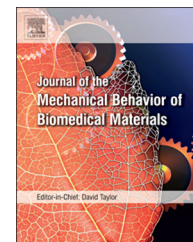


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Research Paper

Improving hydrogels' toughness by increasing the dissipative properties of their network



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ABSTRACT

The weak mechanical performance and fragility of hydrogels limit their application as biomaterials for load bearing applications. The origin of this weakness has been explained by the low resistance to chains breakage composing the hydrogel and to the cracks propagation in the hydrogel submitted to loading conditions. These low resistance and crack propagation were in turn related to an insufficient energy dissipation mechanism in the hydrogel structure. The goal of this study is to evaluate the dissipation mechanism in covalently bonded hydrogels so that tougher hydrogels can be developed while keeping for the hydrogel a relatively high mechanical stiffness. By varying parameters such as cross-linker type or concentration as well as water ratio, the dissipative properties of HEMA-based hydrogels were investigated at large deformations. Different mechanisms such as special friction-like phenomena, nanoporosity, and hydrophobicity were proposed to explain the dissipative behavior of the tested hydrogels. Based on this analysis, it was possible to develop hydrogels with increased toughness properties.

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1. Introduction

Hydrogel systems are widely used for different biomedical applications. They present however two major drawbacks from a mechanical point of view. First, they usually have a low degree of stiffness and second they show a brittle behavior. While the stiffness and rigidity of hydrogels can be controlled and increased by chemical cross-linking (Anseth et al., 1996; Hennink and van Nostrum, 2012), hydrogels have an inherently low toughness, which does not allow them to sustain large deformations (Sun et al., 2012; Abdurrahmanoglu et al., 2009). As large deformations are common in different musculoskeletal tissues, the use of hydrogels is limited in these tissues.

The poor mechanical performance and brittleness of hydrogels have been reported to originate from their very low resistance to crack propagation due to the lack of an efficient energy dissipation mechanism in the hydrogel structure (Sun et al., 2012; Abdurrahmanoglu et al., 2009). To increase hydrogel dissipative properties, modifications at the molecular level have been suggested including reversible interactions like hydrophobic bilayers in a hydrophilic polymer network (Haque et al., 2011), ionic cross-linking (Sun et al., 2012), and physical interactions instead of covalent cross-linking (Abdurrahmanoglu et al., 2009; Tuncaboylu et al., 2011). The obtained noncovalent cross-linked hydrogels usually present a high degree of toughness. However, the stiffness of noncovalent cross-linked hydrogels is significantly

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lower than covalent cross-linked ones (Sun et al., 2012; Haque et al., 2011; Naficy et al., 2011). Noncovalent cross-linked hydrogels can then not be used in load bearing biomedical applications, where a high degree of stiffness and toughness are simultaneously needed. So in this study we focus on covalently bonded hydrogels to develop tougher hydrogels while keeping for the hydrogel a relatively high mechanical stiffness.

Among different hydrogel systems being covalently cross-linked, Poly(2-hydroxyethyl methacrylate) (PHEMA) has received considerable attention as a biocompatible hydrogel with tunable mechanical properties (Voldrich et al., 1975; Lou et al., 2004; Young et al., 1998; Traian, 2001; Moghadam et al., 2014). HEMA monomers have a hydrophilic nature. The primary structure of homogeneous PHEMA hydrogel is a covalently linked three-dimensional network. In conjunction with this covalently bonded structure, PHEMA chains are held together by noncovalent forces in a secondary structure stabilized by hydrophobic bonding (Refojo, 1967). It has been reported that hydrophobic interactions can increase energy dissipation in hydrogels' network under loading by the reversible disengagements of the hydrophobes from the hydrophobic associations (Abdurrahmanoglu et al., 2009; Tuncaboylu et al., 2011). With these special properties, PHEMA hydrogels offer then the possibility to simultaneously increase their stiffness and toughness properties.

