Research Article

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Novel hydrogels based on a high-molar-mass water-soluble dimethacrylate monomer

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Abstract

This report describes the preparation and swelling behaviour of novel hydrogels based on a water-soluble dimethacrylate monomer (EBisEMA), which is characterized by a relatively high molar mass ($M_n \sim 1700$ g mol^{-1}) and contains a high proportion of aliphatic ether bonds in its structure. This feature results in moderately crosslinked and flexible polymer networks. Significant differences were observed in degree of swelling, depending on the synthesis method employed to obtain the hydrogels. The equilibrium water sorption of EBisEMA photopolymerized in bulk was 68 wt% while that of EBisEMA photopolymerized in aqueous solution (0.5 g mL^{-1}) was 104 wt%. Thiol–methacrylate hydrogels were prepared by visible light photopolymerization of EBisEMA with a tetrafunctional thiol (PETMP) at various EBisEMA-to-PETMP molar ratios. These hydrogels contained unreacted thiol groups because of a faster homopolymerization reaction of EBisEMA. Hydrogels were also prepared in bulk by propylamine-catalysed Michael addition reaction. No significant differences in swelling were observed between EBisEMA homopolymer and photocured EBisEMA–PETMP copolymer. Conversely, a marked increase in water uptake (110 wt%) was observed in the EBisEMA–PETMP hydrogels prepared by the Michael addition reaction catalysed by propylamine. These trends are explained in terms of a balance between the mass fraction of hydrophilic groups and the crosslinking density of the network. EBisEMA–PETMP hydrogels formulated with thiol in excess showed a noticeable tendency to adhere to diverse substrates, including paper, metals, glass and skin. This feature makes them especially attractive in applications for which adhesion is particularly critical such as dermatological patches.

Keywords: hydrogel; methacrylate; thiol; photopolymerization

INTRODUCTION

Hydrogels and their response to external environments have attracted much academic and industrial interest because of the potential for many applications including tissue engineering, drug delivery, soft contact lenses and wound dressings.[1] A wide range of natural and synthetic polymers have been used to fabricate hydrogels and innovative formulations are continually being developed in order to fulfil the needs of each particular application. The interest in new formulations of hydrogels is revealed by the considerable number of both papers and patents published by academic research institutions and industrial organizations every year.[2] Although many natural polymers are used to produce hydrogels, the versatility offered by synthetic polymers has increased markedly their practical utility.[3] Mono- and multifunctional (meth)acrylate monomers and their derivatives have been widely used for the synthesis of hydrogels.[4,5] In recent years, hydrogels have been successfully synthesized by the reaction of thiols with ene functionalities, using either photopolymerization or base-catalysed Michael addition reactions.[6–9] Thiol–ene polymerization reactions occur in suitable reaction times under ambient conditions and are not inhibited by water and oxygen. These features have made possible the application of these polymerization reactions in the manufacture of hydrogels for biomedical applications.[10,11]

The purpose of the study reported here was to prepare polymer networks from a high-molar-mass water soluble dimethacrylate monomer (bisphenol A ethoxylate dimethacrylate, EBisEMA; $M_n \sim 1700$ g mol^{-1}) and to examine the swelling behaviour of the EBisEMA-derived hydrogels. EBisEMA is characterized by a relatively high molar mass and contains a high proportion of aliphatic ether bonds in its structure, which act as molecular hinges. This feature results in moderately crosslinked and flexible polymer networks. Hydrogels derived from EBisEMA were prepared at room temperature by both bulk photopolymerization and aqueous solution photopolymerization using either UV or visible radiation. In addition, EBisEMA was copolymerized with a tetrafunctional thiol through free-radical and amine-catalysed Michael addition reactions. EBisEMA was also copolymerized with various proportions of dimethylaminoethylmethacrylate (DMAEMA) and the sensitivity of EBisEMA–DMAEMA networks to changes in pH was examined. To the best of our knowledge, this is the first report describing hydrogels derived from the EBisEMA dimethacrylate monomer.

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EXPERIMENTAL

Materials

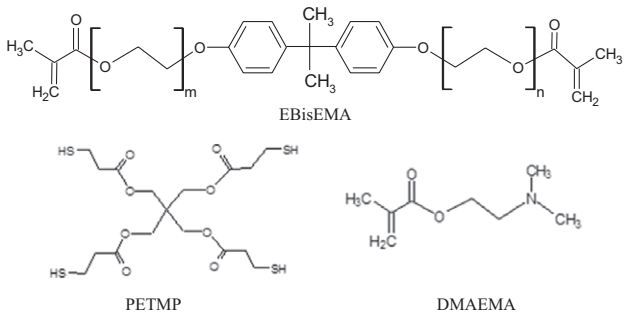
EBisEMA (M_n ~ 1700 g mol^{-1}), pentaerythritol tetra(3-mercaptopropionate) (PETMP; >95%), DMAEMA (98%), propylamine (PAH; >99%) and riboflavin (Rf, >98%) were from Sigma Aldrich, USA. The resins were photoactivated by the addition of either 1 wt% 2,2-dimethoxy-2-phenylacetophenone (DMPA; 99%, Sigma Aldrich, USA) or 1 wt% camphorquinone (CQ; 99%, Sigma Aldrich, USA). All materials were used without further purification. Triethanolamine (TEOHA; Sigma Aldrich, USA) was purified by vacuum distillation before use. The structures of the monomers are shown in Scheme 1. The UV source employed was assembled from a 1.2 W light-emitting diode (LED) with a maximum emittance at 365 nm (LZ1-00UV00, Led Engin, USA). The visible-light source was assembled from a 5 W LED with its irradiance centred at 470 nm (High Power LED SML-LXL99USBC-TR/5 from Lumex, USA). Water was purified through a Millipore Milli-Q system. Buffer solutions (Laboratorios Oliveri, Buenos Aires, Argentina) were used as received.

