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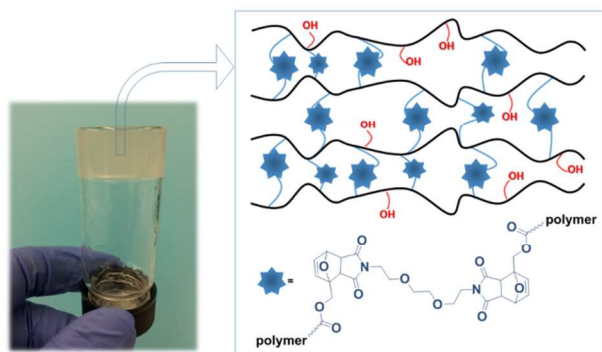
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An efficient controlled process for the preparation of HEMA-based hydrogels by means of Diels-Alder reaction.

## ARTICLE

## Tandem ATRP/Diels-Alder Synthesis of PolyHEMA-based Hydrogels

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The efficient, controlled polymerization of a batch of new poly(hydroxyethyl methacrylate-co-furfuryl methacrylate)s, [poly(HEMA-co-FMA)], of various compositions was achieved using atom transfer radical polymerization (ATRP) in methanol. When the FMA composition did not exceed the 10% mol ratio, the evolution of molecular weight with conversion was linear, and polydispersities were around 1.1 for polymerizations at 15 °C and around 1.3-1.4 at 25 °C, indicating good control over the polymerization process. HEMA-based hydrogels were obtained by means of the Diels-Alder reaction between poly(HEMA-co-FMA) and an hydrophilic bisdienophile. Gelification was monitored by diffusion-filtered <sup>1</sup>H NMR and solution <sup>1</sup>H NMR spectroscopies. Modulated temperature differential scanning calorimetry (MTDSC) suggests the thermo-reversibility of the Diels-Alder coupling reaction of HEMA polymeric networks. Rheological studies showed that the linear viscoelasticity functions of hydrogels were influenced by the chemical composition.

### Introduction

2-Hydroxyethyl methacrylate (HEMA) is an important functional monomer with numerous applications, among which is its wide use in the manufacture of soft contact lenses.<sup>1,2</sup> More than 1700 publications have been devoted to HEMA since the early 70s, 7200 publications or patents mention the homopolymer, and an even higher number of works involve HEMA-incorporating copolymers. Although HEMA homopolymer is hydrophilic with a high degree of hydration, it is not water-soluble, and can form hydrophilic networks or hydrogels. The pioneering work of Wichterle and Lim on cross-linked HEMA hydrogels [cross-linked with ethylene glycol dimethacrylate (EGDMA)],<sup>3</sup> and hydrogels' potential as biocompatible materials, has made them of great interest to biomaterial scientists for many years.<sup>4</sup>

Chemical cross-linking is a highly versatile method of generating hydrogels with good mechanical stability for their use in drug delivery systems.<sup>5,6</sup> The desired mechanical properties of a hydrogel can be achieved by changing the degree of cross-linking. Thus, when the degree of cross-linking is increased, the system results in a stronger gel.<sup>7</sup> However, a high degree of cross-linking leads to a more brittle structure. Hence, a compromise has to be reached between the degree of cross-linking and the elasticity of the hydrogel.

To prepare these gels, the networks need to be formed by covalent cross-linking. One of the methods that can be used to generate the so-called 'permanent hydrogels' (aqueous three-dimensional networks) is the Diels-Alder reaction. Since its discovery in 1928,<sup>8</sup> more than 17,000 papers have been published concerning the synthetic, mechanistic, and theoretical aspects of the Diels-Alder reaction.<sup>9</sup> This [4 + 2] cycloaddition reaction in which a conjugated diene adds to a dienophile is probably today the most widely used method in organic synthesis. Many conjugated dienes and dienophiles have been reported for use in the Diels-Alder reaction.

The Diels-Alder reaction has also received some attention in polymer chemistry. Polymers have been synthesized *via* consecutive Diels-Alder reactions in various ways.<sup>10-12</sup> Another very interesting application of this reaction in polymer chemistry is the formation of thermally reversible networks. Polymers bearing pendant diene or dienophile groups have been cross-linked by reaction with a bisdienophile or a bisdiene respectively.<sup>13-15</sup> The furan ring is one of the most important heterocycles used as the diene for the formation of these networks. On the dienophile side, maleimides are among the most-commonly used reagents because of their high reactivity.<sup>15</sup> These copolymers produced cross-linked elastomers in high yields in dichloromethane.<sup>16-18</sup> An exhaustive recent review from Gandini<sup>19</sup> summarizes the work

to date in the development and characterization of Diels–Alder polymers.

In 1980, Rideout *et al.* showed that some Diels–Alder reactions were vastly accelerated (up to 700 times faster) if carried out in aqueous media.<sup>20</sup> When reacting anthracene-9-carbinol with *N*-ethylmaleimide, they found the reaction to be slower in polar solvents than in nonpolar hydrocarbon solution, with the exception of water, where the rate was very high. This acceleration was therefore put down to a hydrophobic effect—enforced hydrophobic interactions and hydrogen bond interactions—rather than a polarity effect. The research of hydrogel formation *via* Diels–Alder in aqueous-based media is thus of great interest.<sup>21</sup>

Due to the high impact of polyHEMA copolymers, and their potential use in the preparation of hydrogels, the synthesis of highly precise statistical HEMA-furfuryl methacrylate (FMA) copolymers with narrow polydispersities is of importance for the further generation of polymer networks *via* the Diels–Alder reaction. One of the most robust methods to get materials with narrow polydispersities is the atom transfer radical polymerization (ATRP), which is a very versatile process, and a wide variety of suitable monomers can be polymerized using this technique.