The mechanical properties, hydrophobicity, and pore size of HEMA-based hydrogels are tunable by controlling the type and the amount of cross-linkers as well as their water content (Baker et al., 2009; Peppas et al., 1985). In particular, these hydrogels can be produced with nanoscale pore size (Peppas et al., 1985). Nanopores provide a large pore surface area, which generates a unique nanofluidic behavior generating high friction between liquid and solid phase when the fluid flows through the nanopores (Surani et al., 2005; Zhao et al., 2009; Kong and Qiao, 2005).

Previous studies have investigated the effect of cross-linking density on PHEMA swelling, stiffness, and stress relaxation (Refojo, 1967; Baker et al., 2009; Peppas et al., 1985; Mabileau et al., 2006). These studies showed that the degree of stiffness increases with increasing cross-linker concentration and polymer to water ratio during polymerization (Janacek, 1973). Since dissipation is a measure of toughness (Haque et al., 2011), in the present study, we further evaluate the effect of cross-linker type or concentration as well as water ratio on the dissipative properties of PHEMA hydrogels. We also investigated how we can increase the toughness of fragile hydrophilic hydrogels by increasing their hydrophobicity via copolymerized with HEMA. Based on the obtained results, we develop hydrogels presenting high toughness properties while keeping high degree of stiffness allowing them to sustain large deformations.

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA, 97%) was purified by basic aluminum oxide column chromatography to remove inhibitor. 2,2-dimethoxy-2-phenylacetophenone (DPAP) (Irgacur-651, 99%) was used as photoinitiator and prepared as an

ethanolic solution of DPAP (57 mg/mL solution, each mL=0.2 mmol). Ethylene glycol dimethacrylate (EGDMA, 98%), poly(ethylene glycol dimethacrylate) (PEGDM) 550 and 750, triethylene glycol dimethacrylate (TEGDM), and poly(ethylene glycol methacrylate) (PEGM) 360 were purified with the same method as HEMA. All materials were purchased from Aldrich (Bucks, Switzerland) and were stored at 4 °C until use.

2.2. Hydrogel preparation

2.2.1. PHEMA hydrogels

PHEMA hydrogels were prepared with different PEGDM ($C_3H_5C(O)(OCH_2CH_2)_nOC(O)C_3H_5$) family cross-linkers (EGDMA, TEGDM, PEGDM 550 and 750) as well as with different concentrations of cross-linker (4% and 6% of mol HEMA). These cross-linkers are linear molecules differing with respect to their molecule length. EGDMA is the shortest molecule of the chosen cross-linkers with one ethylene glycol (OCH_2CH_2) functionalized with 2 methacrylate groups. PEGDM 750 is the longest one with 13 ethylene glycols (OCH_2CH_2). By using these cross-linkers, we can then evaluate the effect of cross-linker length on hydrogels dissipation. In parallel, the volumetric ratio of water was varied among 20%, 40%, and 50% of volume of mixture. The different combinations of parameters as well as the material volume ratio used in the preparation of the HEMA-based hydrogel are summarized in Table S1 (Supplementary material). Specifically for the EGDMA cross-linker, a wider range in concentration of this cross-linker (2%, 4%, and 6%) and water ratio (20%, 40%, 50%, 60%, and 70%) were evaluated. The mixture containing the photoinitiator DPAP (0.1% of mol HEMA) was stirred and sonicated for 1 min. It was then transferred to cylindrical wells (8 mm diameter and 4 mm depth), placed under a UV lamp (365 nm, 8 W) positioned 10 cm from the sample and irradiated for 15 min, whilst maintaining the temperature below 25 °C. Hydrogels were then carefully removed from the wells, washed to remove unreacted material, and immersed in water for one week before mechanical test. Four samples per group were prepared.

2.2.2. HEMA-PEGM hydrogels

To investigate how hydrophobic interactions affect the dissipation properties and toughness of fragile hydrophilic hydrogels, PHEMA hydrogels were copolymerized with poly(ethylene glycol methacrylate) (PEGM). PEGM hydrogel has been reported to be very hydrophilic and highly swellable in water (Lei et al., 2013). For this experiment, we used EGDMA as cross-linker and kept cross-linker ratio equal to 6% of total monomers molarity. Forty percent volumetric ratio of water was adjusted for all HEMA-PEGDM-EGDMA hydrogels. We prepared hydrogels with different molar ratios of HEMA and PEGM (6.5%, 12.5%, and 25% of mol of HEMA) as well as PEGM without HEMA. The polymerization process was similar as for the HEMA-based hydrogel.

