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Rheology and adhesive properties versus structure of poly(acrylamide-co-hydroxyethyl methacrylate) hydrogels

Nadia Baït^{1, 2, 3*}, Christophe Derail^{3,4}, Ahmed Benaboura², Bruno Grassl³

1- Centre de Recherche Scientifique et Technique en Analyses Physico-Chimiques (CRAPC),
BP 384, Bou-Ismaïl, 42004 Tipasa, Algérie.

2 - Laboratoire de Synthèse Macromoléculaire et Thio-Organique Macromoléculaire, Faculté
de Chimie, USTHB, BP 32, El-Alia, Bab-Ezzouar 16111, Algérie.

3 - Université de Pau et des Pays de l'Adour, E2S-UPPA, UMR IPREM CNRS/UPPA 5254,
Equipe de Physique et Chimie des Polymères, Technopole Hélioparc, 2 Avenue du Président
Angot, 64053 Pau Cedex 9, France.

4- Université de Pau et des Pays de l'Adour, E2S-UPPA, UMR IPREM CNRS/UPPA 5254,
LERAM, Technopole Hélioparc, 2 Avenue du Président Angot, 64053 Pau Cedex 9, France.

Corresponding author : Nadia Baït

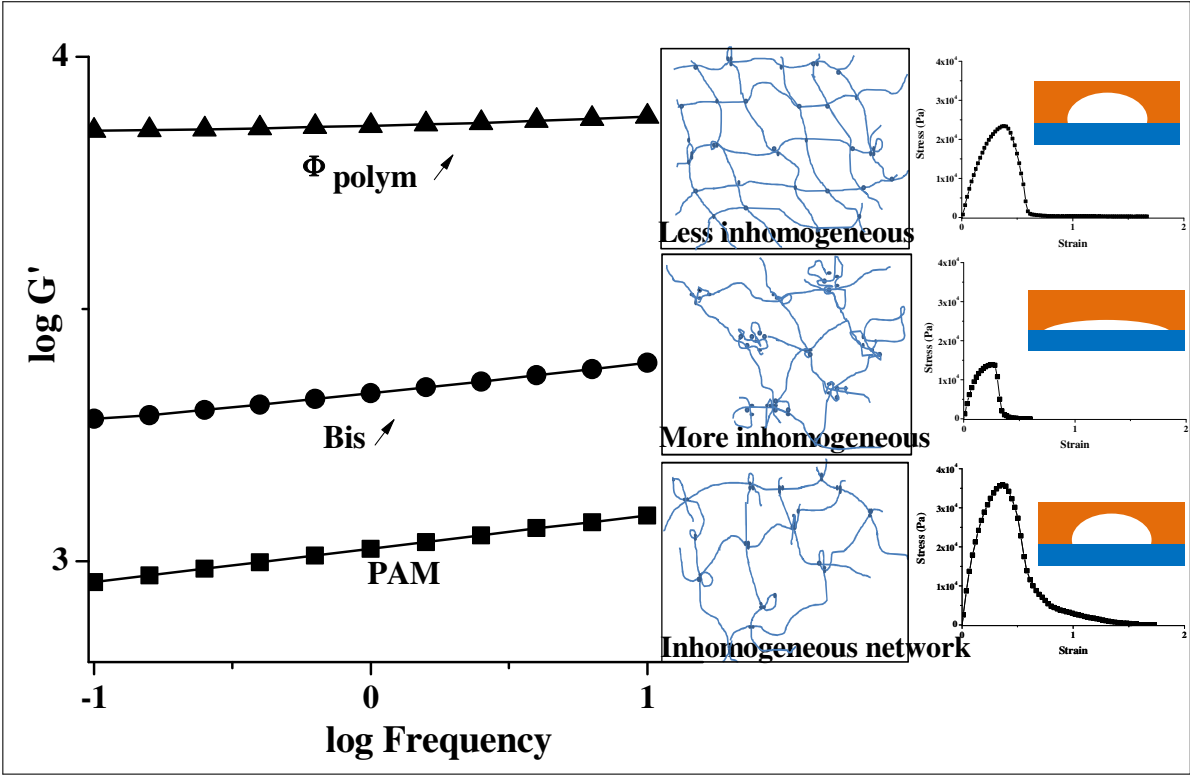
E-mail : wisali2003@yahoo.fr

Abstract

This study investigates the relationship between structure, rheological properties and adhesive performances of poly(acrylamide-co-hydroxyethyl methacrylate) P(AM-HEMA) hydrogels. The microstructure and, as a consequence the rheological behavior, of polyacrylamide-based hydrogels have been modulated by varying the precursory reaction mixtures composition. Elastic G' and loss G'' shear moduli measurements highlighted their inhomogeneous structure. Structural parameter values predicted by the rubber elasticity theory showed that P(AM-HEMA) networks are constituted by dense polymer regions interconnected by more dilute polymer ones as a result of multiple cross-linking reactions. We demonstrated that increasing the cross-linker composition allows to increase G' values however the inhomogeneity degree of the networks is higher. Contrarily, HEMA introduction into the feed and the increase of monomers' composition suppress the extent of PAM network inhomogeneity. Probe test tack experiments evidenced the effect of P(AM-HEMA) structure on the rheological properties and adhesion energy as well as the detachment type.

Keywords: Hydrogels, Rheology, Gelation, Inhomogeneity, Adhesive properties.

Graphical abstract



1. Introduction

Polymeric hydrogels have a significant role in several technological fields such as drug release, probes, superabsorbent materials, tissue engineering [1-7]. In a previous work we showed the ability of acrylamide AM and (2-hydroxyethyl methacrylate) HEMA based hydrogels to be used as pressure sensitive adhesives (PSAs) to design a one-layer transdermal drug delivery system (TDDS) constituted only by a hydrogel. We clearly pointed out that hydrogels can act as PSAs because of the similarities that exist between these two classes of materials in some respects such as the combination of the solid-like and liquid-like behaviors. In fact, from a macroscopic-structural viewpoint, hydrogels behave as viscoelastic materials, while they can be considered as polymeric solutions from a microscopic-structural viewpoint. P(AM-HEMA) hydrogels are enough cohesive to exhibit an interfacial failure when they are removed from the skin and their adhesion properties are, as for PSAs, controlled by the balance between elastic and dissipative properties according to peeling rate. We have also showed a promising way to enhance PAM P(AM-HEMA) hydrogels adhesion by incorporating Polystyrene PS and Poly (Butyl Acrylate) PBuA nanoparticles within their networks during synthesis [8,9].

For application based on hydrogels, such as the design of a one-layer transdermal drug delivery system, precise informations on hydrogels molecular constitution as well as on their elastic properties are necessary. Thus, it is important to elucidate the effects of the hydrogel networks synthesis conditions on the structure-properties relationship in the aim to optimize their performances. Like a liquid, a gel can undergo great deformations without breaking, but contrary to it, a gel recovers its initial form as soon as the imposed strain ceases. Moreover, like rubber, a gel is a polymeric network with the great difference that it contains an important liquid amount. Consequently, gel deformation theoretical studies derive from rubber elasticity and viscoelasticity theories [10-12]. Thereby, dynamic rheology is suitable for hydrogel mechanical characterization through the determination of elastic G' and loss G'' moduli derived from spectromechanical analysis [2, 11-15].

