Asymmetric Bihomologous Crosslinkers for Bicomponent Gels—The Way to Strongly Increased Elastic Moduli

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ABSTRACT: 2-Hydroxyethylmethacrylate (HEMA) and acrylamide (AA) have been copolymerized via free radical mechanism, in the presence of 5 mol % of four different crosslinker systems, the symmetric ethylenglycoldimethacrylate (EGDMA), bisacrylamide (BIS), a mixture of EGDMA and BIS, and the asymmetric acrylamideethylenmethacrylate (METAA). The polymerizations have been monitored with a rheometer, exhibiting the gel obtained with the asymmetric METAA, an elastic modulus that is dramatically increased compared with those of the gels prepared with the other three crosslinker systems. A kinetic analysis using the terminal model has been used to build probabilistic surfaces that give information about how the crosslinker is incorporated into the network. This analysis shows a high dissimilarity between the reactions using the asymmetric and the mixture of symmetric crosslinkers, what has been correlated to the difference in modulus. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 896–900, 2010

Key words: bicomponent networks; copolymerization; crosslinking; reactivity

INTRODUCTION

A hydrogel is a class of polymeric material that has the ability to hold substantial amount of water, showing soft and rubbery-like consistency, low interfacial tension, and physical properties similar to those of living tissues. Hydrogels have therefore attracted much interest in the past as excellent biomaterials.[1] Among many important hydrogels, polyHEMA(2-hydroxyethyl methacrylate) was the first one successfully employed for biological use.[2] PolyHEMA hydrogels are versatile for many applications and have been employed, for example, in the postsurgical reconstruction of female breasts,[3] nasal cartilages,[4] artificial corneas,[5] wound dressings in the control of wound infection,[6] as artificial skin,[7] soft lenses,[8] as scaffolds for regeneration of soft tissues, e.g., nerve tissue[9] or controlled release of anticancer and other drugs.[10,11] However, the main disadvantage in utilization of hydrogels based on polymers and copolymers from HEMA is its poor mechanical properties after swelling. These poor mechanical properties have their origin in the different type of heterogeneities introduced in the system during chain and network formation.

It is well known that radical copolymerization of comonomers with different reactivities leads to compositional heterogeneity.[12] If one crosslinks these copolymers to prepare bicomponent networks, additionally to the compositional heterogeneity of the copolymers, there will be a second level of heterogeneity of the final system that is related to the crosslinking density and depends on the crosslinker used. This has been described for other networks and functionalities similar to those described in this work—methacrylates/acrylamides.[13] Taking as example the one used here, that is the free radical copolymerization of equimolar HEMA and acrylamide (AA), it has been described that HEMA is more reactive than AA[14] (assuming the terminal model, reactivity ratios of r_{HEMA}= 1.89 and r_{AA}= 0.05 or r_{HEMA}= 0.98 and r_{AA}= 0.14 can be found in literature[14]). This fact makes this reaction to be compositionally heterogeneous since there is a continuous compositional drift along the conversion. At the beginning of the reaction, HEMA is preferentially consumed while AA is incorporated preferentially at high conversions. If one wishes to crosslink these copolymers to prepare bicomponent networks, the first choices will be the standards EGDMA or BIS, being the crosslinker functionalities homologous just to one of the comonomers (mono-homologous toward HEMA or AA if EGDMA or BIS are chosen, respectively). That means that additionally to the mentioned compositional heterogeneity of the copolymers, there will be a further heterogeneity of the final system, which is due to the use of the

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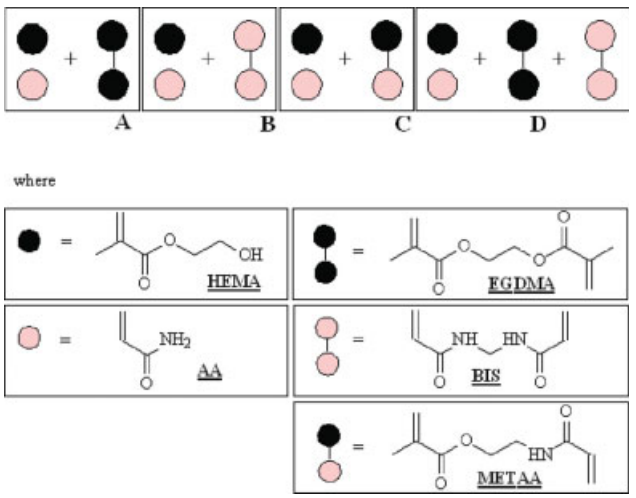