Armes *et al.* published an account<sup>22</sup> of the polymerization of HEMA *via* ATRP under very mild conditions. The best results were obtained at 20 °C using a CuBr[bpy]<sub>2</sub> catalyst in pure methanol (conversion ~95% after 3–4 h, with  $M_w/M_n$  of just 1.1). To date, only two attempts have been published for the synthesis by ATRP of FMA copolymers with styrene<sup>23</sup> or methyl methacrylate<sup>24</sup> as co-monomer. The reaction vessels needed to be sealed in both cases, and the polymerizations proceeded in benzonitrile or toluene at high temperature (100 °C and 90 °C, respectively). None of the examples showed high conversions (all were lower than 60%) and polydispersities ranged between 1.4 and 1.9. Consequently, finding a good method for the preparation of FMA-based copolymers remains elusive.

This paper describes a practical, mild polymerization process for the preparation by ATRP of polyHEMA-based copolymers that incorporate a small mole fraction of a diene-containing monomer, namely FMA. The kinetics of the copolymerization is studied. The kinetics of the cross-linking reaction of HEMA-FMA copolymers with a synthesized hydrophilic bisdienophile *via* the Diels–Alder reaction in water-based media is also investigated by diffusion NMR and solution <sup>1</sup>H NMR, and the rheological properties of the resulting polymeric networks are discussed.

## Experimental

### Materials and Methods

Unless otherwise stated, materials and solvents were purchased from Aldrich Chemical Co. and used as received. 2-Hydroxyethyl methacrylate (HEMA) and furfuryl methacrylate

(FMA) were passed through a basic alumina column. The monomers were freshly distilled prior to use. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F254 (E. Merck) with detection by UV light or charring with H<sub>2</sub>SO<sub>4</sub>. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer equipped with an ATR diamond accessory. Nuclear Magnetic Resonance (NMR) spectra were recorded at the CITIUS Service (University of Seville) at 303 K on the following equipment: a Bruker AMX-300, a Bruker Avance AV-500, a Bruker AMX-500, or a Bruker Avance AV-700. 2D NMR spectra (COSY and HSQC) were used to assist in the assignment of the <sup>1</sup>H and <sup>13</sup>C NMR spectra, and conventional Bruker pulse programs were used. Chemical shifts ( $\delta$ ) are reported as parts per million downfield from Me<sub>4</sub>Si. For the kinetic studies of the gel formation, the <sup>1</sup>H NMR and diffusion-filtered <sup>1</sup>H NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer equipped with a 5 mm TCI cryoprobe at 298 K. Diffusion-filtered <sup>1</sup>H NMR spectra were carried out using the standard bipolar-gradient-pulse-pair longitudinal-eddy-current-delay (BPP-LED) pulse sequence.<sup>25</sup> A diffusion delay of 250 ms and bipolar pulsed gradient pairs of total duration 3 ms were used. The gradient amplitude was set to 95% of the maximum amplitude value. Accumulation of 32 scans was preceded by 4 dummy scans for each spectrum. Mass spectra were obtained using a Kratos MS80RFA instrument. Gel permeation chromatography (GPC) analyses were performed using a Waters apparatus equipped with a Waters 2414 refractive-index detector and two Styragel® HR columns (7.8 x 300 mm) linked in series, thermostatted at 60 °C, using *N,N*-dimethylformamide (DMF) as the mobile phase, at a flow rate of 1.0 mL min<sup>-1</sup>. Molecular weights were estimated against poly(methyl methacrylate) (PMMA) standards. The phase transitions exhibited by the prepared thermosensitive gels were examined by modulated temperature differential scanning calorimetry (MTDSC), using a TA DSC Q-200 Instrument (calibrated with indium) and a refrigerated cooling system (RCS) to ensure proper temperature cycling. The chemically cross-linked hydrogels were pre-equilibrated at room temperature before testing. Accurately weighed 5–10 mg samples were then hermetically sealed into aluminum DSC pans, and the equipment was operated in modulation mode. Calorimetric scans were carried out at a scanning rate of 2 °C/min under nitrogen atmosphere over an appropriate temperature range. Modulation amplitude was  $\pm 0.5$  °C every 60 s. The rheological characterization of the gels was carried out in a controlled-strain (ARES, Rheometric Scientific) rheometer, at 25 °C.