2.3. Hydrogel mechanical characterization

To characterize elastic and viscoelastic behavior of hydrogels under compressive loading at large deformations, the total input energy and dissipated energy were chosen as measures. These measures, unlike elastic and lost moduli, are valid to quantify material properties at large deformations and in nonlinear

regime (Lakes, 1999). We also introduced the damping ratio as the ratio of dissipated work to total input work that the material received during deformation. This ratio represents the viscous behavior of the material over its elastic behavior (Vogel and Pioletti, 2012).

2.3.1. Dissipation measurement

The dissipation of PHEMA hydrogels was obtained by integrating the hysteresis force–deformation loop appearing during sinusoidal compressions of the hydrogel (Lakes, 1999; Li and Xu, 2007). The dissipation was normalized to the volume of the sample. The sinusoidal compression was applied on each sample with an Instron E3000 linear mechanical testing machine (Norwood, MA, USA). During the test, samples were immersed in water. A 10% pre-strain was imposed on the sample followed by a sinusoidal 15% compressive strain at 1 Hz for 100 cycles. The dissipation was measured on the last 10 cycles and averaged.

2.3.2. Damping ratio measurement

To further compare the dissipative properties of different hydrogels, the damping ratio is a useful variable as it quantifies the capacity of a material in dissipating the input work, which is the total energy given to material during loading and unloading. A metric valid in case of large deformations and then relevant for hydrogel characterization is the damping ratio (ψ), which normalizes the dissipation over total input work (Vogel and Pioletti, 2012)

$$\psi = \Delta W / W \quad (1)$$

where ΔW is the energy loss per cycle or hysteresis and W is the total input work during the mechanical loading. Input work is calculated by integrating the surface under the force–deformation curve during mechanical loading. Since the amount of input work is proportional to the material stiffness, the input work is considered as a measure of material stiffness. The damping ratio normalizes the dissipation over the material stiffness. Material with higher damping ratios presents higher viscous properties compared to material with the same stiffness but lower damping ratios (Lakes, 1999; Vogel, 2011).

3. Results

Fig. 1 shows the typical hysteresis loop of hydrogels with different cross-linker types. As it can be qualitatively observed from Fig. 1, the area of the hysteresis loop reduces with the increase of the cross-linker chain length. By keeping the cross-linker concentration and the deformation magnitude fixed in all tests, it can also be seen in Fig. 1 that the maximum reached force and the amount of input work (the gray area) for the samples cross-linked with TEGDM, PEGDM550 and PEGDM750 do not significantly change between different tested samples. This result suggests that increasing cross-linker length has not an effect on the hydrogels' stiffness as significant as on their dissipative properties. As can be observed on the same Figure, hydrogels cross-linked with EGDMA had a 40% increase in the maximum force. Correspondingly, these hydrogels receive more input work. Furthermore, their hysteresis loop is much wider

than the other three cases. This suggests that EGDMA highly increases the stiffness and dissipation of the hydrogels.

3.1. Effect of cross-linker

From a quantitative point of view, the dependency of dissipation and damping ratio of HEMA hydrogels to the type and the concentration of cross-linkers as well as to its water ratio are reported in Figs. 2 and 3. In particular, we can observe from Fig. 2 that increasing PEGDM cross-linker molecule length decreases dissipation. EGDMA induces the highest dissipation and PEGDM 750 the lowest one. Also for all types of developed hydrogels, increasing cross-linker concentration increases dissipation magnitude, but on the other hand it slightly decreases the damping ratio ψ (Fig. 3). Since the damping ratio represents the damping properties of materials over its elastic behavior, this decrease confirms that increasing the cross-linker concentration increases the elastic properties of hydrogel more than its viscous properties as it is generally reported.