Figure 1 Schematic design of the studied crosslinking processes of the HEMA-AA copolymers. A and B are the reactions carried out with the symmetric monohomologous EGDMA and BIS respectively. C is the one with the asymmetric bihomologous METAA, and D refers to the process using a mixture of EGDMA and BIS. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

crosslinker. If only EGDMA is used, the statistical incorporation of HEMA (which is higher at the beginning of the reaction) will be overlapped with a statistical incorporation of EGDMA leading to a higher crosslinking degree at low conversions, while the copolymer fractions richer in AA formed at higher conversions will be less crosslinked. If only BIS is chosen, we are in the "mirror" situation to the first case: the statistical incorporation of AA (higher at high conversions) will be overlapped with a statistical incorporation of BIS, which means a higher crosslinking in the final steps, while in the HEMA-richer fraction the crosslinking will be lower.

To study the influence of this type of heterogeneity on the mechanical properties of the final gel, we have compared the gelation process of gels prepared from a HEMA/AA comonomer mixture using four different crosslinking systems: (a) the symmetric EGDMA whose polymerizable groups correspond to HEMA, (b) the symmetric BIS whose polymerizable groups corresponds to AA, and (c) the asymmetric bihomologous acrylamideethylenmethacrylate (METAA) exhibiting polymerizable groups that correspond to HEMA on one end and to AA at the other (see Figure 1, reactions A–C). A fourth system using a mixture of the symmetric EGDMA and BIS has also been studied for comparative purposes (D in the figure). The free radical copolymerizations—the curing processes—have been monitored by performing rheological measurements. Besides, a kinetic analysis of the incorporation of the different crosslinkers has been carried out.

EXPERIMENTAL

Reagents

HEMA, EGDMA, AA, BIS, vitamin C, sodium persulfate, 2-aminoethanol hydrochloride, methacryloyl chloride, acryloyl chloride, triethylamine, and solvents used in this work were purchased from Aldrich and used without further purification.

Synthesis of METAA

METAA was obtained in a two-step synthesis. In the first step, 0.2 mol of 2-aminoethanol hydrochloride were suspended in 200 mL acetonitrile. 200 mg of hydrochinone as inhibitor and 0.2 mol of methacryloyl chloride were added, and the mixture was heated to reflux for three hours. On cooling, a white precipitate (nonreacted 2-aminoethanol) was formed and eliminated by filtration. The filtrate was dried under reduced pressure and used without further purification for the second step (yield: 45%). It was suspended in 300 mL of chloroform and cooled to 0°C. Under a stream of N_2, the equimolar amount of acryloyl chloride and the double molar amount of triethylamine were added. The reaction mixture was allowed to warm up to room temperature. After 3 h, the organic phase was washed three times with water, dried with $MgSO_4$, and the solvent stripped off. Purification of the raw product was carried out by column chromatography using silica gel and CH_2Cl_2 as the eluent. Yield: 91%

1H-n.m.r. ($CDCl_3$): $\delta = 1.3$ (s, 3H), $\delta = 3.8$ (t, 2 H), $\delta = 4.2$ (t, 2 H), $\delta = 5.5$–6.2 (m, 5 H).

Polymerization and monitoring with the rheometer

Equimolar amounts of HEMA and AA were dissolved in 1 mL ethanol (260 and 142 mg respectively, total monomer concentration 2 M). Then, 5% crosslinker (molar percentage based on total monomer concentration) was added to the monomer mixture. Two percent initiators (molar percentage, based on total monomer concentration) were used. First, vitamin C was added directly to the mixture, but sodium persulfate was weighted in a separate vial and freshly dissolved in 1 mL water. The persulfate solution was added to the master batch right after addition and dissolving of vitamin C. A 400 μL solution was dispersed onto the bottom part of the parallel plate of the rheometer. The parallel plate was covered with silicon oil to avoid evaporation.