Synthesis of hydrogels

A set of hydrogels was prepared by bulk polymerization. Since the EBisEMA, PETMP and DMAEMA monomers and their mixtures are liquid prior to polymerization they can be placed in a mould of choice to produce specimens of the desired shape. The liquid resins containing the photoinitiator system were sandwiched between two thin glass plates separated by a 3 mm thick rubber sheet with either a circular or a rectangular hole. The hole of the rubber sheet was filled with the reactive mixture and the assembly was held using small clamps. The resins were polymerized at room temperature under UV or visible irradiation to form either 1 mm thick rectangular slabs (10 mm × 25 mm) or 3 mm thick × 10 mm diameter circular discs. Hydrogels were also synthesized by photopolymerization from aqueous solutions of EBisEMA employing Rf and TEOHA as sensitizer and co-initiator, respectively. Typically, 2 mL of a deaerated aqueous solution containing 1 mL of EBisEMA, Rf (0.3 absorbance units at 470 nm, measured in 1 mL path cells) and TEOHA (0.03 mol L^{-1}) was placed in a merry-go-round photochemical reactor containing eight 470 nm LEDs (3 W, Luxeon, Philips) and irradiated for 2 h. Tubes were broken and uniform discs, 10.5 mm in diameter and around 2.5 mm in thickness, were cut from the hydrogels. Figure 1 shows images of hydrogels prepared in bulk and in water solution. Hydrogels from EBisEMA copolymerized with the PETMP tetrafunctional thiol were prepared through free-radical Michael addition reaction in resins photoactivated with 1 wt% CQ irradiated at 465 nm. EBisEMA was also copolymerized with PETMP by Michael addition reaction catalysed with 1 wt% PAH. Hydrogels from EBisEMA–PETMP mixtures were prepared at either stoichiometric proportion (EBisEMA-to-PETMP molar ratio of 2:1) or with thiol in excess (EBisEMA-to-PETMP molar ratio of 1:1). EBisEMA was copolymerized with various proportions of DMAEMA. Photopolymerization of mixtures EBisEMA and DMAEMA photoactivated with 2 wt% CQ was carried out by visible light irradiation at 465 nm. The various methods used for the preparation of the EBisEMA-derived hydrogels are illustrated in Scheme 2.

Characterization techniques

The conversion of methacrylate groups as a function of irradiation time was monitored at room temperature (20 °C) using near-infrared (NIR) spectroscopy with a Nicolet 6700 (Thermo Scientific). The NIR spectra were acquired over the range 4500–7000 cm^{-1} from 16 co-added scans at a resolution of 2 cm^{-1}. The resins were contained in a 10 mm diameter well constructed from a rubber gasket material sandwiched between two glass plates. The thickness of the samples was 3 mm. With the assembly positioned in a vertical position, the light source was placed in contact with the glass surface. The samples were irradiated at regular time intervals and the spectra were collected immediately after each exposure interval. The absorption band at 6165 cm^{-1} was used to calculate the conversion of methacrylate groups. Two replicates were used in the measurement of conversion.



Scheme 1. Structures of the monomers used in this study.

Raman spectroscopy studies were performed at room temperature (*ca* 20 °C) with an Invia Reflex confocal Raman microprobe (Renishaw). Details concerning this technique have been reported elsewhere.[12] The conversions of C=C double bonds and S—H groups were calculated from the decay of the bands located at 1642 and 2575 cm^{-1}, respectively. Two replicates of each of the resins were used in the measurement of conversion.

Measurements of water uptake in hydrogels were carried out using a classic gravimetric sorption technique. Slabs or discs of prepared hydrogels were first weighed and then immersed in distilled water at 25 ± 1 °C. For the swelling measurements of hydrogels based on EBisEMA–DMAEMA resins the specimens were also immersed in buffer solutions at pH = 2. Swollen specimens were removed from solutions at regular time intervals, blotted with filter paper and weighed. The degree of swelling (S_w) was calculated as follows:

$$S_w\ (\%) = \frac{m_t - m_d}{m_d} \times 100$$

where m_d and m_t are the weights of dry and swollen test specimens, respectively. Measurements were performed in triplicate.

Dynamic mechanical thermal analysis was performed in torsion deformation mode from −70 to 100 °C at a heating rate of 5 °C min^{-1} using an MCR 301 rheometer (Anton Paar GmbH). Rectangular specimens with dimensions of *ca* 40 ± 0.5 mm × 10 ± 0.05 mm × 1.5 ± 0.05 mm (length × width × thickness) were tested at 1 Hz. Previously, a strain sweep test of a representative sample was performed at 20 °C and 1 Hz in order to determine the linear viscoelastic range and select a strain value to apply in temperature sweeps. The selected strain value was 0.05%. A small axial force (around −0.5 N) was applied in all test specimens in order to maintain a net tension.

RESULTS AND DISCUSSION

This section is divided into three parts concerned first with studies of novel hydrogels based on EBisEMA, followed by a discussion of thiol–methacrylate hydrogels prepared from EBisEMA