As EGDMA cross-linker induced the highest dissipation between all tested cross-linker, we further characterized its performance. From Fig. 4 we can observe that even at the lowest cross-linker concentration used, the damping ratio of HEMA–EGDMA remains high (0.72 ± 0.3). Therefore, under high loads and large deformations, HEMA–EGDMA hydrogels damp most part of the input work.

3.2. Effect of water ratio

Fig. 2 shows that increasing water ratio during polymerization decreases the amount of dissipation. On the other hand, the damping ratio seems not to be sensitive to water concentration (Fig. 3). The low sensitivity of the damping ratio on water content suggests that the input work also decreases by increasing water ratio meaning that the hydrogel becomes softer while keeping its dissipative properties. However for EGDMA cross-linker with the water ratio above 60%, the damping ratio also decreases (Fig. 4B).

3.3. Effect of hydrophobicity

To further confirm the effect of increasing hydrophobicity on the toughness of hydrophilic hydrogels, we studied the effect of adding PHEMA chains to the backbone of highly hydrophilic PEGM hydrogels. In particular, Fig. 5 shows the effect of adding HEMA on the dissipation of PEGM hydrogels. Having PEGM, even at a low concentration (7.5%), decreased the dissipative properties of hydrogels (Fig. 5A). On the other hand, the swelling of the hydrogels increased (Fig. 6A). Decreasing the damping ratio by increasing PEGM concentration in hydrogel network shows that hydrophilic polymers like PEGM increases the elastic properties of hydrogels. PEGM hydrogels were not resistant to large deformations when the percentage of PEGM increased. In some cases after mechanical tests (1 Hz, 1000 cycles of 15% deformation), several cracks were visually apparent (Fig. 6B). Hydrogels made of PEGM without HEMA were very fragile. They highly swelled in water but could not resist large deformation (Fig. 6).

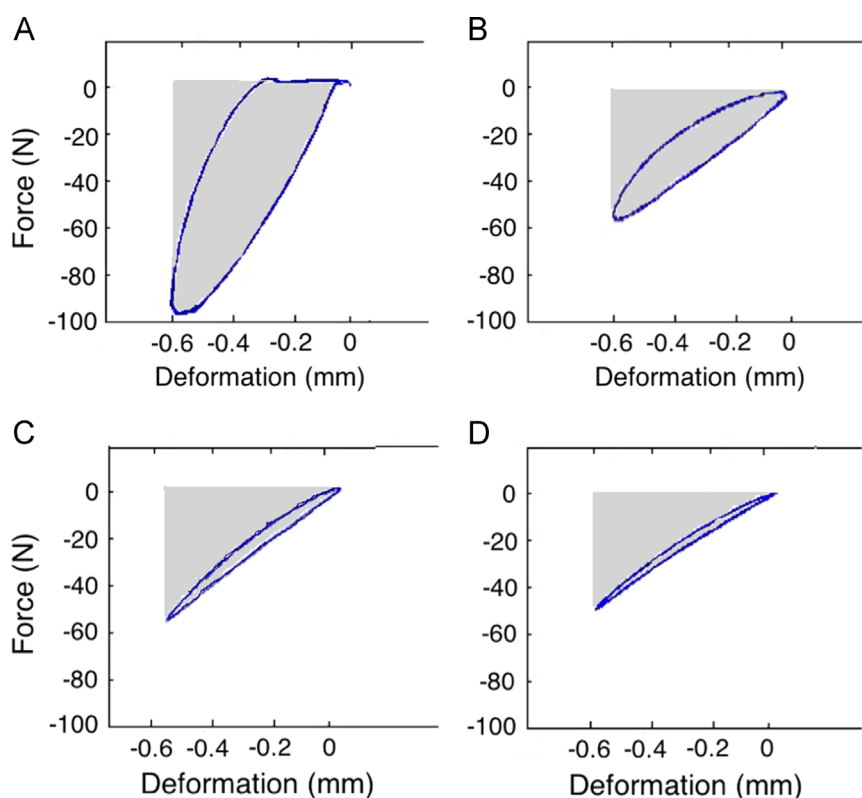


Fig. 1 – Hysteresis loop of HEMA hydrogels and input work (gray area) obtained with different types of cross-linker at 6% and water at 40% (A: HEMA-EGDMA (Supplementary Table 1), B: HEMA-TEGDM (S14), C: HEMA-PEGDM550 (S15), D: PEGDM750 (S16)).