The dynamic rheological data[15] were obtained with a TA ARG2 rheometer at 23°C, using a parallel plate system (25 mm diameter) at a gap of 600 μm. Preliminary strain and frequency sweeps were performed to choose the final conditions. One percent strain and 1 rad/s were finally chosen, being the

data in the linear viscoelastic region. TA rheometer Data Analysis software was used to obtain the experimental data and to calculate storage (or elastic) modulus (G'), loss (viscous) modulus (G''), and complex viscosity (η^*). The rheological measurements were conducted twice. Results reported were an average of both measurements.

Kinetic analysis of the crosslinking: Building of probabilistic surfaces

We have carried out a kinetic analysis of reaction probabilities of both methacrylate and acrylamide functionalities (called M and A, respectively), using as starting point the terminal model. Assuming an identical reactivity for all the homologous functionalities, and being n_{M0} and n_{M1} the numbers of M functionalities at time 0 and t_1, respectively, the probability of a given M functionality of participating at time t_1 in the reaction is given by the probability of being unreacted at that time multiplied by the probability of participating:

$$p_{M1} = p_{\text{unreacted at } t_1} p_{\text{participating at } t_1} = \frac{n_{M1}}{n_{M_0}} \frac{f_{M\text{inst copol}}}{n_{M1}} = \frac{f_{M\text{inst copol}}}{n_{M0}} = \frac{f_{M1}}{n_{M0}} \quad (1)$$

Being $f_{M\text{inst copol}}$ the instantaneous molar fraction M in the copolymer. The probability is therefore proportional to the instantaneous M copolymer molar fraction at time t_1. We may describe a similar probability for the acrylamide functionalities. If we focus on a crosslinker molecule with double methacrylic functionality (EGDMA) and with a molar methacrylic percentage MP_M with respect to the total methacrylics, the conditional probability of the two functionalities $M1$ and $M2$ of a given crosslinker to participating at times $t1$ and $t2$ respectively is:

$$p_{M1M2} = p_{M1} p_{M2} = \frac{f_{M1} MP_M f_{M_2} MP_M}{n_{M0}^2} \propto f_{M1} f_{M2} \quad (2)$$

that is, proportional to the product of instantaneous M copolymer fractions at time $t1$ and $t2$ (which corresponds to conversions $c1$ and $c2$).

If a mixture of EGDMA and BIS crosslinkers is used, the conditional probability of the two general functionalities $E1$ and $E2$ (being EM or A) participating at times $t1$ and $t2$ is:

$$p_{E1E2} = p_{M1} p_{M2} + p_{A1} p_{A2} = \frac{f_{M1} MP_M f_{M2} MP_M}{n_{M0}^2} + \frac{f_{A1} MP_A f_{A2} MP_A}{n_{A0}^2} \propto f_{M1} f_{M2} + f_{M1} f_{M2} \quad (3)$$

Since we are performing equimolar reactions and $MP_M = MP_A$, this probability is proportional to $f_{M1} f_{M2} + f_{A1} f_{A2}$

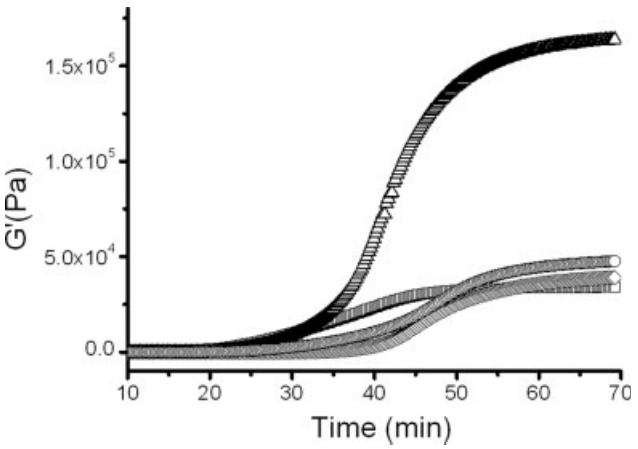


Figure 2 Elastic modulus G' of the reaction medium versus crosslinking time for four different crosslinkers (□: EGDMA, ◇: BIS, △: METAA, ○: EGDMA+BIS).