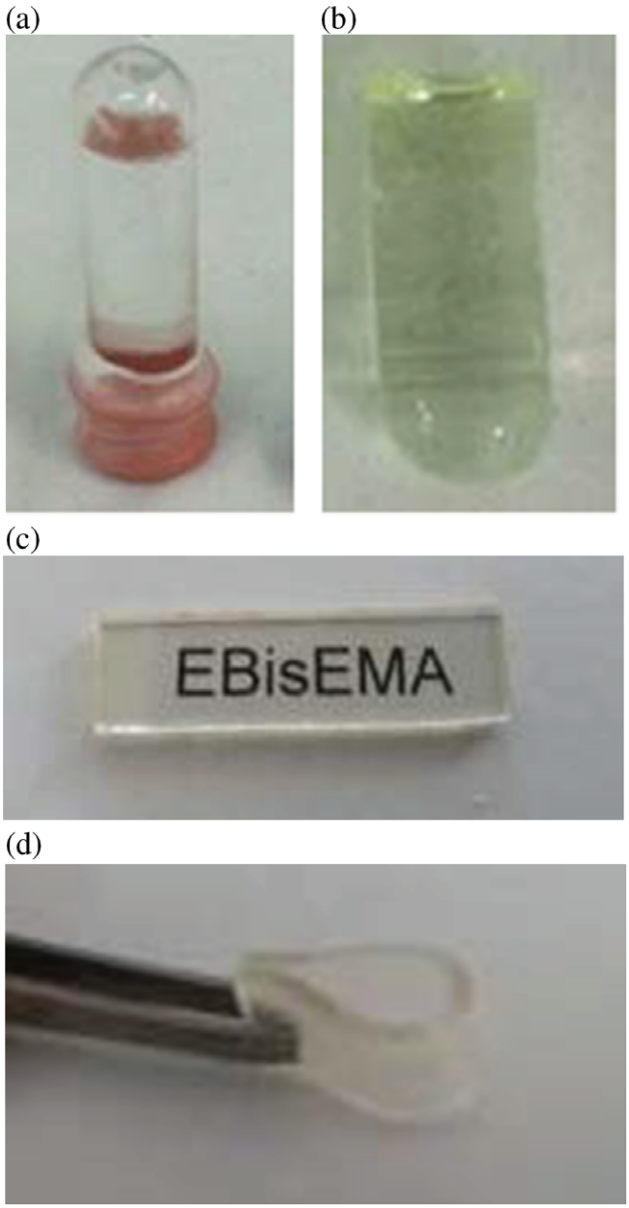


Figure 1. (a) Tube containing aqueous solution of EBisEMA to be photopolymerized, and hydrogels prepared from (b) photopolymerization in aqueous solution of EBisEMA, (c) bulk photopolymerization of EBisEMA and (d) bulk polymerization of EBisEMA–PETMP catalysed with PAH (C=C/SH molar ratio equal to 2:1).

and PETMP, and finally discussing hydrogels formulated from EBisEMA–DMAEMA mixtures.

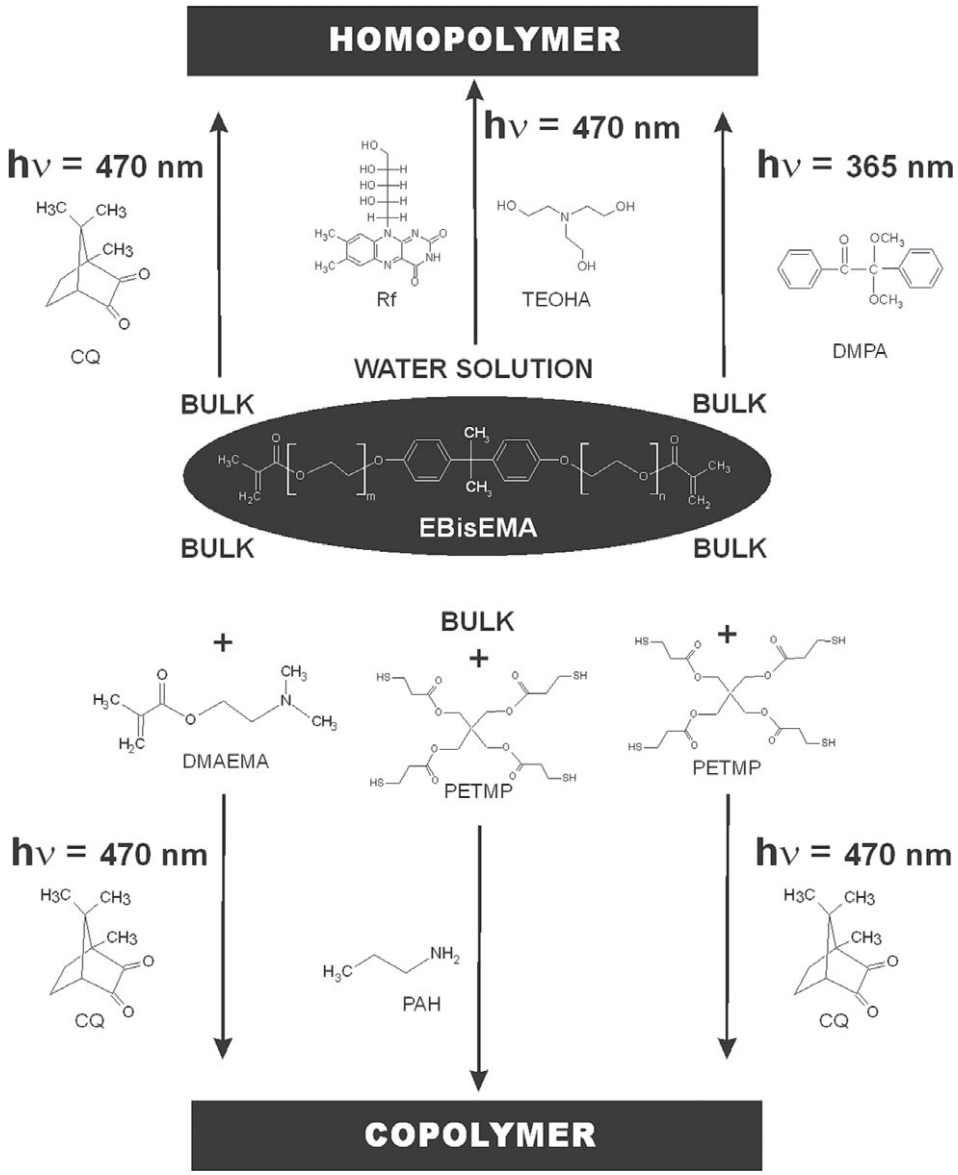
Hydrogels based on EBisEMA

Polymerization of EBisEMA photoactivated with 1 wt% DMPA was carried out under UV irradiation (365 nm). The conversion of methacrylate groups versus irradiation time in a 3 mm thick sample is shown in Fig. 2. It is seen that the conversion reached about 98% after 40 s exposure, and then increased up to 100% after about 30 min in the dark due to the presence of reactive free radicals in the polymer network. EBisEMA was also polymerized under visible light irradiation (470 nm), in resins photoactivated with 1 wt% CQ. Under visible light irradiation, CQ is excited to a singlet state which converts to a reactive triplet state CQ* via intersystem crossing. Initiating radicals are generated by electron and proton transfer through a charge transfer intermediate complex between CQ* and hydrogen donors such as tertiary amines. The polymerization reaction is initiated by the reactive amine radicals while the ketyl radicals dimerize.[13–16] Alternatively, polymerization photoinitiated by CQ in the absence of co-initiator has been reported in methacrylate monomers containing hydrogen donor groups such as methylene ether (—O—CH_2—).[17] Figure 2 shows that CQ is an efficient photoinitiator of EBisEMA in the absence of added amine co-initiator. The conversion of C=C reached almost 100% after 240 s irradiation. This indicates that, in agreement with previous research,[17] CQ oxidizes the methylene ether (—O—CH_2—) groups present in EBisEMA, and that the radicals derived from EBisEMA via hydrogen abstraction are highly reactive towards double bonds (Fig. 2). This feature contrasts with the lack of polymerization observed for other methacrylate monomers photosensitized with CQ in the absence of amine.[18] Many amines have been suggested as co-initiators of CQ, but owing to the inherent toxicity of many tertiary amines, research has been directed towards the use of alternative amines with improved biocompatibility.[19] Thus, from the results presented in Fig. 2 it emerges that a great advantage of EBisEMA is that its polymerization photoinitiated by CQ requires no additional co-initiator because of the presence of a high proportion of ether bonds in its structure.