### Synthesis of furfuryl isobutyrate

Furfuryl alcohol (5 mL, 1 eq.) was dissolved in THF (20 mL) in a dry, round-bottomed flask, and stirred with triethylamine (10 mL, 1.25 eq.). The solution was cooled to 5 °C, and isobutyryl chloride (6.1 mL, 1.0 eq.) was added dropwise. The mixture was stirred for 2 h at 20 °C. The reaction was worked up by diluting with dichloromethane (30 mL), filtered through a celite plug to remove the triethylammonium chloride, and the solvent

was removed under vacuum. The residue was purified by silica column chromatography using (1:5) *tert*-butylmethyl ether-hexane (TLC:  $R_f$  0.54) to give an oil (8.5 g 88% yield). IR,  $\nu$ , ( $\text{cm}^{-1}$ ): 3145, 3124 (=C-H st), 1737 (C=O st), 816, 745 (C-H  $\delta$ , furan ring).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz),  $\delta$  (ppm): 7.41 (m, 1 H, H-5'; furan ring), 6.39 (bd, 1 H, H-3',  $J_{3',4'} = 3.3$  Hz; furan ring), 6.35 (dd, 1H, H-4',  $J_{4',5'} = 1.8$  Hz; furan ring), 5.06 (s, 2 H,  $\text{CH}_2\text{O}$ ), 2.57 (sept, 1 H,  $\text{CH}(\text{CH}_3)_2$ ,  $J = 6.9$  Hz), 1.17 (d, 6 H,  $\text{CH}(\text{CH}_3)_2$ ,  $J = 6.9$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz),  $\delta$  (ppm): 176.7 (C=O), 149.8 (C-2'; furan ring), 143.1 (C-5'; furan ring), 110.5, 110.3 (C-3', C-4'; furan ring), 33.9 [ $\text{CH}(\text{CH}_3)_2$ ], 18.9 [ $\text{CH}(\text{CH}_3)_2$ ]. CI-Mass Spectrometry.  $m/z$ : 168 ( $\text{M}^+$ ), 97 [( $\text{OCH}_2\text{-fur}$ ) $^+$ ], 81 (main peak) [( $\text{CH}_2\text{-fur}$ ) $^+$ ], 71 [( $\text{CH}_3)_2\text{CHCO}$ ) $^+$ ]. HRMS: Theoretical molecular weight for  $\text{C}_9\text{H}_{12}\text{O}_3$  ( $\text{M}^+$ ) 168.078644, experimental molecular weight: 168.078182.

### Synthesis of 1,8-dimaleimide-3,6-dioxaoctane (DMDOO)

Two solutions were prepared: one of 1,8-diamine-3,6-dioxaoctane (7.84 mL, 1 eq.) in DMF (16 mL), and the other of maleic anhydride (10.5 g, 2 eq.) in DMF (32 mL). The two solutions were added together, making sure that the temperature did not exceed 80 °C, and the mixture was then stirred at 80 °C for 20 min. Acetic anhydride (20.23 mL, 4 eq.), nickel acetate (106 mg, 0.008 eq.), and triethylamine (3 mL, 0.4 eq.) were then added, and the solution was stirred at 80 °C for 1 h.  $\text{H}_2\text{O}$  (40 mL) was added, and the residue was extracted with dichloromethane (300 mL). The organic layer was dried with magnesium sulfate and stirred with silica (70 g), filtered through a celite column, and washed with chloroform (400 mL). The slightly colored solution was dried under vacuum and purified by silica column chromatography using (9:1) *tert*-butylmethyl ether-hexane (TLC:  $R_f$  0.33) (11.9 g 72% yield). M.p. 97-98 °C (from  $^1\text{BME}$ ). IR,  $\nu$ , ( $\text{cm}^{-1}$ ): 3168, 3100 (=C-H st), 1703 (C=O st), 1109 (O- $\text{CH}_2$  st).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz),  $\delta$  (ppm): 6.72 (s, 4 H, = $\text{CH}$ ), 3.72 (t, 4 H, N- $\text{CH}_2$ ,  $J = 5.8$  Hz), 3.62 (t, 4 H, N- $\text{CH}_2$ - $\text{CH}_2\text{O}$ ,  $J = 5.8$  Hz), 3.56 (s, 4 H, O- $\text{CH}_2$ - $\text{CH}_2\text{O}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz),  $\delta$  (ppm): 170.6 (C=O), 134.1 (=CH), 70.0, 67.8 (N- $\text{CH}_2$ - $\text{CH}_2\text{O}$ ), 37.2 (O- $\text{CH}_2$ - $\text{CH}_2\text{O}$ ). CI-Mass Spectrometry.  $m/z$ : 309 [( $\text{M}+1$ ) $^+$ ], 124 [( $\text{C}_4\text{H}_2\text{O}_2\text{N-CH}_2\text{-CH}_2$ ) $^+$ ], 184 [( $\text{M-124}$ ) $^+$ ].

### Synthesis of HEMA-FMA copolymers

In a typical experiment for the preparation of poly(HEMA $_{90\%}$ -FMA $_{10\%}$ ) (Figure 1), the initiator ethyl-2-bromo-2-methylpropionate (EBiB, 36 mg, 0.186 mmol), the HEMA monomer (4.05 mL; 33.4 mmol), and the FMA monomer (0.57 mL; 3.71 mmol) were dissolved in 5 mL of pure methanol. To this degassed solution the 2,2'-bipyridyl ligand (bpy, 73 mg; 0.47 mmol) and the CuBr catalyst (27 mg; 0.186 mmol) were added, while stirring, at 25 °C, to produce a 50% (w/v) dark brown solution. Purification was achieved by stirring the reaction suspension with silica in methanol and later passing it through a diatomaceous earth column to remove the Cu(II) catalyst joined to the silica gel. The resulting colorless solution

was evaporated under vacuum to produce white copolymers in very high yield ( $\geq 95\%$ ).

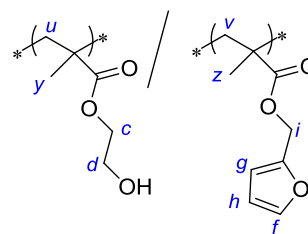


Figure 1: poly(HEMA-random-FMA) structure.