When using the asymmetric METAA crosslinker:

$$p_{E1E2} = p_{M1} p_{A2} = \frac{f_{M1} MP_M f_{A2} MP_A}{n_0^2} \propto f_{M1} f_{M2} \quad (4)$$

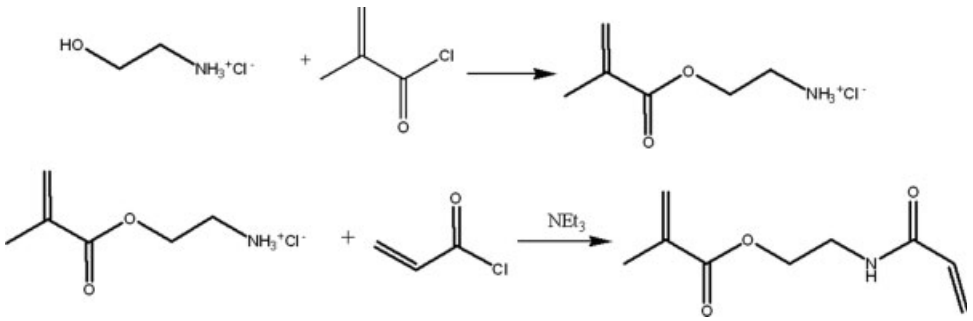
With the products of the instantaneous molar fractions of eqs. (3) and (4), we can build therefore probabilistic surfaces of p_{E1E2} versus $c1$ and $c2$ like those represented in Figure 3 for the copolymerizations carried out using METAA or a mixture of EGDMA and BIS. The instantaneous molar fractions are given by the terminal model

$$f_{M1} = 1 - f_{A1} = \frac{r_M F_{M_1}^2 + F_{M1}(1 - F_{M1})}{r_M F_{M1}^2 + 2F_{M1}(1 - F_{M1}) + r_A (1 - F_{M1})^2} \quad (5)$$

using as reactivity ratios $r_M = 1.89$ and $r_A = 0.05$, according to literature data.[14]

RESULTS AND DISCUSSION

The asymmetric acrylamide-ethylenemethacrylate, METAA, containing simultaneously methacrylate and acrylamide functionalities (see Fig. 1), has been synthesized according to the description given in the experimental part. This compound had been prepared previously by an alternative route.[16] However, the synthetic path we present here gives higher yields and a higher degree of purifty. One starts with 2-aminoethanol hydrochloride where the amino group is strongly deactivated and allows the selective reaction of the alcohol with methacryloyl chloride. In the second step, the hydrochloride protecting group is eliminated by a base (triethylamine). The free amine can then be reacted with acryloyl



Scheme 1 Synthetic route to the asymmetric crosslinker METAA.

chloride to give the desired end product in good yield. The reaction is depicted in Scheme 1.

In Figure 1, the four polymerizations are depicted schematically. Assuming the same reactivities for the different methacrylic units in HEMA, EGDMA, and METAA and for the different acrylamide units ins AA, BIS, and METAA, the symmetric crosslinkers are homologous to just one of the comonomers—EGDMA to HEMA and BIS to AA—while the asymmetric METAA is bihomologous. To analyze the influence of the different crosslinkers, we have monitored the polymerization and formation of the four network types by rheological measurements, starting from the same number of functional groups and varying the crosslinker nature (1-EGDMA, 2-BIS, 3-(EGDMA and BIS), 4- METAA). Basically, we have carried out four equimolar reactions of HEMA and AA using a 5% molar amount of the crosslinkers. In Figure 2, the elastic modulus of the reaction medium is represented versus time. G' exhibits the typical curing variation of a gelification process, from a liquid solution to a swollen network. Comparing the four systems, there is a very high increase of G' when using the asymmetric molecule compared with the symmetric EGDMA or BIS, these two showing both similar modulus. Using the mixture of EGDMA and BIS slightly increases the elastic modulus compared with the individual symmetric crosslinkers but is far away from the result observed for the asymmetric METAA.

Also, the qualitative analysis of the gelification timing is coherent with the crosslinker reactivities. Because of its lower reactivity, the reaction with BIS exhibits a delay of about 15 min related to the crosslinking with EGDMA. The METAA shows an intermediate behavior, starting to cure with EGDMA and finishing with BIS. The mixture of EGDMA and BIS starts before BIS and finishes at the same time.

