thermal stability of the hydrogels determined by TGA under air are shown in Figure 4. This results support apparent single-step decomposition for the NIPAAm polymer without leaving practically residue, and the 5 % weight loss temperature of NIPAAm polymer is at 33±0.1 °C. In the case of NIPAAm hydrogel the temperature of 5% weight loss is at 81.7±0.1 °C and for the sample of NIPAAm-MMA gel this 5% weight loss temperature is at 72.1±0.1 °C, also, both without leaving practically residue. The above indicates that the gels have good thermal stability in comparison with the polymer alone. The difference between the polymer alone and that one with methacrylate, support the fact of the addition. In the case of the hydrogel the difference with respect to the polymer alone is because the significantly amount of moisture that it is able to retain in its structure.

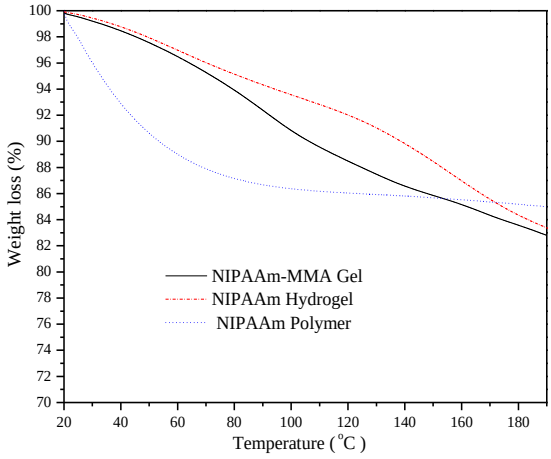


*Fig. 4. TGA of NIPAAm hydrogel, (NIPAAm-MMA) gel and NIPAAm polymer*

The surface morphology of the gels was studied by atomic force microscopy. Figure 5 (a) shows the surface of the NIPAAm hydrogel in three dimensions. It is observed a horizontal flat film. In Figure 5 (b), can observe the surface of the copolymer NIPAAm-MMA gel, it is important to note that the surface morphology of the copolymer has the arrangement of small grains forming. Finally it is observed the surface morphology of the copolymer NIPAAm-MMA gel, showed an arrangement of small grains aligned in a horizontal rough film. The differences in morphology support the fact of the addition of the MMA.