IR,  $\nu$ , ( $\text{cm}^{-1}$ ): 3385 (O-H), 2991 (=C-H st, furan), 2946 (-C-H st), 1718 (C=O st), 1483, 1452 ( $\gamma$  ring skeleton furan), 1151 (C-O st ester).  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 700 MHz – see Figure 1 for assignments),  $\delta$  (ppm): 7.67 (s, 1 H,  $\text{H}_f$ ), 6.52, 6.47 (2 s, 2 H,  $\text{H}_g, \text{H}_h$ ), 4.98 (s, 2 H,  $\text{H}_i$ ), 4.82 (s, 1 H, OH), 3.91 (bs, 2 H,  $\text{H}_d$ ), 3.59 (bs, 2 H,  $\text{H}_c$ ), 2.03-1.62 (2 m, 4 H,  $\text{H}_u, \text{H}_v$ ), 1.06-0.58 (2 m, 6 H,  $\text{H}_y, \text{H}_z$ ).  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ , 175 MHz),  $\delta$  (ppm): 177.3-176.4 (C=O), 143.7 ( $\text{C}_f$ ), 111.3, 110.9 ( $\text{C}_g, \text{C}_h$ ), 66.2 ( $\text{C}_d$ ), 58.7 ( $\text{C}_c$ ), 58.3 ( $\text{C}_i$ ), 53.4 ( $\text{C}_u, \text{C}_v$ ), 18.2-16.5 ( $\text{C}_y, \text{C}_z$ ).

### Kinetic studies of the ATRP synthesis of poly(HEMA $_{90\%}$ -random-FMA $_{10\%}$ )

The ATRP formation of poly(HEMA $_{90\%}$ -FMA $_{10\%}$ ) was carried out as mentioned above. Aliquots were taken at regular intervals to assess the extent of polymerization by  $^1\text{H}$  NMR spectroscopy and DMF GPC, respectively. The collected samples were passed through a micro-silica column to remove the ligand-catalyst system before the analyses.

### Diels-Alder reaction

#### Diels-Alder reaction of furfuryl isobutyrate with DMDOO

DMDOO (289 mg, 0.94 mmol) was dissolved in dichloromethane (3 mL), and furfuryl isobutyrate (315 mg, 1.88 mmol) was added. This was left stirring at 20 °C for 160 h. The Diels-Alder adduct was purified by silica column chromatography using first dichloromethane ( $R_f$  0.15) and then (10:1) dichloromethane-methanol ( $R_f$  0.73). A colorless oil was obtained (495 mg, 82% yield), with an endo-exo ratio of 78/22. IR,  $\nu$ , ( $\text{cm}^{-1}$ ): 3086 (=C-H st), 1737 (C=O st ester), 1702 (C=O st imide), 1192 (C-O st ester), 1110 (O- $\text{CH}_2$  st).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz – see Figure 2 for assignments),  $\delta$  (ppm): 6.48 (dt, 2 H,  $\text{H}_g, \text{H}_g', J_{g',h'} = 5.7$  Hz,  $J_{g',f} = J_{g',k'} = 1.6$  Hz), 6.33 (dd, 2 H,  $\text{H}_h, \text{H}_h', J_{h',f} = 2.1$  Hz), 5.34 (m, 2 H,  $\text{H}_f$ ), 4.89 (d, 2 H,  $\text{H}_{f1}, J_{f1,i2} = 12.8$  Hz), 4.63 (d, 2 H,  $\text{H}_{i2}$ ), 3.68 (m, 2 H,  $\text{H}_j$ ), 3.53 (s, 4 H,  $\text{H}_n$ ), 3.58-3.51 (m, 8 H,  $\text{H}_l, \text{H}_m$ ), 3.40 (dt, 2 H,  $\text{H}_k, J_{j,k'} = 7.7$  Hz;  $J_{i,k'} = 1.3$  Hz), 2.67 (sept, 2 H,  $\text{H}_q, J_{p,q} = 7.0$  Hz), 1.22 (d, 12 H,  $\text{H}_p$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz),  $\delta$  (ppm): 176.52, 174.44 (C=O), 135.62 ( $\text{C}_g$ ), 134.44 ( $\text{C}_h$ ), 89.92 (quaternary carbon in bicyclic systems), 79.64 ( $\text{C}_f$ ), 69.90, 67.04 ( $\text{C}_l, \text{C}_m$ ), 61.82 ( $\text{C}_i$ ), 47.79 ( $\text{C}_j$ ), 46.73 ( $\text{C}_k$ ), 37.75 ( $\text{C}_n$ ), 33.86 ( $\text{C}_q$ ), 18.95 ( $\text{C}_p$ ). FAB-Mass Spectrometry.  $m/z$ : 667 [( $\text{M}+23$ ) $^+$ ], 499 [( $\text{M}+23-168$ ) $^+$ ], 331 (base peak) [( $308+23$ ) $^+$  = ( $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_6\text{Na}$ ) $^+$  = ( $\text{M}_{\text{DMDOO}} + \text{Na}$ ) $^+$ ], 309 (308 + 1) $^+$  = ( $\text{M}_{\text{DMDOO}} + \text{H}$ ) $^+$ ], 124 [( $\text{C}_4\text{H}_2\text{O}_2\text{N-CH}_2\text{-CH}_2$ ) $^+$ ], 81 [( $\text{CH}_2\text{-fur}$ ) $^+$ ].