Swelling of polymers derived from EBisEMA was studied with samples prepared by photopolymerization in bulk or in solution. Bulk polymerization was carried out in EBisEMA resin photoactivated with 1 wt% DMPA and irradiated at 365 nm using an LED. Polymerization in solution was performed in aqueous solutions of EBisEMA (0.5 g mL^{-1}) containing Rf and TEOHA by irradiation at 470 nm (Fig. 1). Results of swelling experiments presented in Table 1 indicate that the water uptake of samples polymerized in bulk reached a plateau of 68 wt% after 24 h immersion in water while hydrogels prepared in solution reached a plateau of 104 wt% after 48 h immersion. The capacity of the EBisEMA-derived polymer for absorbing water is attributed to the presence of a high proportion of hydrophilic ether groups in it structure. The higher value of water uptake of hydrogels prepared in solution (Table 1) is attributed to the presence of pores in the structure. Pores are formed during the polymerization reaction due to the segregation of the solvent from the polymer network.[20] In the case of a porous sample, in addition to the nanopores present in the sample prepared in bulk, the expansion of the network entails the increase in size of the larger pores formed during polymerization. After removal of water from samples by evaporation the pores collapse and the density of the sample is that of the network polymerized in bulk. When the porous network is immersed in liquid water, the pores open and the amount of water absorbed is greater than that of the samples polymerized in bulk.[20] The possibility of controlling the amount and morphology of pores increases markedly the spectrum of possible applications of hydrogels prepared from synthetic polymers. This study demonstrates that porous crosslinked methacrylate hydrogels can be easily prepared because of the solubility of EBisEMA in water.

Hydrogels based on EBisEMA–PETMP

Thiol–methacrylate (EBisEMA–PETMP) monomer mixtures were photoactivated with 1 wt% of CQ and photopolymerized by irradiation at 470 nm. The polymerization mechanism presented in Scheme 2(a) shows that methacrylate groups homopolymerize through a chain growth mechanism and they also abstract a hydrogen from the thiol group (chain transfer



Scheme 2. Methods used for preparation of hydrogels derived from EBisEMA.

reaction).[6–9,21,22] Consequently, when a mixture of methacrylate and thiol monomers is polymerized the radicals derived from the methacrylate groups participate in both propagation through another double bond and hydrogen abstraction from the thiol group. The thiol-derived radicals (thiyl radicals), also react with methacrylate groups by propagating through the C=C double bond. Termination occurs by radical–radical coupling. Raman spectroscopy was used to assess the conversion of thiol and methacrylate groups during irradiation because of the low intensity of the absorption band of the —SH group in the mid-IR range (2572 cm^{-1}). Representative spectra of an EBisEMA–PETMP mixture (2:1 mole ratio) are illustrated in Fig. 3. Figure 4 shows the conversion of C=C and SH groups in mixtures prepared with various EBisEMA-to-PETMP molar proportions.

Again, a great advantage of the use of CQ to initiate the copolymerization of EBisEMA and PETMP is that no additional co-initiator is required. Figure 3 shows the disappearance of the absorption band of methacrylate groups while a fraction of thiol groups remained unreacted. The faster homopolymerization reaction of the EBisEMA monomer resulted in about 70 or 50% unreacted thiol groups in cured samples having EBisEMA-to-PETMP molar ratios equal to 1 or 2, respectively. Previous reports on the ratio of thiol–ene addition *versus* homopolymerization through ene functional groups demonstrated that the occurrence of an equal conversion of both ene and thiol groups or a higher conversion of the ene functional group depends on the ene monomer used.[23–26] The slower homopolymerization rate in the formulation with thiol in excess (EBisEMA-to-PETMP molar ratio of 1:1) is attributed to the participation of thiols in termination reactions through a chain transfer mechanism, which decrease the polymerization rate.

In addition to the thiol–ene free radical reaction described previously, thiol–ene addition reactions can also proceed through base- or nucleophile-catalysed Michael addition reaction.[11,27] Scheme 3(b) illustrates that in the presence of primary/secondary amines, deprotonation of the thiol occurs leading to the formation of thiolate anion and ammonium cation. The thiolate anion adds into the double bond at the β-carbon producing an intermediate carbon-centred anion which is a very strong base. The thiol–ene