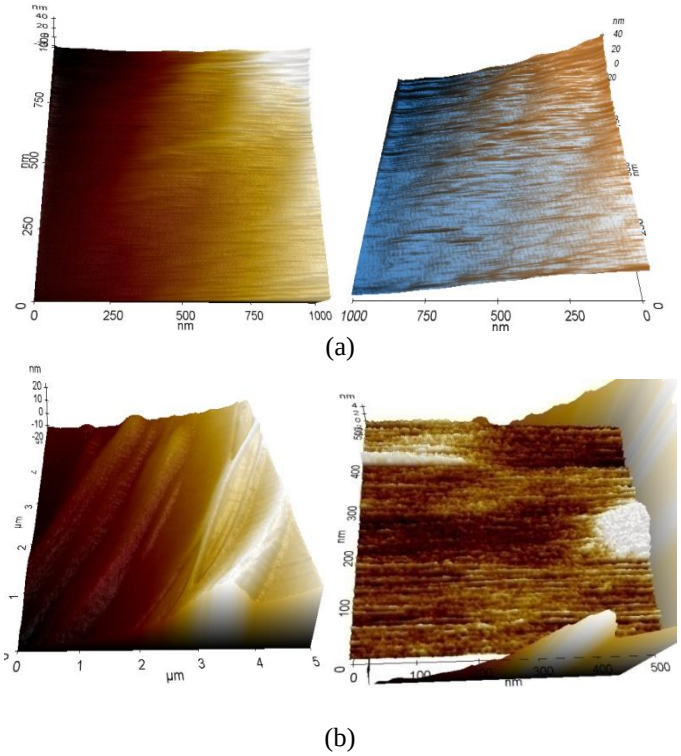


*Fig. 5. AFM micrographs of hydrogel of NIPAAm (a) gel of NIPAAm-MMA (b)*

All the samples were tested for water absorption at temperatures close to that of the human body to determine the degree of crosslinking and percentage of humidity as time passes. These tests were made at this temperature range to know their behavior and proving possibilities for applications as implants or soft tissue repair in the human body or as drug deliverers [4,5]. According the results, the NIPAAm hydrogel could release a drug in that range of temperatures, conversely the NIPAAm-MMA gel, could not release any drug in the same range of temperatures, it does not suffer any change in its diameter and weight, and this stability in his structure gave it possibilities for use in humid environments, as shows in Figure 3. The changes in expansion of the NIPAAm hydrogel had been tried to be explained on the fact that when the hydrogel is putting in contact with the water presents interaction of hydrogen bridges type [18-19] and is able to trap water molecules as outlined in Figure 1 (b). In the case of the NIPAAm-MMA gel we assumed that there is less interaction between the hydrogen in comparison with the polymer alone and the hydrogel due to presence of the monomer of MMA in his structure as shown in the scheme in Figure 1 (c), that on the other hand gave it the great flexibility to this material. The functional groups of the gels synthesized characterized by FT-IR are similar to those ones already published for a series of hydrogels composed by *N*-isopropylacrylamide (NIPAAm) and Maleilated Chitosan (MC) [20-21]. The decomposition curve of NIPAAm polymer showed apparent single-step decomposition, related to the previous result of other authors [22], however, they only exhibited values of the NIPAAm polymer. The decomposition curves of the both gels revealed a similar thermal stability for temperatures close to the human body up to 60 $^{o}$C.

## 4. Conclusions

There was a change of swelling of the NIPAAm hydrogel at the temperature range of 22 to 37 $^{o}$C as expected. The NIPAAm-MMA gel prepared by the same method did not suffer any change at the same temperatures, it is a crosslinked gel but flexible. Hydrophobic-hydrophobic and hydrogen-bonding interactions need to be considered in careful connection with their fine chemical structure to understand their behavior of flexibility and good thermal stability. We have

compared the morphology of the hydrogel of NIPAAm with the copolymer NIPAAm-MMA gel, it was possible to observe differences in the surface of this samples.

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## References

[1] T. Tanaka, S. Ishiwata, C. Ishimoto, Physical Review Letters, **38,** 771 (1977).
[2] T. Tanaka, Physical Review Letters, **40**, 820, (1978).
[3] L. Zha, B. Banik, F. Alexis, Soft Matter, **7**, 5908, (2011).
[4] B.H. Lee, B. West, R. McLemore, C. Pauken, B.L. Vernon, Biomacromolecules, **7**, 2059 (2006).
[5] Z. Cui, B.H. Lee, C. Pauken, B.L. Vernon, Journal of Biomedical Materials Research Part A., **98**, 159, (2011).
[6] K. Raemdonck, J. Demeester, S. De Smedt, Soft Matter, **5**, 707, (2009).
[7] A. V. Kabanov, S. V. Vinogradov, Angewandte Chemie International Edition **48**, 5418, (2009).
[8] B. E. B. Jensen, L. Hosta-Rigau, P. R. Spycher, E. Reimhult, B. Stadler, A. N. Zelikin Nanoscale, **5**, 6758, (2013).
[9] Y. Sasaki, K. Akiyoshi, The Chemical Record, **10**, 366, (2010).
[10] W. Funke, O. Okay, B. Joos-Müller, Advances in Polymer Science, **6**, 136, (1998).
[11] P. Ulanski, S. Kadlubowski, J. K. Jeszka, Materials Science-Poland, **24**, 467, (2006).
[12] U. Brasch, W. Burchard, Macromolecular Chemistry and Physics, **197**, 223, (1996).
[13] P. Ulanski, I. Janik, J. M. Rosiak, Radiation Physics and Chemistry, **52**, 289, (1998).
[14] P. Ulanski, J. M. Rosiak, Nuclear Instruments and Methods in Physics Research Section B, **151**, 356, (1999).
[15] S. Kadlubowski, J. Grobelny, W. Olenjniczac, M. Cichomsky, P. Ulanski, Macromolecules, **36**, 2484, (2003).
[16] K. F. Arndt, T. Schmidt, R. Reichelt, Polymer, **42**, 6785, (2001).
[17] A. Licea-Claveríe, E. Rogel-Hernández, R. Salgado-Rodríguez, J. A. López-Sánchez, L. A. Castillo, J. M. Cornejo-Bravo, K. F. Arndt, Macromolecular Symposia **207**, 193, (2004).
[18] A. Licea-Claveríe, E. Rogel-Hernández, J. A. López-Sánchez, L. A. Castillo, J. M. Cornejo-Bravo, K. F. Arndt, Designed Monomers and Polymers, **6**, 67, (2003).
[19] C. Obeso-Vera, J. M. Cornejo-Bravo, A. Serrano-Medina, A. Licea-Claveríe, Polymer Bulletin, **70**, 653, (2013).
[20] K. Pagonis, G. Bokias, Polymer Bulletin, **58**, 289, (2007).
[21] M. S. Shin, H. S. Kang, T. G. Park, J. Wong, Polymer Bulletin, **47**, 451, (2002).
[22] D. Kucklingl, H. J. P. Adler, L. Ling, W. D. Habicher, K. F. Arndt, Polymer Bulletin **44**, 269, (2000).