CI-Mass Spectrometry.  $m/z$ : 309  $(308 + 1)^+ = (M_{\text{DMDOO}} + \text{H})^+$ , 124  $[(\text{C}_4\text{H}_2\text{O}_2\text{N}-\text{CH}_2-\text{CH}_2)^+]$  81 (base peak)  $[(\text{CH}_2-\text{fur})^+]$ .

### Synthesis of poly(HEMA-random-FMA) copolymer-based hydrogels “via” the Diels-Alder reaction. Study of their rheological properties

In a typical procedure, pHEMA<sub>90%</sub>-FMA<sub>10%</sub> (2.735 g, 2.04 mmol furfuryl methacrylate) was dissolved in a 50% v/v mixture of methanol-water (30.6 mL) and stirred for 1 h. A solution of DMDOO (320 mg, 1.04 mmol, 2% excess) in DMF (4.5 mL) was added, leading to a homogeneous solution with a final copolymer concentration of 7.8% w/v. The reaction mixture was stirred at 25 °C for 48 h. The resulting gel was characterized by means of NMR (data recorded below), rheological, and thermal properties. The rheological characterization was carried out in a controlled-strain rheometer, at 25 °C. Small-amplitude oscillatory shear (SAOS) tests, inside the linear viscoelasticity region, were performed in a frequency range of 0.05-100 rad/s, using a serrated plate-and-plate geometry (25 mm diameter, 1 mm gap). Strain sweep tests, at the frequency of 1 Hz, were previously performed on each sample to determine the linear viscoelasticity region. All the samples had the same recent-past thermal and mechanical history. At least two replicates of each test were carried out on fresh samples.

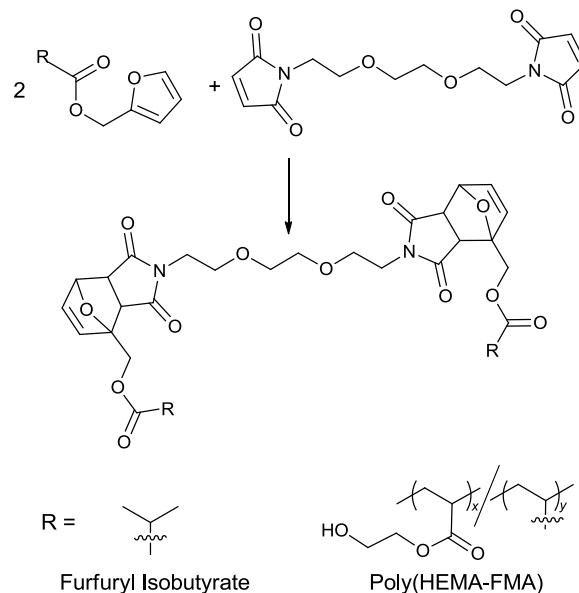
### Kinetic studies of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) copolymer-based hydrogels obtained by the Diels-Alder reaction

Poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>) (79.8 mg, 0.06 mmol furfuryl methacrylate) was dissolved in a 50% v/v mixture of deuterated methanol-D<sub>2</sub>O (0.88 mL) and stirred for 1 h. A solution of DMDOO (10 mg, 0.033 mmol, 10% excess) in DMSO-d<sub>6</sub> (0.12 mL) was added and the reaction mixture was introduced into an NMR tube. The final copolymer concentration in the homogeneous mixture was 8.0% w/v. <sup>1</sup>H NMR spectra were recorded at 298 K over 25 hours at regular intervals (30 min). All the spectra were acquired with a relaxation delay of 5 seconds, 64 k data points and spectral width of 6 kHz (acquisition time of 5.5 seconds), and a pulse length corresponding to a 30° flip angle, accumulating 32 scans after 4 dummy scans. The spectra were zero-filled to 64 k data points, Fourier transformed without weighting function, and baseline- and phase-corrected. NMR data of the obtained gel are as follows: <sup>1</sup>H NMR (D<sub>2</sub>O, CD<sub>3</sub>OD, DMSO-d<sub>6</sub>, 44:44:12; 500 MHz - see Figures 1 and 6 for assignments),  $\delta$  (ppm): 7.61 (bs, H<sub>f</sub>), 6.95 (bs, H<sub>j</sub>, H<sub>k</sub>), 6.86-6.25 (m, H<sub>g</sub>, H<sub>h</sub>, H<sub>e</sub>, H<sub>h</sub>), 5.44 (bs, H<sub>f</sub>(endo)), 5.32 (bs, H<sub>f</sub>(exo)), 4.07 (bs, H<sub>d</sub>), 3.80 (bs, H<sub>c</sub>), 3.84, 3.58 (H<sub>j</sub> (endo and exo)), 3.72-3.51 (m, l', m', n'), 3.27, 3.17 (bs, H<sub>k</sub>(endo and exo)), 2.15-1.86 (m, H<sub>u</sub>, H<sub>v</sub>), 1.09 (bs, H<sub>z</sub>), 0.91 (m, H<sub>y</sub>). <sup>13</sup>C NMR (D<sub>2</sub>O, CD<sub>3</sub>OD, DMSO-d<sub>6</sub>, 44:44:12; 125 MHz),  $\delta$  (ppm): 180.6-179.6 (C=O), 145.0 (C<sub>f</sub>), 138.8-135.0 (C<sub>g</sub>, C<sub>h</sub>, C<sub>g'</sub>, C<sub>h'</sub>), 135.7 (C<sub>j'</sub>, C<sub>k'</sub>), 82.0 (C<sub>f</sub>(exo)), 80.7 (C<sub>f</sub>(endo)), 70.8-68.5 (C<sub>l</sub>, C<sub>m</sub>, C<sub>n</sub>), 68.6-67.8 (C<sub>d</sub>), 60.9-60.2 (C<sub>c</sub>), 55.1 (C<sub>u</sub>), 53.1 (C<sub>v</sub>), 51.2, 49.5(C<sub>k'</sub> (endo and exo)), 48.8, 47.6 (C<sub>j</sub> (endo and exo)), 19.8 (C<sub>z</sub>), 17.8 (C<sub>y</sub>).