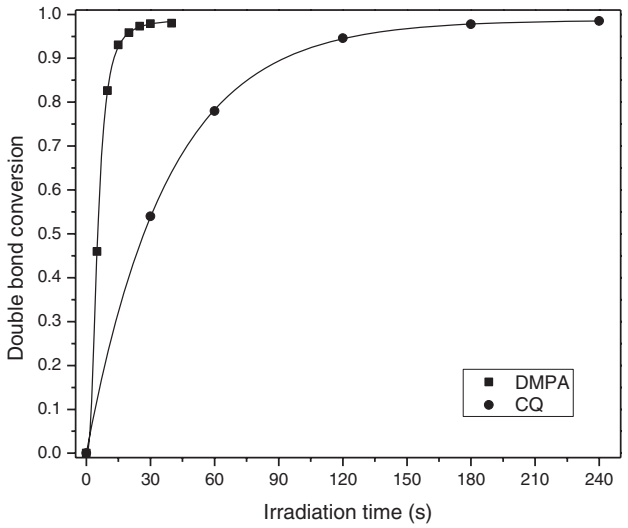
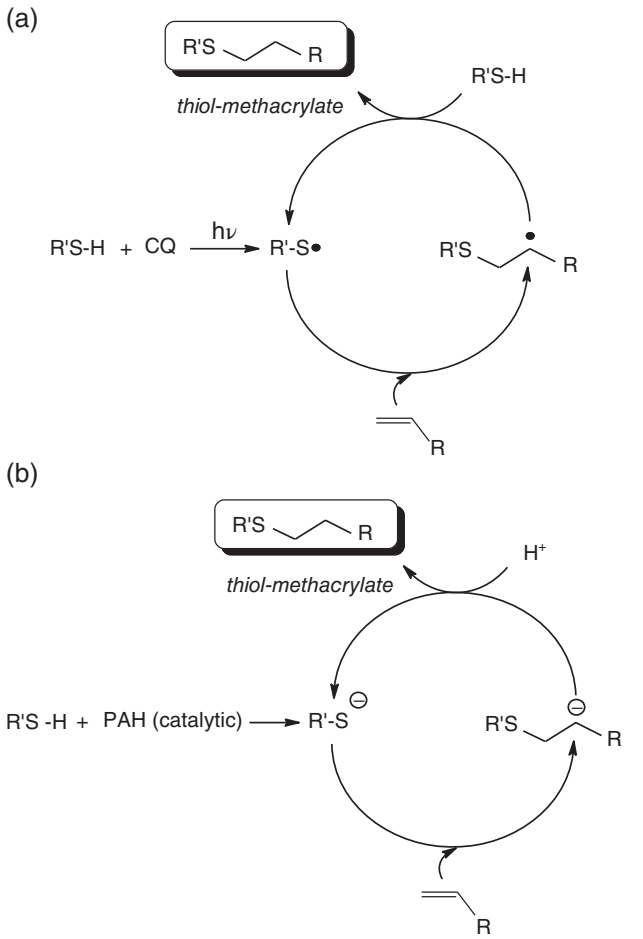


Figure 2. Conversion of methacrylate groups versus irradiation time in EBisEMA photoactivated with either 1 wt% CQ or 1 wt% DMPA. The specimens were 10 mm in diameter and 3 mm thick.

Table 1. Degree of swelling of EBisEMA-based hydrogels prepared by photopolymerization either in bulk or in aqueous solution (EBisEMA at 0.5 g mL^{-1})

Time (h)	Water uptake in bulk (%) (± SD)	Water uptake in solution (%) (± SD)
24	67 (±0.3)	71 (±0.4)
48	68 (±0.4)	104 (±0.3)
144	68 (±0.3)	104 (±0.6)



Scheme 3. (a) Idealized thiol–ene polymerization by free radical addition reaction. (b) Idealized thiol–ene polymerization by base-catalysed Michael addition reaction.

product is formed when the enolate anion picks up a proton either from a thiol group or from the ammonium cation.

The Michael addition between EBisEMA and PETMP was carried out at ambient temperature in the presence of PAH as catalyst. The conversion of C=C and SH as a function of time was studied in mixtures having EBisEMA-to-PETMP molar ratio of either 1 or 2. Figure 5 shows the conversion of C=C bonds calculated using NIR spectroscopy from the decay of the absorption band located at 6165 cm^{-1}.

Raman spectra acquired from the samples used for measurements of C=C conversion by NIR showed a complete conversion of SH groups for the EBisEMA-to-PETMP molar ratio of 2:1. On the other hand, 50% of the SH groups remained unreacted in EBisEMA–PETMP mixtures with thiol in excess ($r = 1$). The higher polymerization rate in mixtures having $r = 1$ in Fig. 5 is attributed to a higher rate of deprotonation of the thiol to the corresponding thiolate anion in mixtures containing thiol in excess. Despite the large number of unreacted thiol groups in the final networks (Table 2), the percentage of extractable thiol monomers is very low because the PETMP monomer is tetrafunctional.[28]

Thiol–ene networks are usually prepared from stoichiometric proportions of reactants. Recently, Khutoryanskiy and co-workers reported that materials with mucoadhesive properties, i.e. able to stick on mucosal surfaces, can be prepared from non-stoichiometric thiol–ene formulations.[29] Studies of thiol–methacrylate reactions with non-stoichiometric ratio of reagents for the synthesis of hydrogels containing unreacted thiol functional groups were encouraged by the results reported in the aforementioned reports. No specific study of adhesion was made in the present study; however, it was observed that there was a marked tendency of hydrogels with thiol in excess to adhere to a variety of substrates, including metals, glass, paper and skin. This feature makes them especially attractive in applications for which adhesion is particularly critical.[30]

Figure 6 shows the water uptake of thiol–methacrylate networks prepared by free radical and Michael addition reactions. The plot of water sorption of the EBisEMA-based hydrogel is also shown for comparison.

No significant differences in swelling are observed between photocured specimens prepared from pure EBisEMA and specimens prepared from EBisEMA–PETMP photoinitiated by CQ. Conversely, a marked increase in water uptake is seen in the EBisEMA–PETMP hydrogels prepared by the PAH-catalysed Michael addition reaction. The water uptake of hydrogels is caused by the presence of hydrophilic groups in the polymer structure. The higher the number of hydrophilic groups, the greater is the water uptake. In addition, the crosslink density of the network is a critical factor that determines the degree of swelling of hydrogels.[31] Highly crosslinked hydrogels have a tighter structure, and will swell less than hydrogels with lower crosslinking density. According to the mechanisms presented in Scheme 3, each methacrylate double bond reacts with one thiol group, while in a chain-growth radical polymerization two monomers are coupled to each double

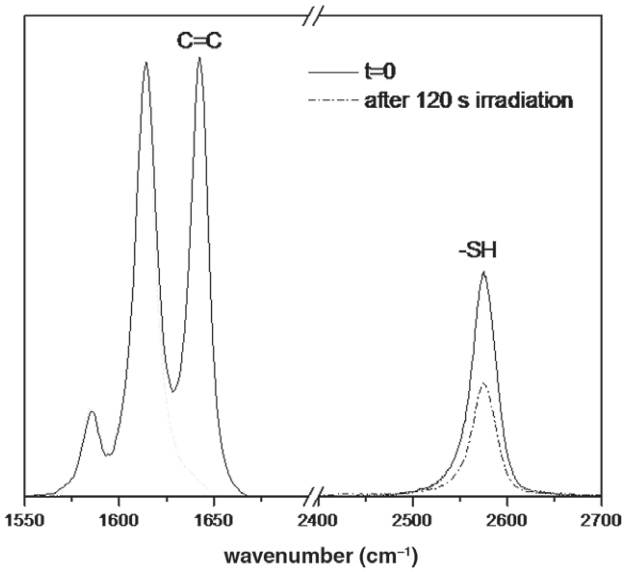


Figure 3. Characteristic peaks in Raman spectra of thiol–methacrylate mixtures. The band at 2575 cm^{-1} is assigned to the S—H group. The band representing the methacrylate double bond is located at 1642 cm^{-1}. The band at 1612 cm^{-1} was selected as internal reference band.