The gelation process is similar to a phase transition between viscoelastic liquid state called "*sol*" and elastic solid state called "*gel*". This transition phenomenon was studied by several authors using various techniques including rheology, high resolution $^1\text{H-NMR}$ and light scattering [16-19]. These studies showed that the gelation process can be well described by the percolation theory [17, 19, 20].

Because cross-linked hydrogels present a rheological behavior similar to rubber, their mechanical characterizations are mainly described by the elastic modulus variation with frequency or time [21-23]. Following the rheological properties as a function of time allows evaluating the gelation process linked to chemical composition. The *in-situ* gelation kinetics and the rheological properties of resulting hydrogels can easily be investigated by using rheological characterization in the linear domain [3, 11, 19, 20, 23-27].

On the basis of this quantitative approach, this contribution deals with the gelation kinetic and some resulting rheological properties during *in-situ* preparation of poly(acrylamide-co-hydroxyethyl methacrylate) P(AM-HEMA) hydrogels. Polyacrylamide hydrogel has been widely studied in terms of network inhomogeneities [30-34] but to our knowledge, there is no work related to poly(acrylamide-co-hydroxyethyl methacrylate) hydrogels structure-rheological properties relationship. The present investigation evaluates the dependence of P(AM-HEMA) hydrogels rheological properties and structure on their precursory reactional mixture composition. In application, it highlights the effect of hydrogels structure and rheological properties on their adhesion performances.

2. Experimental

2.1. Materials

Acrylamide (AM) (purity >99%) and (2-hydroxyethyl methacrylate) (HEMA) (purity >99%) monomers, potassium persulfate (KPS) and N,N'-methylene-bis-acrylamide (Bis) (purity >99%), used as initiator and cross-linking agent respectively, were all purchased from Aldrich and used as received for hydrogels synthesis. Salt-free Milli-Q water with an electrical conductivity of 18.3 MΩ.cm at 25°C was filtered through a 22 μm Millipore filter prior to use. All the reaction mixtures were prepared using this water.

2.2. Hydrogel synthesis

2.2.1. Precursory mixture composition

Poly(acrylamide-co-hydroxyethyl methacrylate) hydrogels were synthesized according to two formulations where the principal parameters taken into account are:

- %M which refers to the total monomers concentration (AM, HEMA and Bis) as a weight content;
- %KPS which refers to initiator weight ratio kept equal to 1%wt ($[KPS] = 4.6 \cdot 10^{-3} \text{ mol.L}^{-1}$);
- %Bis which refers to cross-linking agent weight ratio in the first formulation and to cross-linking agent mole ratio in the second one.

Table 1 summarizes the synthesis conditions of five series of P(AM-HEMA) hydrogels.

Table 1: Formulations of poly(acrylamide-co-hydroxyethyl methacrylate) hydrogels

| Formulation 1 | Series | %M | %Bis (%weight ratio) | Notation |
|---------------|--------|----|----------------------|-----------------------------------|
| | 1 | 7 | 1 | P(AM-HEMA _x)-M7B1 |
| | 2 | 7 | 5 | P(AM-HEMA _x)-M7B5 |
| Formulation 2 | Series | %M | %Bis (%mol ratio) | Notation |
| | 3 | 7 | 0.46 | P(AM-HEMA _x)-B0.46M7 |
| | 4 | 14 | 0.46 | P(AM-HEMA _x)-B0.46M14 |
| | 5 | 28 | 0.46 | P(AM-HEMA _x)-B0.46M28 |

For all series, $x = 5, 10, 15, 20, 30, 50, 80$ and 100 mol %, refers to HEMA molar composition.

2.2.2. Synthesis

All hydrogels were synthesized by free radical polymerization method. In a typical experiment, the monomer(s) AM and HEMA, the cross-linker Bis and the initiator KPS were added to salt-free Milli-Q water under stirring, degassed with nitrogen and then polymerized at 60 °C for 8 h.

2.3. Rheological measurements

Rheological measurements were performed using a dynamic rotational rheometer (DSR, Rheometrics) operating under controlled stress. The apparatus is equipped with a 25 mm diameter stainless steel parallel-plate geometry and water trap to keep the hydrogel's moisture constant and minimize its water evaporation. The temperature is controlled by a Peltier device.

2.3.1. Linear viscoelasticity properties of P(AM-HEMA) hydrogels

Stress sweep tests were performed to determine the linear viscoelasticity region of all synthesized hydrogels. These tests were carried out at various frequencies: 1, 10, 20, 30, 50 $\text{rad}\cdot\text{s}^{-1}$ on samples analyzed in the form of discs immediately after their synthesis, at 25 °C.

G' , G'' curves as a function of stress, showed that the linear viscoelasticity domain is obtained for stress values lower than 20 Pa whatever the frequency value. Spectromechanical analyses have been performed for a stress value equal to 10 Pa to respect linear behavior.

For hydrogels with polymer fraction of 7 % (series 1-3), the linear domain extent varies with their precursory mixture composition in HEMA and Bis. It is noteworthy that its width varies non-monotonically with increasing HEMA composition, the less wide domain is obtained for P(AM-HEMA50)-M7B1 and P(AM-HEMA50)-B0.46M7, *i.e.* for hydrogels with low cross-linking density. Furthermore, the linear stress range decreases with Bis composition increase. A similar result was reported by Calvet et al. [10-12] in their study of the cross-linking effect on PAM gelation. We attribute this result to the high cross-links density which makes retractive forces generated by the network polymer chains deformation not sufficient to allow them to return to their initial dimensions.

Hydrogels with higher polymer fractions (14 and 28%) behave differently, the proportionality between strain and stress is obtained over the entire stress range investigated [0,100Pa]. Thus, the linear domain becomes wider with the increase of P(AM-HEMA) polymer fraction.

2.3.2. Rheology monitoring of gelation process

To monitor the gelation process, a sample of 1 mL of the reactive solution freshly prepared was deposited on the lower plate and then the upper plate was set at a fixed distance (typically

1 mm) at which a disc is formed between the two plates, without normal force. Dynamic storage G' and loss G'' moduli are measured as function of time, at 60°C, under an angular frequency of 10 rad.s⁻¹ and a stress of 10 Pa corresponding to the linear domain.”

2.3.3. Spectromechanical analysis

Hydrogels rheological behavior was evaluated from spectromechanical analyses performed at 25°C, in the linear domain, on samples in the form of discs tested immediately after their synthesis. Previously, we confirmed that the rheological properties remained constant with time by performing time sweep measurements carried out during 2000 s, at 10 rad.s⁻¹. This time was enough sufficient to perform stress and frequency sweeps without notable evolution of the samples.

Moreover we have controlled the reliability and the good repeatability of the measurements demonstrating that hydrogels macrostructure is not damaged during stress sweep and spectromechanical analysis.