## Results and discussion

### Studies on the model compound furfuryl isobutyrate

The first attempt at the Diels-Alder reaction was made using the model compound furfuryl isobutyrate with 1,8-dimaleimide-3,6-dioxaoctane (DMDOO) in dichloromethane, a solvent in which both molecules were completely soluble (Scheme 1).

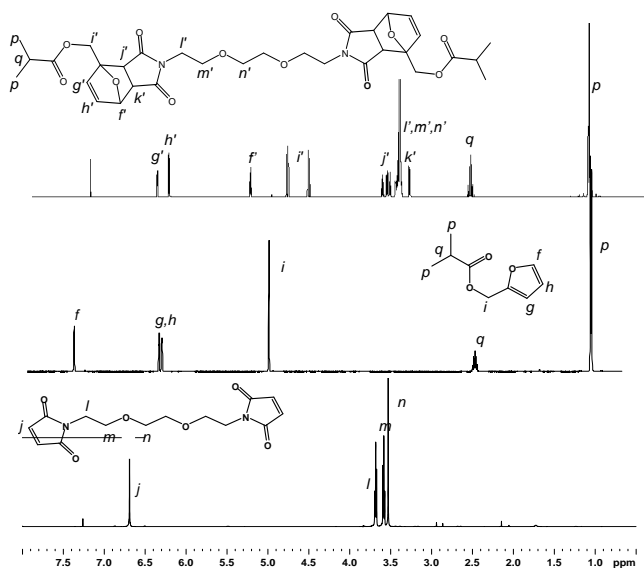


**Scheme 1:** Diels-Alder reaction for furfuryl isobutyrate model compound and poly(HEMA-FMA) copolymers with 1,8-dimaleimide-3,6-dioxaoctane.

The <sup>1</sup>H NMR spectra of DMDOO, furfuryl isobutyrate, and the Diels-Alder product (Figure 2) show that the Diels-Alder reaction has taken place. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are fully elucidated (see experimental). The chemical shifts and integrals obtained from the <sup>1</sup>H NMR spectrum indicate the formation of the Diels-Alder adduct at both maleimide sites of the bisdienophile DMDOO. This is further confirmed by the signals of the methylene protons (Figure 2– protons “i”), which appear as a singlet at 5.06 ppm in the starting furfuryl isobutyrate, but behave as diastereotopic protons, i<sub>1</sub>' (doublet) and i<sub>2</sub>' (doublet), at 4.89 ppm and 4.63 ppm respectively, in the product. On comparing the integrals from the “i” oxymethylene protons in the <sup>1</sup>H NMR of the crude reaction solution (not shown), the stereoselectivity of the Diels-Alder reaction is observed, with an endo:exo ratio of 78:22.

The model Diels-Alder adduct has been studied by both chemical ionization (CI) and fast atom bombardment (FAB) mass spectrometry. Interestingly, in the CI mass spectrum (carried out at temperatures over 80 °C), only fragmentations of the starting materials were observed. Furthermore, since the highest  $m/z$  peak in the CI-MS (309) is due to  $(M_{\text{DMDOO}} + \text{H})^+$ , and there are no fragmentation peaks from the Diels-Alder product, it can be concluded that the retro Diels-Alder reaction has taken place entirely under these conditions. Since the <sup>1</sup>H NMR spectrum shown in Figure 2 has no diene in the product,

it is likely that the retro Diels-Alder reaction has occurred at these higher temperatures.<sup>26</sup>



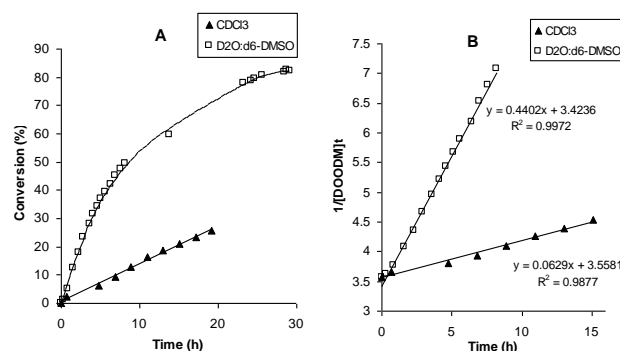
**Figure 2:** <sup>1</sup>H NMR spectrum of 1,8-dimaleimide-3,6-dioxaoctane (bottom), furfuryl isobutyrate (middle), and the Diels-Alder adduct (top).