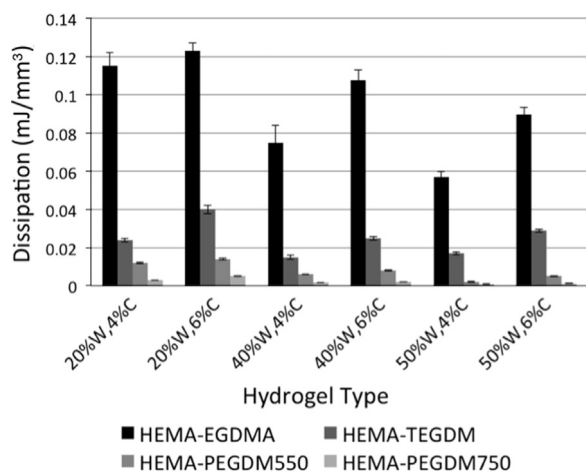


Fig. 2 – Dissipation of HEMA hydrogels: effect of cross-linker type and amount as well as water ratio (W: water, C: cross-linker).

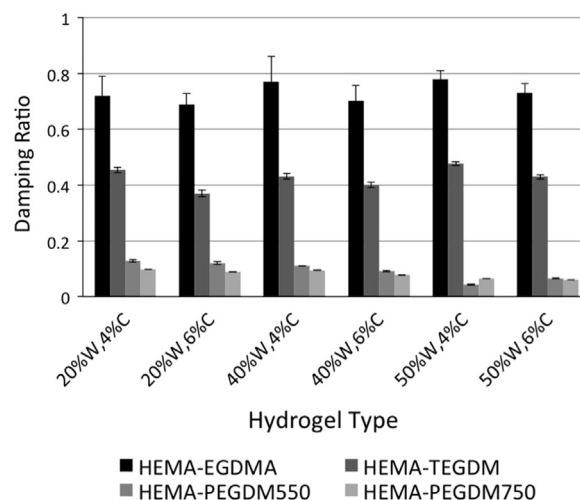


Fig. 3 – Damping ratio (ψ) of hydrogels: effect of cross-linker type and amount as well as water ratio (W: water, C: cross-linker).

4. Discussion

Controlling polymerization conditions can improve the stiffness and rigidity of hydrogels. However, just having a high degree of stiffness is not enough for a biomaterial to be used in load bearing application. The material needs to have enough toughness not to fracture and be destroyed under cyclic load especially at large deformations. To increase toughness of the hydrogel, its dissipative properties should be increased. Our

results showed that due to the special structure of HEMA hydrogels, changing cross-linking molecular length and ratio and water ratio could tune their dissipation properties. Due to this dissipation, the stored energy in hydrogel network is then limited reducing the possibility to reach the crack tip energy of these hydrogels. We showed that using short length cross-linkers like EGDMA results in much higher dissipation when we use the same amount of cross-linker. Since for all of cross-linkers that we used in this study, several studies have already