2.4- Probe tack test experiments

Adhesion properties of PAM-based hydrogels were evaluated using the probe tack test. Experiments were carried out on samples in the form of 32-34 mm diameter discs using a TA-XTAi Texture Analyser (Swantech International, Gennevilliers, France) at 25°C. Typical procedure was reported elsewhere [8, 9]. A flat punch is brought in contact with the sample deposited on a given substrate and a compressive force F_c is applied during the contact time t_c . After t_c , the flat is removed at a constant debonding velocity V_{deb} and, we measured the force *versus* displacement. The adhesion energy value W_{adh} to detach the hydrogel from the substrate is given by the area under the stress-strain curve derivated from this measure ($W_{adh} = \int_0^{\epsilon^{max}} \sigma d\epsilon$) [28, 29]).

This paper reports the results obtained for $V_{deb}=10$ mm.s⁻¹, $F_c = 20$ and 30N and $t_c= 30, 60$ and 120s.

3. Results and discussion

3.1. In-situ (AM/HEMA/KPS/Bis) mixtures polymerization-cross-linking

3.1.1. Gelation dynamic and mechanism

Figure 1 illustrates, as an example, the *in-situ* gelation kinetics based on precursory mixtures of some series 1-3 hydrogels. According to the polymerization-cross-linking reaction time and $G'(t)$ and $G''(t)$ curves, as shown by the insert of figure 1, one can note that the *sol-gel* transition occurs in several stages and can be described as being a continuous passage between different states:

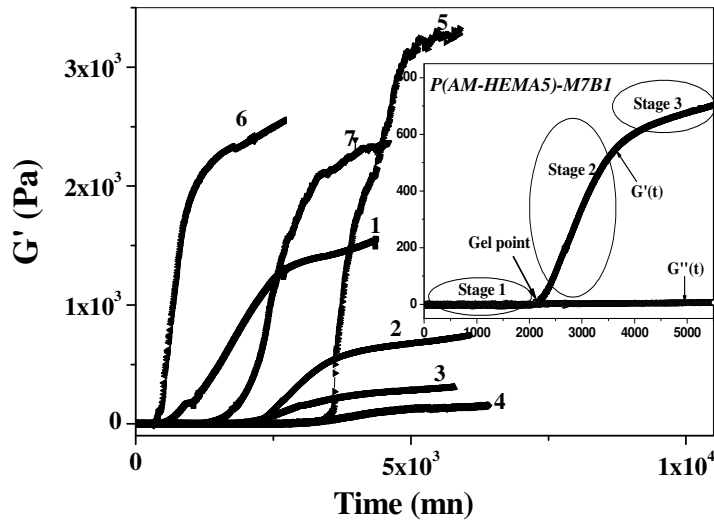


Figure 1:

G' as function of time and gelation dynamic, at 60°C , for

1 = PAM-M7B1, 2 = P(AM-HEMA5)-M7B1, 3 = P(AM-HEMA10)-M7B1, 4 = P(AM-HEMA20)-M7B1, 5 = PHEMA-M7B1, 6 = PAM-M7B5, 7 = P(AM-HEMA20)-M7B5.

Insert: $G'(t)$ and $G''(t)$ curves of P(AM-HEMA5)-M7B1 hydrogel.

- $t < t_{gel}$. This first stage (before the *gel point*) corresponds to a domain, where elastic modulus is negligible describing a viscoelastic liquid state. At this stage called *pregel*, the mixture is in its *sol* form, which corresponds to a dispersed medium composed of polymer chains, compact clusters or microgel particles, formed by free radical copolymerization between the monomer vinyl groups that interact weakly with each other.
- $t = t_{gel}$. At the *gel point*, the mixture suddenly loses its fluidity under the effect of the interconnection between *sol* components *via* chemical cross-linking reactions. In fact, as the reaction proceeds, the microgels connect to each other through their peripheral pendant vinyls and radical ends. This stage corresponds to the formation of a *critical gel* for which $G' = G''$ and whose structure is very different from that of the final network.
- a second stage where G' increases strongly compared to G'' corresponding to the mechanical effect of the *sol-gel transition* and the gel growth. In fact, with junction's number increase, the system progressively loses its viscosity while its elasticity increases significantly. G' becomes higher than G'' characterizing the elastic behavior.
- $t > t_{gel}$. This third stage corresponds to the *elastic solid state*, where G' value increases slightly. This weak increase corresponds to post cross-linking reactions including dangling chains formation. The gelation process is assumed to be complete when G' and G'' reach a plateau. At this reaction stage, a continuous network with molecular weight value diverging towards infinity is formed. The system does not flow anymore and has then a strong elastic character, $G' \gg G''$.

From $^1\text{H-NMR}$ high resolution analyses of the gelation process, Baselga et al. [16], in their study of acrylamide and Bis copolymerization, confirmed these gelation stages.

3.1.2. Factors affecting gelation

$G'(t)$ curves denoted 1-7 in figure 1 illustrates, as an example, *in-situ* polymerization-cross-linking kinetics of some hydrogel precursory mixtures with different HEMA and Bis compositions. All analysis parameters held constant, one can note from these curves that the mixture composition strongly affects the polymerization-cross-linking kinetics.

Curves 1 and 6 reflect the cross-linker composition effect on acrylamide *in-situ* polymerization-cross-linking kinetics monitoring. They show that, if we assume as a first approximation that the gel point is given by $G'(t)$ and $G''(t)$ curves cross-over point, it clearly appears that for the same monomer composition, the gel point is obtained earlier for the mixture with 5% in Bis. When the cross-linker concentration increases, the reactivity, the gel transition and the network formation rate accelerate and consequently the gelation process appears at a shorter time. This result is due to the fact that, being very reactive (Bis more reactive than AM, ($r_{AM} = 0.52$ and $r_{Bis} = 5.2$ [35]) and higher in number in the second mixture, Bis molecules form more easily and more quickly chemical "inter-junctions" between the *sol* components at the *pregel* stage. Furthermore, G' value at the post cross-linking stage is higher in the case of the network formed starting from the mixture with the highest Bis composition. This shows that the number of effective elastic chains increases with increasing Bis concentration. The same finding was observed for P(AM-HEMA20)-M7B1 and its homologous P(AM-HEMA20)-M7B5 as illustrated by the curves 4 and 7. All P(AM-HEMA x)-M7B1 and their P(AM-HEMA x)-M7B5 hydrogels homologous (curves not shown here) behave similarly.

Curves denoted 1 to 5 illustrate HEMA comonomer effect on AM gelation kinetic. They clearly show that the copolymerization of AM with HEMA and HEMA composition strongly affects the precursory mixture rheology. First, the introduction of HEMA delays the gel point appearance, for example 5% mol of HEMA delays (AM/HEMA, Bis 1%) mixture gelation of about 1500 s compared to the case where the mixture is only constituted by acrylamide monomer i.e. (AM, Bis 1%). This copolymerization delay effect was observed for all mixtures with various HEMA and Bis compositions. Moreover, regardless of mixtures formulation, G' values in the post-linking stage vary non-monotonically with HEMA composition increase. However, at this stage, we cannot be affirmative with respect to this finding because we unfortunately could not access to G' value at the plateau for all formed networks, particularly for those resulting from mixtures with higher Bis composition i.e. P(AM-HEMA x)-M7B5 hydrogels (curves not shown here). Indeed on $G'(t)$ curves, we observe a drastic increase in

the elastic modulus value after the post-cross linking phase resulting from water evaporation which leads to an over-estimate of the complex shear modulus value.