FAB mass spectrometry corroborates the formation of the Diels-Alder adduct, with the highest *m/z* peak of the purified product observed at 667 [(*M*+23)<sup>+</sup> = (*M* + Na)<sup>+</sup>], verifying that the Diels-Alder reaction had occurred at both ends of the bisdienophile. Although this is a room temperature technique, the sample temperature can be gently increased as a consequence of the atom bombardment, and—remarkably—evidence of the retro Diels-Alder taking place under these mild conditions was observed. The peak at 499 [(*M* + 23 – 168)<sup>+</sup> = (*M* + Na – furfuryl isobutyrate)<sup>+</sup>] corresponds to the subproduct obtained from the retro Diels-Alder reaction occurring at one site of the analyzed product, with elimination of one furfuryl isobutyrate molecule. The peaks at 331 [308 + 23)<sup>+</sup> = (*M*<sub>DMDOO</sub> + Na)<sup>+</sup>], 309 (308 + 1)<sup>+</sup> = (*M*<sub>DMDOO</sub> + H)<sup>+</sup>], 124 [(C<sub>4</sub>H<sub>2</sub>O<sub>2</sub>N-CH<sub>2</sub>-CH<sub>2</sub>)<sup>+</sup>], and 81 [(CH<sub>2</sub>-fur)<sup>+</sup>] correspond to the bisdienophile and the diene, produced as a consequence of the retro Diels-Alder reaction.

#### Kinetic studies of the Diels-Alder reaction of furfuryl isobutyrate with DMDOO

A <sup>1</sup>H NMR kinetic study was carried out for this model reaction over 15–30 hours [furfuryl isobutyrate:DMDOO molar ratio 2:1 (diene:dienophile 1:1), furfuryl isobutyrate initial concentration 0.28 M] in both CDCl<sub>3</sub> and D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4) (DMSO was used in order to obtain a homogeneous solution required for the NMR experiment). The conversions were calculated by comparing the integral of the signal “j” from the maleimide residue in the bisdienophile with that of the signal “f” from the product (see Figure 2). The conversions of these Diels-Alder reactions were plotted against time for both solvent systems (Figure 3A). This shows a conversion of only 25.7% after 19 h

in CDCl<sub>3</sub>, but a conversion of around 70% over the same time period in D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4).



**Figure 3:** (A) Conversion vs. time plot and (B)  $1/[1,8\text{-dimaleimide-3,6-dioxaoctane}]_t$  vs. time plot, for the Diels-Alder reaction of furfuryl isobutyrate with 1,8-dimaleimide-3,6-dioxaoctane in CDCl<sub>3</sub> and D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4).

It has been reported by several groups that the Diels-Alder reaction for both simple molecules and polymers that contain furan and maleimide functionalities follow second-order kinetics.<sup>27–30</sup> For the cross-linking of maleimide-containing polyamides with a trifunctional furan compound in *N,N*-dimethylacetamide (25 wt%), Liu *et al.* calculated values of *k*, from the second-order model, of  $1.25\text{--}4.83 \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  in the temperature range of 20–60 °C, with an activation energy of 32.1 kJ mol<sup>-1</sup>.<sup>16</sup> This is in reasonable agreement with the other reported values for furan/maleimide Diels-Alder reactions.

In our case, the initial concentration of furan groups (diene) in furfuryl isobutyrate and maleimide groups (dienophile) in DMDOO was 0.28 M. Since we have a 1:1 feed of reacting groups, the integrated rate expression for a second-order reaction, in which *k* is the rate constant, is as follows:

$$\frac{1}{[A]} = \frac{1}{[A]_0} + kt$$

where  $1/[A]$  is the inverse concentration of unreacted maleimide groups at time *t*, and  $1/[A]_0$  is the inverse initial concentration of unreacted maleimide groups. Figure 3B shows plots of the concentration of unreacted maleimide groups at time *t* ( $1/[DMDOO]_t$ ) against time for both solvent systems. Linear least-squares analysis gives values for *R*<sup>2</sup> of 0.988 and 0.997 for the first-order plots in CDCl<sub>3</sub> and D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4), respectively. The intercepts of the linear plots, measured at time zero, are 3.56 dm<sup>3</sup> mol<sup>-1</sup> in CDCl<sub>3</sub>, and 3.42 dm<sup>3</sup> mol<sup>-1</sup> in D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4), which compare well with the real value ( $1/[A]_0 = 3.57 \text{ dm}^3 \text{ mol}^{-1}$ ). All these data support the second-order kinetics mechanism.

From Figure 3B, the rate constant *k* in CDCl<sub>3</sub> was calculated to be  $1.747 \times 10^{-5} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , which is in good agreement with that obtained by other groups.<sup>16</sup> In D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4), the calculated rate constant was  $1.223 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , which is

one order of magnitude greater than in purely organic solvents, despite the quantity of D<sub>2</sub>O being only 20% v/v. This is expected, since it is well known that the presence of water increases the rate of the Diels-Alder reaction between maleimides and furan groups.<sup>31</sup>

### Synthesis by ATRP of a batch of poly(HEMA-random-FMA) copolymers

Three copolymers were synthesized by ATRP at room temperature using methanol as polymerization solvent (theoretical compositions: Copolymer 1 poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>), Copolymer 2 poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>), and Copolymer 3 poly(HEMA<sub>85%</sub>-FMA<sub>15%</sub>). The copolymerization of HEMA and FMA monomers was first attempted in 50:50 v/v methanol/water mixtures. The polymerizations proceeded quickly to give the uncolored precipitates in high yields within 90 minutes at 25 °C. However, although the use of methanol-water as solvent in ATRP accelerated the polymerization process, the polymer could not be totally re-dissolved in good solvents for HEMA-based polymers. This suggests that some degree of cross-linking occurred during polymerization, possibly due to transesterification;<sup>22</sup> consequently, that mixture of solvents was ruled out for the preparation of linear HEMA-based copolymers.