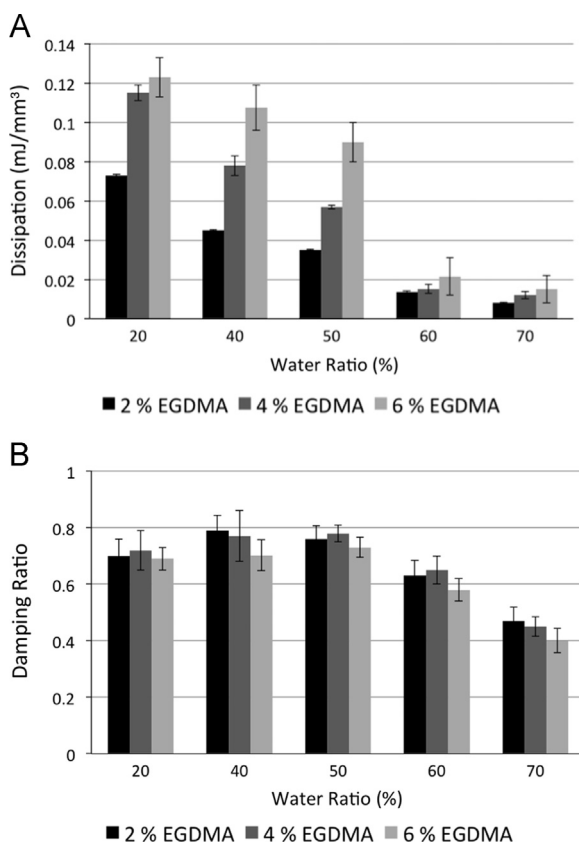


Fig. 4 – HEMA-EGDMA hydrogels: effect of water ratio and cross-linker percentage on A: dissipation and B: damping ratio (ψ).

shown a high monomer conversion with UV polymerization (Baker et al., 2009; Dziubla et al., 2001; Li and Lee, 2005), the sol and gel fraction cannot be the reason for such a high dissipation difference among these hydrogels. A possible explanation for such high dissipative behavior may reside in the conjunction of two specific properties related to solid–fluid interactions in the developed HEMA-EGDMA hydrogels. The first specific property is related to the nanoporous structure of these hydrogels. The average pore size of HEMA-EGDMA hydrogels was quantified to be less than 5 nm (Table S2 (Supplementary material)). This porosity was the result of using very short molecules like EGDMA as cross-linker. Because of the very large pore surface area of nanoporous materials, high friction can be produced when fluids move through the nanopores as it has been previously reported (Kong and Qiao, 2005). The second specific property is related to the increase of the PHEMA hydrogel hydrophobicity, which has been reported to be induced by EGDMA (Peppas et al., 1985). Indeed, it has been shown that having hydrophobic properties along with nanoporous structure induces a special interaction between hydrogels chains and water composing the hydrogel that can highly increase the dissipation (Surani et al., 2005; Zhao et al., 2009; Kong and Qiao, 2005). For such a material immersed in water or in a nonwetting liquid, previous published studies showed that when external mechanical pressure exceeds a critical threshold, the liquid can be forced to defiltrate or infiltrated the hydrophobic nanopores (Surani et al., 2005; Zhao et al., 2009; Kong and Qiao, 2005). In other words, there will be a defiltration

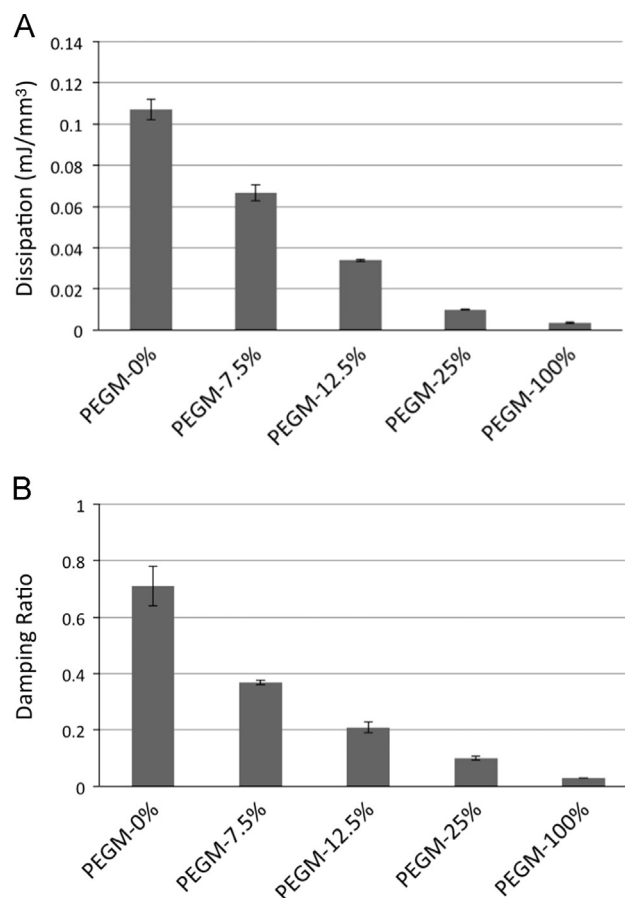


Fig. 5 – Effect of adding hydrophilic elements in hydrogels structure. A: effect on dissipation and B: effect on damping ratio (ψ).