To overcome this problem, we carried out spectromechanical analysis on final hydrogels obtained in the disc form. From our viewpoint, results obtained on a sample analyzed in this form would be more representative of the hydrogel response than a disc cut out starting from a sample synthesized in the form of cylinder. We were comforted in this assumption by the study undertaken by S. Durmaz and O.Okay [36] which showed, during rheological measurements in uniaxial compression, that the elastic modulus value depended on the position where the measurement was taken.

3.2. P(AM-HEMA) spectromechanical analysis

Figure 2 shows, as example, $G'(\omega)$ and $G''(\omega)$ curves obtained for different P(AM-HEMA_x)-M7B1, P(AM-HEMA_x)-M7B5 and P(AM-HEMA_x)-B0.46M28 hydrogels.

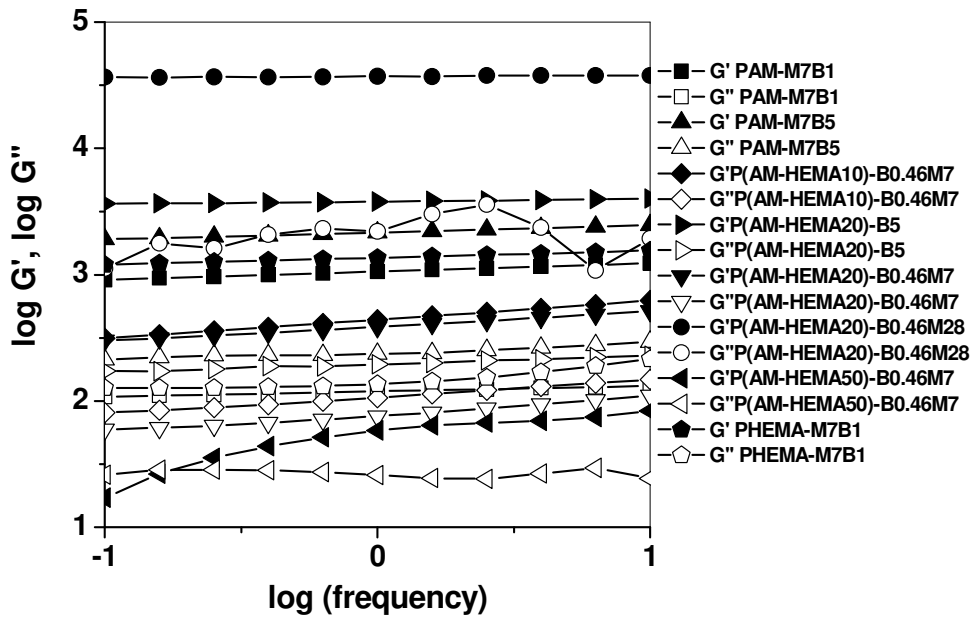


Figure 2:
 G' and G'' versus frequency in double logarithm scale for different
P(AM-HEMA_x)-M7B1, P(AM-HEMA_x)-M7B5
and P(AM-HEMA_x)-B0.46M28 hydrogels.

Samples show a specific behavior which corresponds to a prevalent elastic character ($G' \gg G''$). The low slope values (0.01-0.14) of these curves (except for that of P(AM-HEMA50)M7B1) demonstrate that elastic moduli are frequency independent at a constant temperature. This result indicates clearly that these hydrogels are well cross-linked [3, 23, 35, 37-39].

3.2.1. Chemical composition effect on P(AM-HEMA) hydrogels rheology

$G'(\omega)$ curves comparative examination shows that there is a strong dependence between hydrogels elasticity and their HEMA and Bis composition as well as their polymer fraction.

- The histogram shown in figure 3 gathers G' values of P(AM-HEMA $_x$)-M7B1 (series 1) and P(AM-HEMA $_x$)-M7B5 (series 2) hydrogels which illustrate the cross-linker composition effect on hydrogels elasticity.

It shows that, for a given HEMA composition, passing from 1 to 5% (in mass) in Bis generates a sharp increase in the hydrogel elasticity. This results directly from the increase in the number of entities that can support the imposed stress, i.e. the number of chains elastically active, knowing that the elastic modulus of a polymeric network is closely related to its connectivity [4]. With the increase in cross-links number, polymer chains become shorter, suggesting that the creation of new junctions is not possible. This explain why hydrogels with the highest composition in Bis present $G'(\omega)$ frequency independent variations, as illustrated by PAM-M7B5 and P(AM-HEMA20)-M7B5 $G'(\omega)$ curves shown in figure 2.

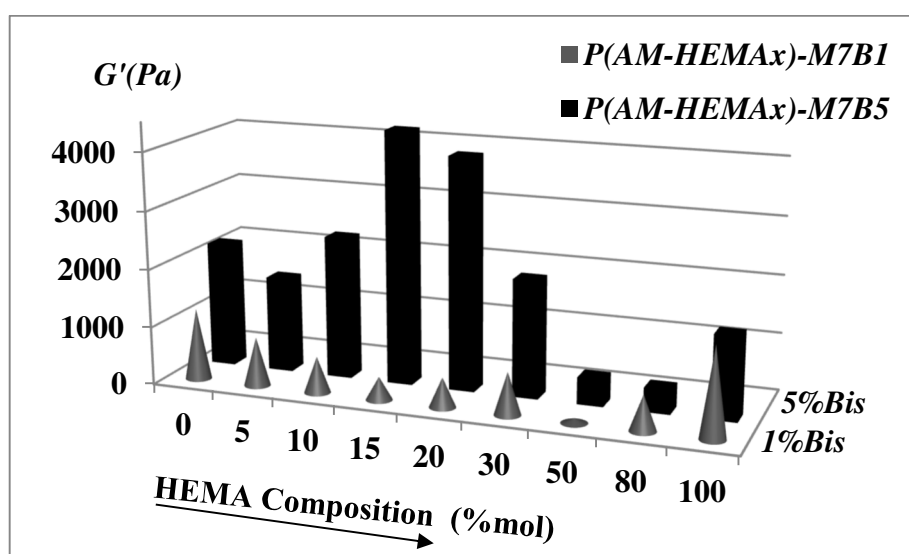


Figure 3:

Bis composition effect on hydrogels elasticity.

(Hydrogels with AM = 7%, $[KPS] = 4.6 \cdot 10^{-3} \text{ mol.L}^{-1}$, %Bis = 1 and 5 wt%).