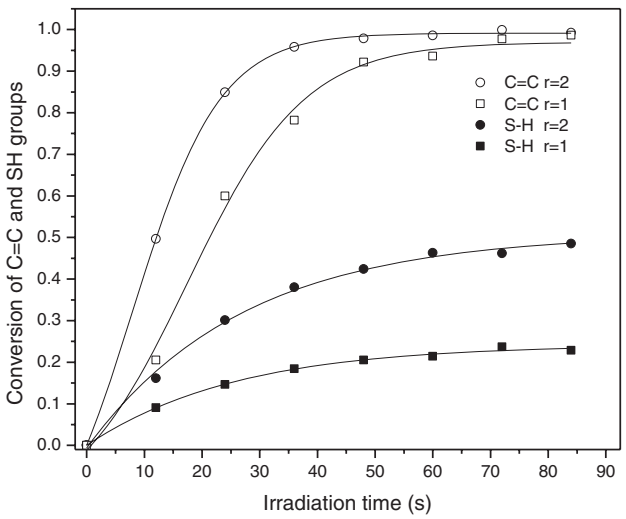


Figure 4. Conversion of C=C and SH groups in mixtures prepared with various EBisEMA-to-PETMP molar ratios (*r*). Samples containing 1 wt% CQ were irradiated at 470 nm. The specimens were 10 mm in diameter and 3 mm thick.

bond. As the effective monomer functionality in the step-growth network is half that observed in chain-growth radical polymerizations, the thiol Michael addition reaction exhibits comparatively lower crosslinking density than the free radical addition reaction. Trends of water uptake presented in Fig. 6 are explained in terms of a balance between the mass fraction of hydrophilic groups and the crosslink density of the network.

The glass transition temperature (T_g) of the hydrogels prepared from EBisEMA was assessed and the values are presented in Table 2. Figure 7 shows a typical plot of tan δ *versus* temperature from dynamic mechanical thermal analysis. EBisEMA monomer contains a high proportion of flexible ether groups and forms a moderately crosslinked polymer due to its high molar mass; therefore, the EBisEMA-derived network displays a low T_g (Table 2).

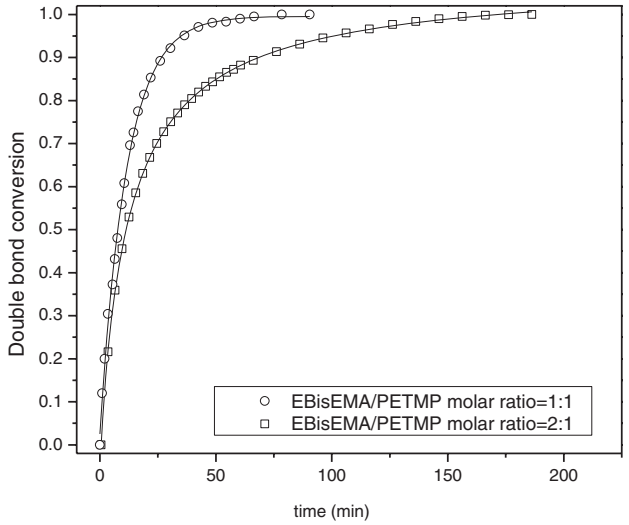


Figure 5. Conversion of C=C *versus* time in mixtures prepared with different EBisEMA-to-PETMP molar ratios (*r*), containing 2 wt% PAH. The conversion of C=C groups was calculated using NIR spectroscopy from the decay of the absorption band located at 6165 cm^{-1}.

Table 2. Conversion of thiol (SH) groups and T_g at 100% conversion of C=C groups[a]

Initiator	*r*	SH conversion (±SD)	T_g (°C)
1 wt% CQ	Pure EBisEMA	–	−35
1 wt% CQ	2 (stoichiometric)	0.48 (±0.01)	−37
1 wt% CQ	1 (thiol in excess)	0.28 (±0.02)	−41
2 wt% PAH	2 (stoichiometric)	1	−37
2 wt% PAH	1 (thiol in excess)	0.48 (±0.02)	−37

[a] Parameter *r* is the EBisEMA-to-PETMP molar ratio. The standard deviation (SD) in T_g values was in the range ± (0–0.25) °C.

Similarly, EBisEMA–PETMP networks formed by thiol Michael addition reactions are characterized by a high content of flexible thioether bonds. The identical T_g values of networks prepared from different EBisEMA-to-PETMP molar ratios contrast with many experimental results reported in the literature showing the dependence of T_g on parameters such as crosslink density and average molar mass between crosslinks.[32] In this sense it is worth noting that the average molar mass between crosslinks is the most important structural factor affecting T_g of rigid networks, but its influence on flexible networks is much less important. This is possibly so because the relaxation of flexible networks preferentially occurs through 'hinges' present in their chemical structures (i.e. ether and thioether bonds), being much less affected by the concentration of crosslinking points.[32]

Hydrogels based on EBisEMA–DMAEMA

In the two past decades stimuli-responsive hydrogels have attracted extensive attention due to their particular applications in drug delivery, tissue culture, microfluidics and sensors. More specifically, hydrogels that swell in response to acidic or basic conditions (i.e. pH-responsive hydrogels) have been studied because of their relevance to pH changes that occur in biological systems. Polymers that respond to pH typically contain ionizable groups that can accept or donate protons in response to the

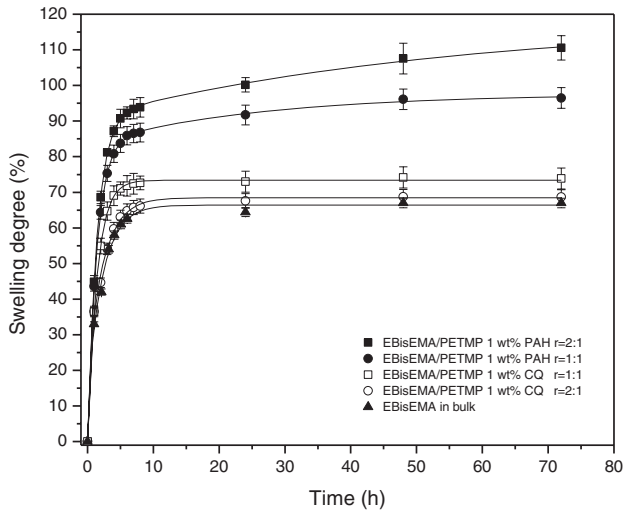


Figure 6. Degree of swelling of EBisEMA–PETMP networks prepared through free radical and amine-catalysed Michael addition reactions at various EBisEMA-to-PETMP molar ratios. The swelling of EBisEMA photopolymerized in bulk is shown for comparison.