(drainage) and infiltration pressure during loading and unloading that increase interfacial energy. In this situation, the forced in and out motion of the liquid molecules will increase the energy dissipation via friction-like interaction between solid and liquid phases (Surani et al., 2005; Zhao et al., 2009; Kong and Qiao, 2005).

Beside the two specific properties related to solid–fluid interactions, the high dissipation of HEMA-EGDMA hydrogels could also be related to the sub-molecular structure of these hydrogels. Depending on the length of the cross-linker molecules, an interaction could be induced between HEMA pendant groups in hydrogel network. As Fig. 7 shows in PHEMA chains structure, there are some pendant groups (Hydroxyethyl groups) dangling from each HEMA unit. These pendant groups make a comb-shape structure connecting with cross-linker molecules. Since the length of these pendant groups is as short as one ethylene glycol, as in EGDMA (Fig. 7A), using EGDMA as cross-linker lets pendant groups (the teeth of comb-shape structures) to be close enough to touch each other and interact when the material deforms during cyclic load. These interactions might produce a local friction that would then also dissipate energy. When longer cross-linkers are used, it is less likely to obtain these interactions (Fig. 7B and C). Despite it is clear that polymer chain does not behave as a rigid beam, but is floppy and flexible, because of the particular structure of HEMA-EGDMA hydrogels, the possibility of friction between

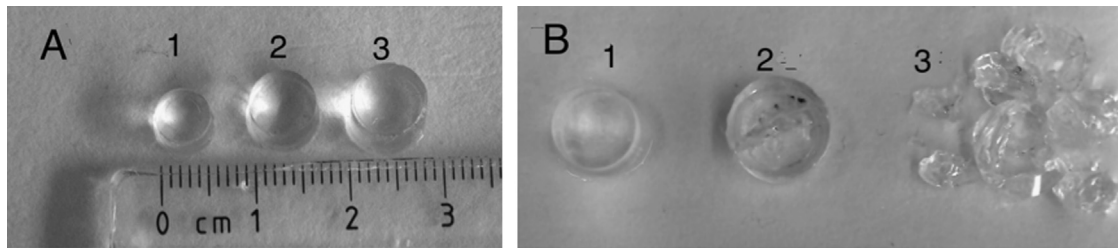


Fig. 6 – HEMA-PEGM hydrogels. A: hydrogel after swelling: 1 HEMA, 2 HEMA+25% PEGM, 3 PEGM. B: hydrogel after applying 1000 cyclic deformations (1 Hz, 15% deformation amplitude).