- The HEMA composition effect is well illustrated by P(AM-HEMA $_x$)-B0.46M7 hydrogels (series 3) whose G' values as function of HEMA composition are shown in figure 4. These hydrogels exhibit an elasticity which varies non-monotonically with HEMA composition increase. Highest G' values are obtained for PAM and PHEMA homopolymer networks. Based on these values we expected P(AM-HEMA $_x$)-B0.46M7 networks elasticity higher or at

least of the same magnitude order of PAM B0.46M7 one. Surprisingly, G' values of copolymer hydrogels are lower and the lowest value is obtained for P(AM-HEMA50)B0.46M7 hydrogel. We attribute these findings to the existence of defects in P(AM-HEMA x)-B0.46M7 networks resulting from the difference in reactivity between the three monomers AM, HEMA and Bis constituting the reaction mixtures: $r_{AM}= 0,41$, $r_{HEMA}= 7,4$ [8] and $r_{AM}= 0,52$, $r_{Bis}= 5,2$ [35].

Moreover it is important to point that for some samples with lower Bis composition (series 1 and 3) there is a light variation of G' with frequency. One can expect that for these networks there is non-permanent junction's formation such as the hydrogen bonds and entanglements between sub-chains or dangling chains.

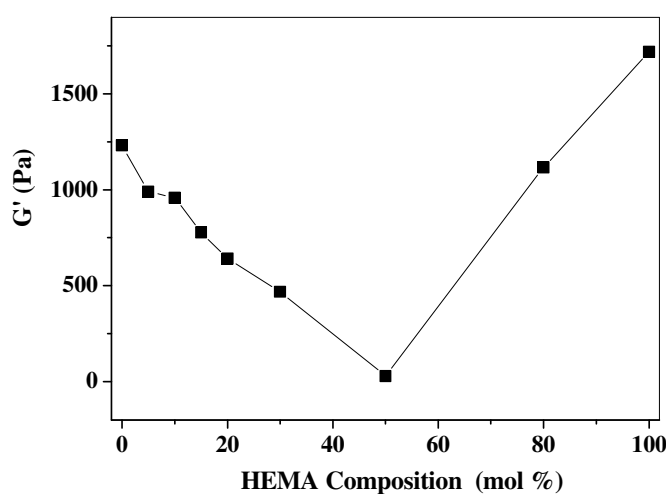


Figure 4:
 G' versus HEMA composition for P(AM-HEMA x)-B0.46M7 hydrogels.

- Polymer fraction effect is illustrated by figure 5 which gathers G' values of P(AM-HEMA x)-B0.46M7, P(AM-HEMA x)-B0.46M14 and P(AM-HEMA x)-B0.46M28 hydrogels (series 3-5) resulting from mixtures with 0.46% in Bis and %M = 7, 14 and 28 % respectively, wherein polymer fraction is equal to %M.

It shows a very marked increase in G' values with increasing networks polymer fraction regardless of their HEMA composition. Depending of the polymer fraction, G' values vary with a power law expressed by equation 1, in fact, G' experimental values exhibit a linear variation with polymer fraction in a logarithmic scale, whose correlation coefficients R and slopes (exponent) b values are shown in figure 5. This finding supposes that polymer fraction increase generates more elastic chains in the network, direct consequence of effective cross-links number increase.

Moreover, the non-monotonic variation of the slope values indicates that for a given polymer fraction, G' evolves in non- monotonic way with the increase of HEMA composition.

$$G' \simeq \varphi_{polym}^b \quad (1)$$

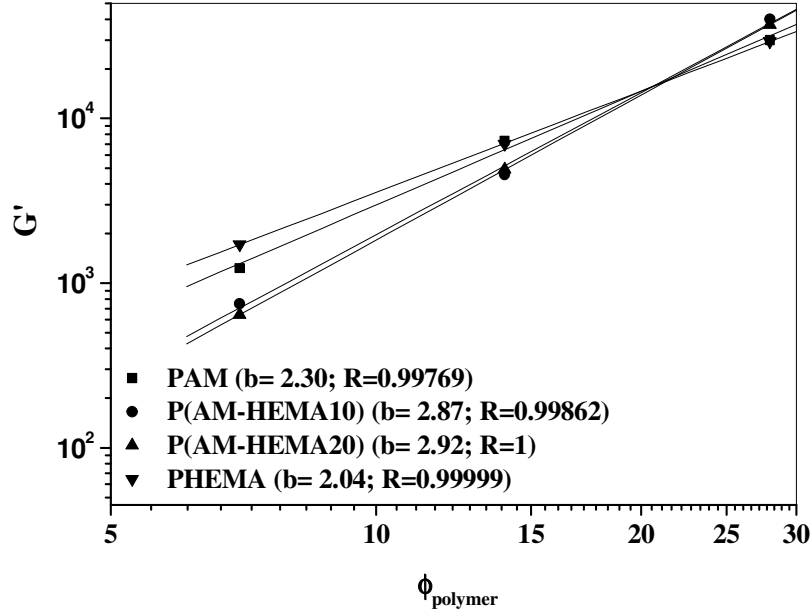


Figure 5:

G' versus φ_{polym} in double logarithm scale,

Polymer fraction effect on hydrogels elasticity.

Fits obtained according to equation 1 with $\varphi_{polym} = \%M$.

3.2.2. Structural parameters and P(AM-HEMA) network inhomogeneities

In addition to the monomer chemical nature that constitute it, a polymer network can be defined through two essential parameters which are the *number of effective chains per unit of volume* ν_e and the *density of effective junctions* n_e . These two parameters are those determining the network elasticity. For hydrogels with permanent cross-links, they can be determined from shear modulus value G_e which can be predicted by the rubber elasticity theory initially developed by Flory [40] and can be expressed as in equation 2 [24].

$$G_e = \left(1 - \frac{2}{f}\right) \nu_e RT \frac{\langle r^2 \rangle}{\langle r_0^2 \rangle} \quad (2)$$

This equation allows the estimation of *effective chain number per volume unit* ν_e (mol.m^{-3}) with:

R: the perfect gases constant of ($8.314 \text{ J.mol.K}^{-1}$);

T: the temperature in Kelvin;

$\langle r^2 \rangle$: the square of the average distance between nodes at the equilibrium state;

$\langle r_0^2 \rangle$: the $\langle r^2 \rangle$ value at the end of the process of gelation. For a gel at the end of the synthesis reaction, as is the case of our samples, $\langle r_0^2 \rangle = \langle r^2 \rangle$;

f : the cross-linking agent functionality which represents the maximum number of junctions this agent can generate. For N,N'-methylene-Bis-acrylamide (Bis), $f = 4$.

In addition, the density ν_e depends on the effective junctions' density (cross-links density) n_e (mol.m^{-3}) in the gel according to the equation 3. From equations (2) and (3) it appears that, at a fixed temperature, the shear elastic modulus is proportional to n_e . Moreover, in the case of a gel, shear modulus value corresponds to G' value in the frequency sweep. It results equation 4.

$$\nu_e = \left(\frac{f}{2}\right) n_e \quad (3)$$

$$G' = n_e RT \quad (4)$$

Knowing the cross-links density, the molar mass of a polymer chain binding two adjacent cross-links (sub-chain), noted M_e (Kg.mol^{-1}), can be determined from equation 5, where $[M]$ (Kg.m^{-3}) is the monomer(s) total concentration, and which combined with equation 4, gives equation 6.

$$M_e = \frac{[M]}{n_e} \quad (5)$$

$$M_e = \frac{[AM]}{G'} RT \quad (6)$$

By using equations (5) and (6), we determined n_e and M_e of all hydrogels (series 1-5). These values enabled us to examine synthesis conditions effect on the structure of obtained networks. Moreover, we examined the cross-linking agent Bis efficiency by comparing n_e and M_e experimental values with those predicted for an ideal networks, through the calculation of their theoretical values according to the equation 7 where m_{Bis} is the cross-linker (Bis) mass, M_{Bis} is Bis mass molar and V_{mixture} the reactional mixture volume, taken in all cases equal to 100 mL.

$$\eta_{e\text{theo}} = \frac{m_{\text{Bis}}}{M_{\text{Bis}} \cdot V_{\text{mixture}}} \quad (7)$$

M_e theoretical values were calculated by using equation (5) and n_e theoretical values.