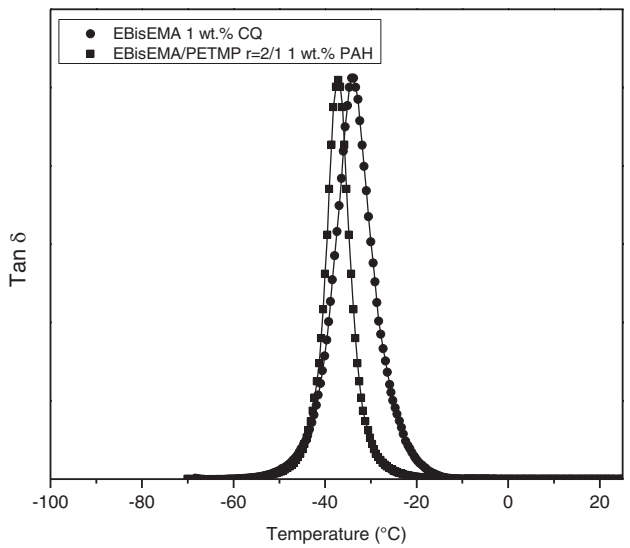


Figure 7. Typical plot of tan δ *versus* temperature for thiol–methacrylate prepared by PAH-catalysed Michael addition reaction. Parameter *r* is the EBisEMA-to-PETMP mole ratio.

environmental pH.[33–37] In this study, hydrogels containing pendant amino groups were prepared from mixtures of EBisEMA and DMAEMA (Scheme 1) in various EBisEMA-to-DMAEMA molar ratios (Table 3). Figure 8 shows the C=C conversion *versus* irradiation time in EBisEMA–DMAEMA mixtures.

The rate of polymerization in Fig. 8 follows a complex behaviour with increasing DMAEMA concentration: first, the polymerization rate increases rapidly with the presence of DMAEMA, attains a maximum value and then decreases as the amount of DMAEMA further increases. This trend is attributed to the known efficiency of amines in retarding polymerization reactions through a transfer mechanism of the polymer radical to the amine following a standard hydrogen abstraction mechanism. Thus, if the amine concentration is large enough, the deactivation and termination reactions become dominant leading to a decrease in the polymerization rate. DMAEMA as a tertiary amine is an effective

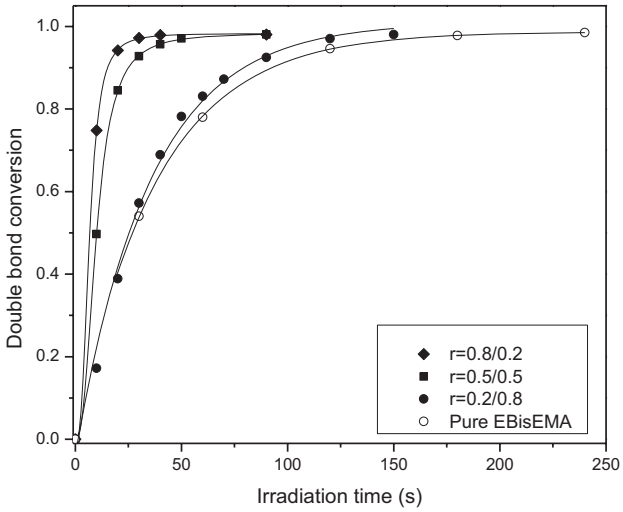


Figure 8. Conversion of methacrylate groups *versus* irradiation time in mixtures prepared with various EBisEMA-to-DMAEMA molar ratios (*r*).

chain-transfer agent,[33] and chain-transfer reactions are competing with chain-growth reactions in this system.

The swelling behaviour of hydrogels prepared by copolymerization of EBisEMA and DMAEMA at various DMAEMA proportions (Table 3) was studied as a function of pH of the medium. Figure 9 shows that at neutral pH the hydrogels reach an equilibrium swelling level that increases with increasing proportion of DMAEMA. This is attributed to a reduced crosslinking density in hydrogels with reduced EBisEMA-to-DMAEMA molar ratio. Hydrogels having an EBisEMA-to-DMAEMA molar ratio equal to 08/02, immersed in water during 2 days, reached an equilibrium swelling level identical to that of the hydrogel prepared from EBisEMA and showed no significant sensitivity to changes in pH. On the other hand, a marked effect of pH on the water uptake is seen for $r > 0.8/0.2$ (Table 3). The hydrogels contain ionizable amino groups that can accept protons in response to changes in pH. In this case, lowering the pH of the environment results in a rapid change in the net charge of the polymer.[34] The presence of a highly charged structure causes the matrix to swell as a result of the high charge repulsion. Therefore, under neutral and basic conditions, the hydrogel remains in a collapsed state and, once the pH is low enough to ionize the pendant amines, the hydrogel swells. This is a desirable property for the design of intelligent materials, such as pH-responsive hydrogels for controlled drug release. Results obtained in this contribution show the magnitude of the water uptake of EBisEMA–DMAEMA hydrogels when the solution pH is decreased, and reveal that at EBisEMA-to-DMAEMA molar ratios $r < 0.8/0.2$ the charge repulsion of protonated amino groups is not high enough to cause the swelling of the polymer network.