The strong increase in G' when using the asymmetric crosslinker has been initially related to the superior network characteristics achieved because of the bihomologous nature of METAA. For an equimolar reaction like this one, using an asymmetric bihomologous crosslinker avoids the earlier described crosslinking heterogeneity that is unavoidable when using symmetric monohomologous crosslinker. While the EGDMA or BIS efficiently crosslink the network fraction rich in the homologous comonomer (HEMA or AA, respectively), the asymmetric METAA lead to a globally efficiently crosslinking.

In Figure 2 is also shown the rheological behavior of the reaction where a mixture of EGDMA and BIS (total molar concentration identical to the other three reactions) is used. The result is very interesting, because this mixture of EGDMA and BIS, which in principle should lead to a more homogeneous network compared with those obtained with each of the individual symmetric crosslinkers, slightly increases G' being its values, however, far away from the result using the asymmetric compound. It seems that combining simultaneously the network efficiency on the two fractions—the rich ones in HEMA and in AA—using the mixture of the two symmetric, does not change much the network performance in terms of G'. However, the use of METAA does.

To analyze this more deeply, a kinetic analysis of the crosslinker incorporation has been carried out, and the probabilistic surfaces of Figure 3 have been

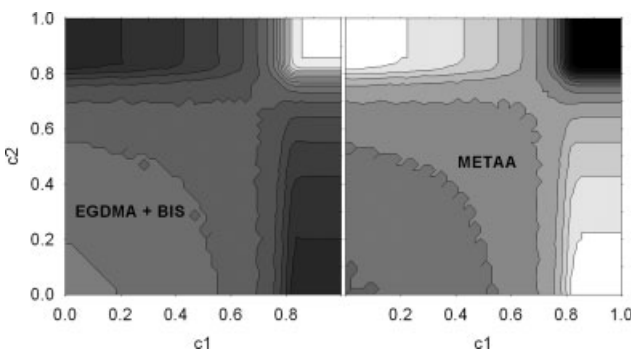


Figure 3 Conditional probabilities p_{E1E2} of the two functionalities ($E1$ and $E2$) of any crosslinker molecule participating at conversions $c1$ and $c2$ (X and Y axis, respectively) for the reactions where symmetric EGDMA and BIS (left) or the asymmetric METAA (right) are used. (□: maximum crosslinking probability; ■: zero crosslinking probability).

obtained (see "Experimental" section). In this Figure, the surfaces for the mixture of symmetric EGDMA and BIS (left-hand side) and for the asymmetric METAA (right-hand side) are depicted. In each graph, the *Y*- and *X*-axis are related to the incorporation of the two functionalities of a given crosslinker molecule. We can see that both reactions are completely different. The highest probabilities are located in opposite corners. When using the mixture of symmetric crosslinkers, the lightest region correspond to the incorporation of both functionalities at high conversion, that is, the preferential incorporation of BIS in acrylamide-rich chains formed in the last stages of the reaction. The next lightest area is the low conversion–low conversion corner, which correspond to the preferential incorporation of EGDMA in HEMA-rich chains. When using the asymmetric METAA, we are in a totally different scenario: the lightest regions are the low conversion–high conversion regions, which is related to the preferential incorporation of the methacrylic functionalities at low conversions (HEMA-rich chains) and the preferential incorporation of the acrylamide functionalities at high conversion (AA-rich chains). In other words, using a mixture of symmetric crosslinking systems tends to an interpenetrated network (IPN) topology while using asymmetric METAA tends to a conetwork structure.

CONCLUSIONS

In this work, it is shown that using an asymmetric bihomologous crosslinker (METAA) leads—in terms of elastic modulus—to superior networks in bi-component systems of equimolar HEMA and AA when compared with the use of symmetric monohomologous crosslinkers (EGDMA or/and BIS). The reactivity parameters of HEMA and AA differ considerably from each other. It is therefore understandable that the structures obtained by crosslinking the monomer mixture with EGDMA, BIS, or EGDMA + BIS on the one hand and with METAA, on the other hand, leads to the high differences in modulus shown here. We propose that the asymmetric METAA leads to a completely different network not only in terms of crosslinking density but also in topology. A probabilistic kinetic analysis has shown that using asymmetric METAA tends to the formation of a conetwork, while using the mixture of symmetric EGDMA and BIS tends to an IPN formation.

This new approach for the preparation of hydrogels with largely improved mechanical stability by the selection of an appropriate crosslinker can be expected to have a strong impact in the field of new and improved biomaterials.

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