Table 2 gathers the experimental structural parameters of the five hydrogel series. It allows to examine the effect of Bis and HEMA composition and polymer fraction on the networks structure.

Table 2: n_e and M_e experimental values of the five series of hydrogels with $[KPS] = 4.6 \cdot 10^{-3} \text{ mol.L}^{-1}$ and %Bis the weight percent for series 1 and 2, and (mol/mol) percent for series 3-5.

| Hydrogel | %M | %Bis | n_e (mol.m^{-3}) | M_e (Kg.m^{-3}) | $(n_e / n_e \text{ theo}) (\%) =$ $(M_e \text{ theo} / M_e) (\%)$ |
|---------------------|-----------|-------------|--|---|--|
| PAM | 7 | 1 | 0.5 | 140 | 11 |
| | 7 | 5 | 1.0 | 70 | 4 |
| | 7 | 0.46 | 0.5 | 140 | 11 |
| | 14 | 0.46 | 3.1 | 45 | 33 |
| | 28 | 0.46 | 12.3 | 22 | 67 |
| P(AM-HEMA10) | 7 | 1 | 0.3 | 277 | 6 |
| | 7 | 5 | 1.0 | 70 | 4 |
| | 7 | 0.46 | 0.3 | 231 | 7 |
| | 14 | 0.46 | 1.9 | 74 | 22 |
| | 28 | 0.46 | 16.3 | 17 | 96 |
| P(AM-HEMA20) | 7 | 1 | 0.2 | 336 | 4 |
| | 7 | 5 | 1.6 | 43 | 8 |
| | 7 | 0.46 | 0.3 | 270 | 7 |
| | 14 | 0.46 | 2.2 | 63 | 28 |
| | 28 | 0.46 | 15.3 | 18 | 97 |
| PHEMA | 7 | 1 | 0.6 | 111 | 14 |
| | 7 | 5 | 0.6 | 120 | 2 |
| | 7 | 0.46 | 0.7 | 100 | 28 |
| | 14 | 0.46 | 2.8 | 49 | 57 |
| | 28 | 0.46 | 12.9 | 21 | 129 |

3.2.2.1. Bis composition effect on P(AM-HEMA) networks structure

By comparing n_e and M_e experimental and theoretical values of P(AM-HEMA)M7B1 and P(AM-HEMA)M7B5 hydrogels (series1 and 2) for a given HEMA composition, one can note that:

- As we supposed during the synthesis, Bis composition increase in the reactional mixture generates an increase in effective node number in the resulting networks and less dangling chains. Moreover for the constant polymer fraction that we considered (7%), the sub-chains become shorter (M_e values decrease). The increase in n_e values and thus the decrease in M_e ones (n_e and M_e are inversely proportional) with Bis composition increase are at the origin of less porous and more elastic networks formation. Higher Bis composition networks have higher and frequency independent G' values as we reported in section 2.2.1.

- n_e and consequently M_e values are very different from the theoretical prediction. n_e experimental values are much lower and consequently the sub-chains are much longer than the theoretical ones calculated for an ideal network. These results are attributed to the cross-linker efficiency as it will be detailed in section 3.2.2.2.
- In the case of PAM hydrogel, with Bis composition increase, the ratio $n_e/n_{e\ theo}$ value decreases from 11 to 4%. This shows that with their increase in the reactional mixture, cross-linker molecules are less effective in junctions' formation. Our result is corroborated by those reported in the literature by Kizilay et al. [32], Calvet et al. [23] et Thevenot et al. [35] for PAM hydrogel synthesized by free radical polymerization with different initial Bis concentrations. The same result was also reported by Nie et al. [18] for N-isopropylacrylamide (NiPAM)-Bis system, but unlike AM-Bis system, for NiPAM-Bis system, the Bis efficiency is independent of its concentration in the reaction mixture.
- The introduction of HEMA comonomer within the reactional mixtures does not change this established fact. Indeed, for P(AM-HEMA)-M7B1 and P(AM-HEMA)-M7B5 hydrogels (even for HEMA composition of 5, 15, 30, 50 and 80% whose structural parameters are not shown here), the cross-linker Bis efficiency decreases with Bis composition increase.

3.2.2.2. AM and HEMA copolymerization effect on P(AM-HEMA) networks structure

HEMA composition effect on networks structure is evidenced by n_e and M_e experimental and theoretical values of P(AM-HEMA_x)-B0.46M7 hydrogels which show that:

- n_e experimental values (consequently those of M_e) follow the profile of G' value evolution (shown in figure 3), i.e. a non-monotonous evolution with HEMA composition increase. The effective cross-links density decreases up to a minimal value of 0.03 corresponding to the P(AM-HEMA50)-B0.46M7 network then increases. This result allows us to suppose that Bis reactivity is influenced by the presence of HEMA in the reactional mixture.
- For PAM hydrogel, n_e value counts for less than 11% of theoretical cross-linking density as shown by $(n_e / n_{e\ theo})$ value. The effective junctions' concentration of this network is different from that predicted by the cross-linking agent concentration used in its precursory reactional mixture. This indicates that Bis molecules are not all effective in generating effective nodes, and that Bis efficacy is not inevitably dependent on HEMA introduction in the reactional mixture, as we initially supposed it. This result is attributed to multiple cross-links reactions where several Bis molecules can gather between them and contribute to only one elastically effective junction. These reactions lead to the formation of chains dangling and chains cyclization that are not network effective chains. The obtained PAM network deviate

from ideality and is therefore an inhomogeneous gel constituted by areas of strong polymer concentrations (clusters) surrounded by areas of weak polymer concentrations. These deviations from ideality are at the origin of inhomogeneities that characterize hydrogels' network, mainly those resulting from free radical polymerization [18, 23, 41]. The clusters formation and the concentration fluctuations in hydrogels network have been reported by several authors [30, 35, 42] and can easily be detected by light scattering [32, 41, 43].

- $n_e/n_{e,theo}$ values of copolymer hydrogels different from those obtained in the case of PAM hydrogel show that the cross-linker Bis efficiency is affected by AM and HEMA copolymerization. In fact, to the difference in reactivity between AM and Bis ($r_{AM} = 0,52$; $r_{Bis} = 5,2$) [35] is added that existing between AM and the HEMA ($r_{AM} = 0,41$; $r_{HEMA} = 7,4$) [8]. The reactional mixture becomes a three-component system of different reactivities which increases the probability of cyclization and multiple cross-linking reactions and promotes the inhomogeneous networks formation. This inhomogeneity is more marked for P(AM-HEMA50)-B0.46M7 hydrogel, for which there is the formation of more compact clusters (lowest $n_e/n_{e,theo}$ value, not shown here) surrounded by a more dilute phase consisting of sub-chains longer than those of PAM hydrogel as shown by its highest M_e value (not shown here). The microgels' connectivity of this network is weak, hence its lowest G' value reported in section 2.2.1.