Hydrogels prepared from methacrylate monomers have been used as biomaterials in a wide range of applications.[2–5] In

Table 3. Molar proportion of each monomer in copolymers prepared from EBisEMA and DMAEMA

DMAEMA (mol)	EBisEMA (mol)	DMAEMA (wt%)	EBisEMA (wt%)
0.2	0.8	2.26	97.74
0.5	0.5	8.45	91.55
0.8	0.2	26.98	73.02

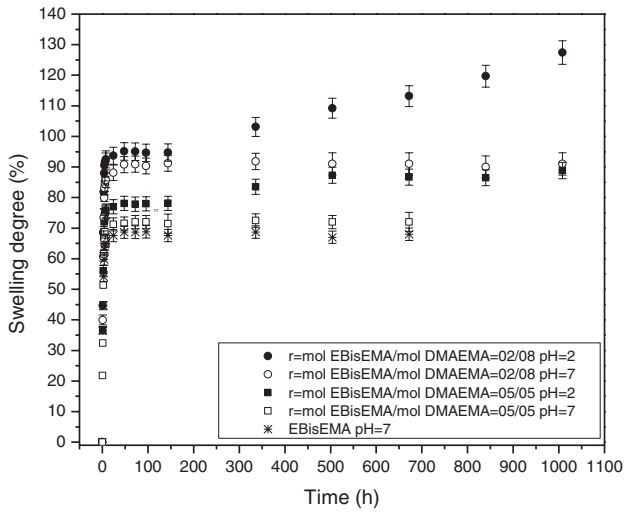


Figure 9. Degree of swelling of EBisEMA–DMAEMA copolymers having various EBisEMA-to-PETMP molar ratios. The swelling of EBisEMA photopolymerized in bulk, at pH = 7, is shown for comparison.

particular, poly(ethylene glycol) dimethacrylate (PEGDMA) hydrogels of several molar masses, in the range 1000–8000 g mol^{-1}, have been prepared and characterized by Lin-Gibson *et al.* for controlled release of hydrophobic drugs.[38] Different from PEGDMA, EBisEMA contains one bisphenol A unit in its structure which is equivalent to around five ethylene glycol units on a mass basis. Thus, the higher proportion of ethylene glycol groups per mole of PEGDMA compared with that in EBisEMA will influence the water sorption capacity of the derived hydrogels. Kisaalita and co-workers studied the swelling of hydrogels prepared from PEGDMA having molar masses equal to 550 or 1000 g mol^{-1}.[39] Those authors found that the equilibrium water sorption was in the range 500–1000 wt%, which is well above the water sorption capacity of the hydrogels prepared in the present study. The presence of the aromatic group in the central part of EBisEMA increases its stiffness and hampers its mobility, while the ether linkages in the PEGDMA molecule give rise to only slight barriers to free rotation about the bonds.[40] Moreover, PEGDMA, being a flexible molecule, has been found to cyclize in addition to forming crosslinks.[41] Primary cycles formed by reaction of pendant double bonds increase conversion, but do not contribute to network formation. Thus, physical properties that depend on the crosslink density, e.g. the water sorption capacity, are affected by the presence of cycles. The lower swelling of EBisEMA hydrogels compared with PEGDMA might be associated with a reduced formation of cycles, e.g. a higher crosslink density in EBisEMA.

In analogy with PEGDMA, which exhibits excellent biocompatibility,[39] EBisEMA is expected to be appropriate for biomedical applications. The aromatic group in the central part of EBisEMA is also present in the structure of monomers that have been successfully used in light-cured dental restorative resins during the last three decades.[18] Similarly, PETMP has been used in the development of *in situ* forming biomaterials for drug delivery applications and tissue engineering.[28] The CQ photoinitiator has shown excellent biocompatibility after three decades of use in light-cured dental resins. Moreover, a great advantage of EBisEMA is that its polymerization is photoinitiated by CQ in the absence of added amine co-initiator. All these factors make EBisEMA attractive for biomedical applications. At this point, it is worth mentioning that widely used soft contact lenses are prepared from poly(2-hydroxyethyl methacrylate) (HEMA) in combination with ethylene glycol dimethacrylate (EGDMA) as crosslinking agent.[5] T_g of dry HEMA–EGDMA copolymer hydrogels used for contact lens is in the range 100–120 °C,[42] while T_g values of hydrogels derived from EBisEMA are below room temperature. Consequently, the room temperature polymerization of HEMA–EGDMA is stopped by vitrification making necessary a thermal post-curing treatment at temperatures above their T_g in order to polymerize the unreacted monomer.[2] Conversely, the photopolymerization of EBisEMA is carried out at room temperature (above its T_g), reaching complete conversion of methacrylate groups after a few seconds of irradiation. The simplicity of fabrication of structures from EBisEMA compared to traditional HEMA–EGDMA copolymer hydrogels makes EBisEMA very attractive for biomedical applications such as contact lenses and wound dressings. Results of photopolymerization and water sorption capacity of EBisEMA-derived hydrogels obtained in this study encourage further research with regard to their application as biomaterials. Further investigations concerning preparation and characterization of hydrogels according to standard protocols are now in progress.

CONCLUSIONS

The work carried out demonstrates the versatility of EBisEMA for obtaining hydrogels using various synthesis pathways. The properties of the materials vary significantly depending on the materials and routes of synthesis employed, which makes them versatile in the manufacture of hydrogels for various applications (contact surfaces, tissue engineering, encapsulation/drug release, etc.).

The water-soluble, high-molar-mass EBisEMA dimethacrylate monomer photopolymerized either in bulk or in aqueous solution results in moderately crosslinked and flexible hydrogels. The photopolymerization activated with CQ occurs in the absence of co-initiator because highly reactive initiator radicals are formed through hydrogen abstraction from methylene ether (—O—CH_2—) groups present in EBisEMA by CQ.

Hydrogels formulated from EBisEMA–PETMP, by PAH-catalysed Michael addition reaction, result in a marked increase of water uptake compared with the hydrogels derived from pure EBisEMA. Conversely, no significant differences in water uptake were seen between hydrogels formulated from EBisEMA and PETMP prepared by photopolymerization. These trends are attributed to a balance between the proportion of hydrophilic groups and the crosslinking density of the networks.

Hydrogels sensitive to pH were prepared by copolymerization of EBisEMA with DMAEMA. Swelling studies showed that, as a result of the high molar mass of EBisEMA, the sensitivity to pH changes was evident at EBisEMA-to-DMAEMA molar ratios lower than 0.2:0.8.

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