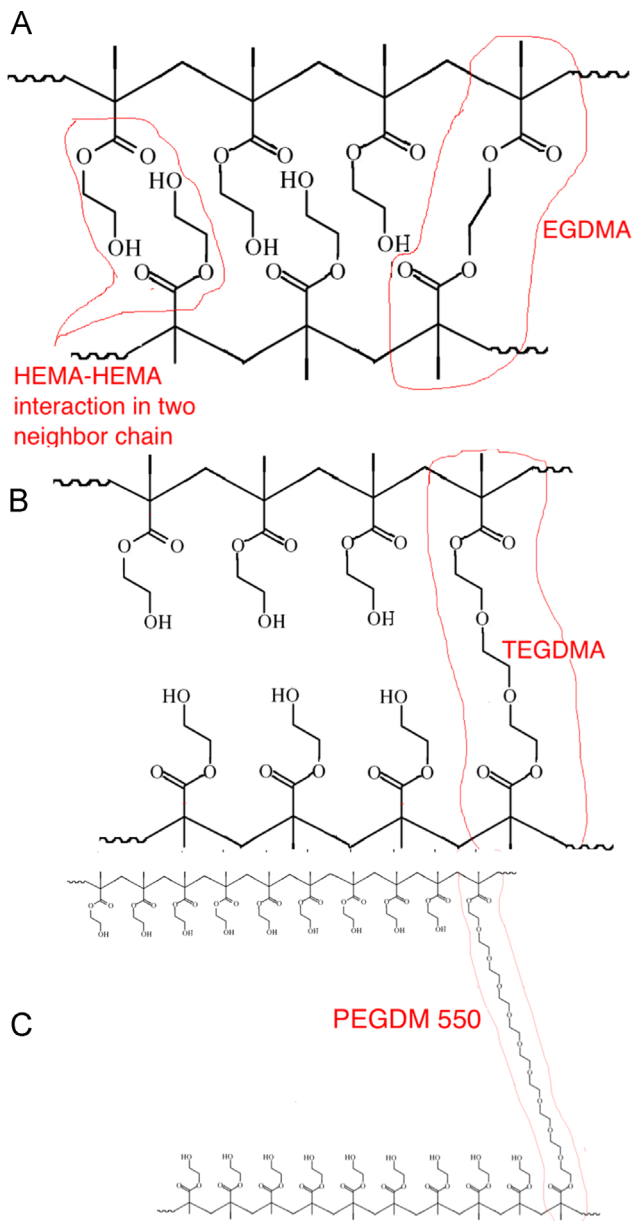


Fig. 7 – Structure of HEMA hydrogel cross-linked with A: EGDMA, B: TEGDM and C: PEGDM 550. Due to the short length of EGDMA, we propose that dissipation due to friction of the pendant groups of two neighbor HEMA chains is increased while the long molecules of TEGDM or PEGDM prevent such an interaction.

chains is more probable comparing to other linear hydrogels without this comb-shape structure. Changing the magnitude of EGDMA cross-linker allows us to tune the stiffness of these hydrogels without affecting their high dissipative properties. With these particular properties, HEMA-EGDMA hydrogels can be considered as tough hydrogels with tunable stiffness.

Beside cross-linker, water ratio of HEMA hydrogels during polymerization has a considerable effect on their mechanical properties. Based on our results, water ratio can regulate the stiffness of hydrogels but does not have a significant effect on damping properties. This property suggests that with controlling water ratio, we can have hydrogels with wide range of stiffness and high toughness. However, very high water ratio (more than 60%) decreases the damping properties as well. This behavior was expected since it has been reported that in PHEMA hydrogels when the water ratio is high (more than 60%), the network becomes microporous (Baker et al., 2009). We propose that having such a highly porous structure may decrease the solid-fluid surface and consequently the corresponding friction due to nanoporous liquid-solid interactions. Moreover, when water ratio increases, more water molecules are trapped in the hydrogel network during polymerization and may weaken the hydrophobic interactions (Refojo, 1967; Baker et al., 2009).

Furthermore, we showed that copolymerizing HEMA hydrogels with brittle and mechanically poor hydrophilic hydrogel networks improved the toughness and mechanical properties of those hydrogels. Hydrophilic materials show a spring-like behavior due to its high tendency to keep the water molecules (Surani et al., 2005; Zhao et al., 2009; Kong and Qiao, 2005). Under loading the friction like behavior related to water flow discussed earlier is less likely to happen to dissipate the input work. In such a situation if we apply high forces, the energy stored in the material during loading can reach the crack tip energy, resulting to the fracture of the material (Abdurrahmanoglu et al., 2009). These observations confirm the positive effect of hydrophobicity to increase hydrogel toughness.

5. Conclusion

The present study focused on characterizing dissipative properties of HEMA-based hydrogels. Since the dissipation is a measure of toughness, such a study led us to understand the origin of the toughness of these hydrogels. Based on the obtained results, hydrogels formulation presenting high

dissipation and toughness could be proposed for load bearing applications. We showed that the dissipative properties of HEMA-based hydrogels significantly increase when they are cross-linked with short-length molecules like EGDMA. We related such a high dissipation to special friction-like phenomena, to the hydrogel nanoporosity and to the hydrophobicity, which can be obtained when EGDMA is used as cross-linker.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jmbbm.2014.10.010>.

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