3.2.2.3. Polymer fraction effect on P(AM-HEMA) networks structure

Our prospection of polymer fraction effect on P(AM-HEMA) network structure is illustrated by results concerning hydrogels with %M=7 , 14 and 28% and %Bis = 0.46, (series 3-5) reported in table 2. One can easily note that:

- For PAM hydrogel, at a constant Bis concentration, effective nodes number increases with the polymer fraction increase. We recall that the polymer fraction is taken equal to the reactional mixture's monomer fraction, knowing that ¹H-RMN results showed that AM and HEMA converted completely during gelation [8]. For a regular polymer fraction increase, n_e increase (and M_e decrease) is much more marked when passing from 14 to polymer 28%. In the case of the network with 28% polymer fraction, Bis efficiency calculation shows that n_e experimental value counts for 67% of the theoretical one, thus, Bis molecules become more effective with the network's polymer fraction increase. This increased efficiency results from the reduction in the probability of cyclization and multiple reticulation reactions. Similar behavior has been reported for poly(acrylamide)[43], poly(N-isopropylacrylamide)[18] and poly(acrylic acid)[44] hydrogels. Moreover, these authors showed that hydrogel structure and consequently its properties strongly depend on monomers initial dilution extent [30, 43]. Using light scattering, Kizilay et al. [43] pointed out the existence of a maximum degree of inhomogeneities corresponding to a critical polymer concentration.

- For P(AM-HEMA) hydrogels, we also recorded an increase in n_e value and a reduction in M_e value with monomers initial composition increase. As in the case of PAM network, copolymer networks pore size becomes smaller with the increase in their polymer fraction.
- The introduction of 10 and 20% moles of HEMA within AM-Bis mixtures, combined with 28% polymer fraction generates an efficiency improvement of Bis molecules more marked than that obtained in the case of PAM hydrogel. n_e experimental values count for more than 96% of the theoretical ones. Copolymerization is therefore in favor of the reduction in concentration fluctuations within P(AM-HEMA_x)-B0.46M28 networks.
- PHEMA hydrogel constitutes a particular case. Indeed, n_e experimental value obtained in the case of the network with 28% polymer fraction exceeds the theoretical value predicted for an ideal network. This is allotted to the existence of entanglements which constitute permanent physical cross-links that are elastically active, knowing that in equation (8), n_e is the sum of chemical junctions' number and permanent entanglements. This network would be thus the least porous.

At the end of this rheological study of P(AM-HEMA) hydrogels synthesized by free radical polymerization with different HEMA composition, cross-linking density and polymer fraction, it appears that P(AM-HEMA) hydrogels with 7 % of polymer fraction and the weakest compositions in Bis, namely 1 % in mass or 0,46 % (mol/mol), present weak elastic moduli but whose values are however in the range generally found for hydrogels. P(AM-HEMA) networks are constituted by clusters of strong polymer concentrations surrounded by areas of weak polymer concentrations. Moreover on the basis of the present study results and our previous study [8] the sub-chains are formed during polymerization-cross-linking reaction with a certain tendency to form blocks of HEMA followed by AM ones because of the highest value of r_{HEMA} compared to r_{AM} one.

By increasing Bis composition of the reactional mixtures, elastic modulus values of hydrogels with 7 % polymer fraction increase. This improvement of elasticity is however accompanied by the increase in the resulting networks inhomogeneity degree.

The increase in monomers concentration of the precursory reactional mixtures, whose Bis composition is maintained constant and equal to 0.46 % (mol/mol), generates hydrogels with higher elastic moduli and less inhomogeneity degree.

3.3. Structure and rheological effect on adhesion properties of P(AM-HEMA) hydrogels

Figure 6 and its insert illustrate the results of the probe test tack conducted on PAM with three different compositions: PAM-M7B1(PAM-B0.46M7), PAM-M7B5 and PAM-B0.46M14. The adhesion work values of these hydrogels obtained for a contact force F_c of 20N and a contact time t_c of 120s are correlated to G' values and the networks degree of inhomogeneities translated by the ratio $n_e/n_{e\ theo}$.

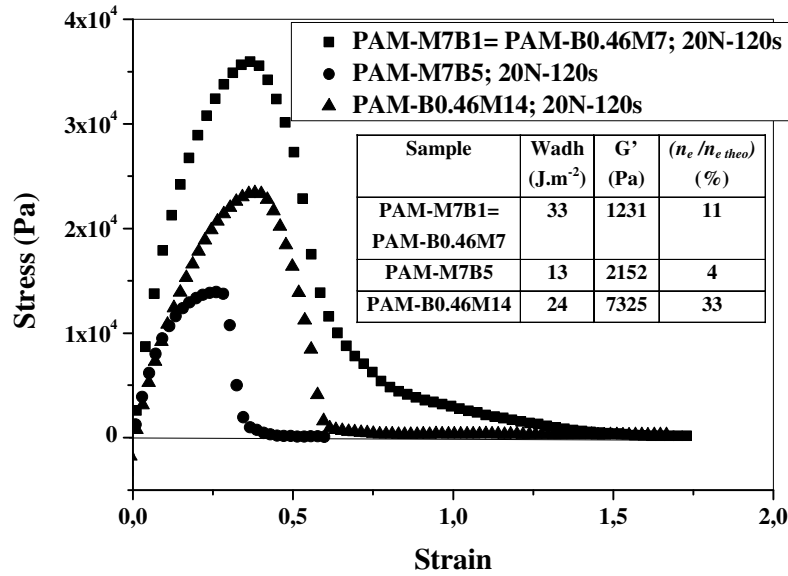


Figure 6:

Formulation effect on adhesion performances of PAM hydrogel.

It is well known that the adhesion properties of a pressure sensitive adhesive are affected, among others, by its rheological properties such as the elastic modulus [45-48]. Moreover, each part of the stress-strain curve corresponds to precise phenomena that take place in the adhesive during the sample detachment phase [49].

In the case of our hydrogels, the stress-strain tack curve of the reference hydrogel PAM-M7B1 suggests that the cavities appearing at the hydrogel/metal interface propagate in the hydrogel. It results a gradual decrease in the stress after its maximum, a large area under the curve and a high strain at break leading to a high value of the total adhesion work W_{adh} .

The PAM-B0.46M14 hydrogel suggests a debonding mechanism with a propagation of the cavities in the hydrogel bulk whereas in the case of PAM-B5M7 hydrogel the cavities propagate at the hydrogel/metallic substrate interface (interfacial detachment) as illustrated by its tack curve where: (i) the stress decreases sharply after its maximum and (ii) the stress maximum and the debonding are at comparatively low strains. Creton et al. reported that the formation of fibrillar structure, in the case of the detachment with cavities propagating in the sample, occurs through the growth of individual cavities into a honeycomb structure, where

the walls between the cavities are long-bearing structures [50]. In the case of PAM-M7B5 hydrogel, the inhomogeneities (dangling chains, chain cyclization...) being higher in number, they hinder the cavities propagating in the hydrogel bulk leading to interfacial detachment.

With the increase of the cross-linking density (the case of PAM-M7B1 and PAM-M7B5 hydrogels) G' value increases whereas the work adhesion value W_{adh} decreases. The same trend is observed with the increase of the polymer fraction (the case of PAM-Bis0.46-M17). This finding suggests that G' increase acts to the detriment of the hydrogels adhesion performances.

By comparing between the hydrogels with the highest cross-linking density and the highest polymer fraction, it appears that even G' of PAM-B0.46M14 is three times higher that of PAM-M7B5, its adhesion work is twice higher. This result suggests that the elasticity of the network is not the only parameter governing the adhesion performances of a hydrogel.

On the other hand, by comparing between PAM-M7B1 and PAM-M7B5, one can note the decrease of W_{adh} with the increase of the degree of hydrogel inhomogeneities (decrease of $n_e/n_{e\ theo}$). This observation is corroborated by the behavior PAM-M7B1 and PAM-B0.46M15. We suppose that the inhomogeneities act against the hydrogels adhesion properties.

Figure 7 illustrates the stress-strain curves of copolymer hydrogels P(AM-HEMA) with 5 and 20% of HEMA and two different cross-linking densities obtained for $F_c=20$ and 30N and a contact time $t_c=30, 60$ and 120 s. Table 3 gathers W_{adh} values recorded for these conditions correlated to G' and $(n_e/n_{e\ theo})$ values.

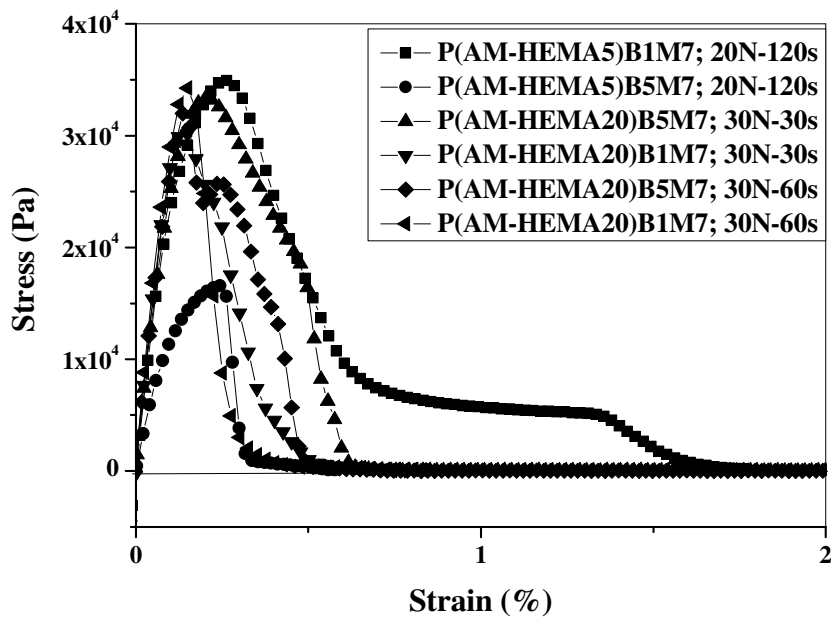


Figure 7:

Formulation effect on P(AM-HEMA) hydrogels stress-strain curves.

Table 3: Adhesion Work of P(AM-HEMA) hydrogels correlated to their elastic modulus and degree of inhomogeneities.

| Hydrogel | %M | %Bis | G' (Pa) | $(n_e/n_{e\ theo})$ (%) | W_{adh} ($J.m^{-2}$) | | |
|--------------|----|------|-----------|----------------------------|--------------------------|---------|---------|
| | | | | | 20N,120s | 30N,30s | 30N,60s |
| P(AM-HEMA5) | 7 | 1 | 843 | 8 | 42.25 | 40.49 | 43.24 |
| | | 5 | 1643 | 3 | 9.84 | 17.22 | 3.20 |
| P(AM-HEMA20) | 7 | 1 | 514 | 4 | 18.57 | 15.21 | 12.22 |
| | | 5 | 3995 | 7 | 21.05 | 32.91 | 23.66 |

The experimental tack results evidenced by figure 7 and table 3 show that, whatever is the applied force and the time contact in the probe test tack, :

- for the copolymer hydrogel with 5% mol in HEMA, W_{adh} values decreases with the increase of G' and the extent of inhomogeneities.
- for the copolymer hydrogel with 20% (mol) in HEMA, although there is an increase in G' the adhesion performances are enhanced with the decrease of the network inhomogeneities.

These results support our previous assumptions that the rheological properties and the network inhomogeneities would be among the factors that, acting together or oppositely, would govern the adhesion performances of P(AM-HEMA) hydrogels.

4. Conclusions

We have proposed an exhaustive study of the relationship between structure and rheological properties and their effect on adhesion performances of (acrylamide-co-hydroxyethyl methacrylate) P(AM-HEMA) hydrogels intended to be used as transdermal drug delivery system. We initially showed that the rheological properties of P(AM-HEMA) hydrogels are mainly dependent on the network architecture. Specifications of this architecture appear during the cross-linking polymerization process and strongly depend on the copolymerization of acrylamide (AM) with the (2-hydroxyethyl methacrylate) HEMA, and the precursory mixtures composition in these monomers and the cross-linking agent N,N'-methylene-bis-acrylamide. Thus, we have highlighted P(AM-HEMA) hydrogel elasticity dependence on their inhomogeneous structure resulting from the difference in reactivity of AM, HEMA and Bis monomers and the synthesis route. Moreover, we demonstrated that for a given AM concentration, the increase in the cross-linker Bis concentration gives rise to a PAM network

with enhanced elasticity but which on the other hand has more network defects. These deviations from ideality can be minimized by increasing the monomer concentration of the precursory mixture. The most important finding the rheological part of this study pointed out is that an ideal PAM network, *i.e.* with $(n_e/n_{e\ theo})$ tending to 1, could be obtained by copolymerizing AM with HEMA. The optimal synthesis condition for attaining the maximum elasticity and the suppression of PAM network inhomogeneities is a total monomers (AM and HEMA) concentration of 28% and a weight ratio of HEMA to AM in the feed ranging between 10-20%. The probe tack test carried out on PAM and P(AM-HEMA) hydrogels revealed, on one hand, that these materials exhibit a good balance of solid and liquid characteristics which confers them the properties of pressure-sensitive adhesives. On the other hand, the stress-strain curves and the adhesion work values showed the partial dependence of the adhesion performances of P(AM-HEM) hydrogels on their elasticity. Indeed, the correlation between the hydrogels tack behavior and their structural parameters evidenced that the hydrogel network inhomogeneities would constitute another factor that combined with the rheological properties would govern the hydrogel adhesion performances.

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