Next, copolymerizations were attempted in pure methanol. The target degree of polymerization was 200. When the mol percentage of FMA in the feed did not exceed 10%, the reactions proceeded smoothly with almost total consumption of FMA and HEMA monomers after 5 h, even at the aimed-for high degree of polymerization. The synthesis details and characterization data for various statistical HEMA-FMA copolymers are summarized in Table 1.

Under these conditions, linear and totally soluble HEMA-FMA copolymers were obtained in very high yields (> 90% over the isolated polymer) and narrow polydispersities were exhibited up to 70% conversion, reaching values close to 1.6 under monomer-starved conditions. Temperature seemed to have a marked impact on polydispersities, with values below 1.2 at 15 °C after 3 h. This is consistent with the occurrence of minor transfer reactions involving the capture of free radicals by the

heterocycle.<sup>32</sup> Conversely, side reactions could be responsible for the lower yields obtained (83% after 5 h) for poly(HEMA<sub>85%</sub>-FMA<sub>15%</sub>), probably due to transesterification or to electron-transfer reactions.

The compositions of the copolymers were calculated by <sup>1</sup>H NMR, comparing the integral of the signal “d” from the HEMA residue at 3.91 ppm with that of the signal “i” from the FMA moiety at 4.98 ppm (see Figure 1).

The incorporation of both monomers into the copolymers was in excellent agreement with the theoretical at every HEMA and FMA conversion [actual compositions: Copolymer 1 (poly(HEMA<sub>94%</sub>-FMA<sub>6%</sub>), Copolymer 2 (poly(HEMA<sub>89%</sub>-FMA<sub>11%</sub>), Copolymer 3 (poly(HEMA<sub>85%</sub>-FMA<sub>15%</sub>)).

### Kinetic studies of the synthesis by ATRP of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) copolymer

Kinetic studies of the synthesis *via* ATRP of poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>) copolymer were carried out over a 24-hour period. The conversion was calculated by comparing the integral of the residual peak of one of the vinyl protons from the unreacted monomers at 5.69 ppm with those of the broad signals at 3.91 ppm and 4.98 ppm corresponding to the “d” protons from the HEMA and the “i” protons from the FMA in the copolymer, respectively.

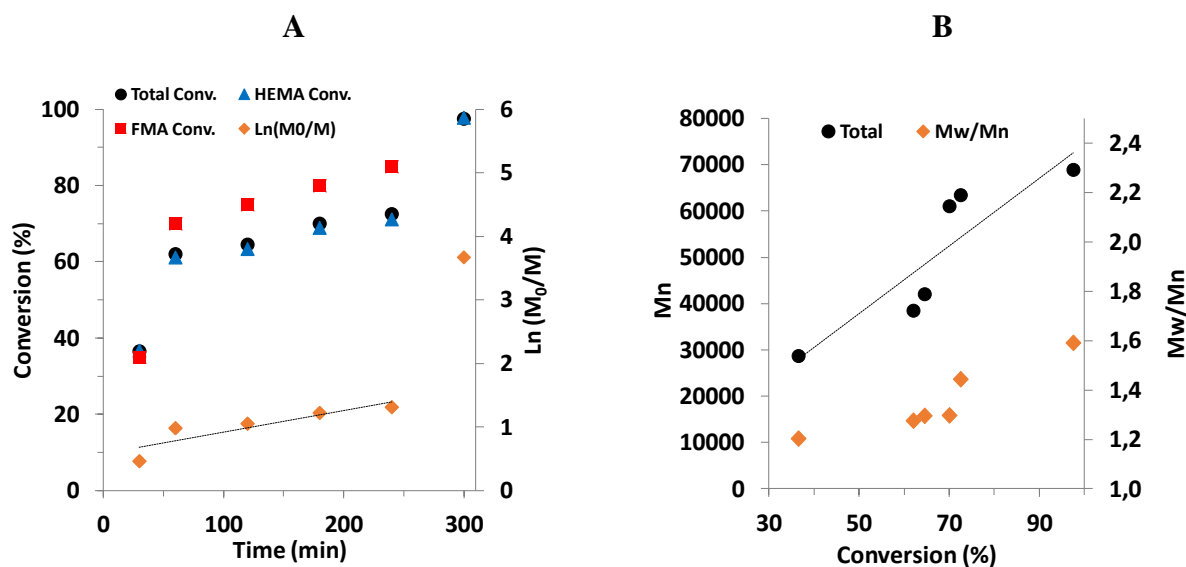
Overall conversion higher than 70% was achieved within 4 h at 25 °C; FMA monomer was incorporated into the copolymer chains slightly quicker than HEMA monomer (Figure 4A).  $M_n$  was measured by GPC; its evolution was linear with conversion (Figure 4B). Polymerization was first-order with regard to HEMA and FMA monomers up to around 70% conversion. After 5 h of reaction at 25 °C, 98% and 95% conversions of HEMA and FMA monomers were achieved, respectively. Despite polydispersities remaining low throughout the polymerization,  $M_w/M_n$  was slightly higher at the end of the polymerization process, which suggests that, to some extent, ineffective termination reactions occur under these conditions. This phenomenon could be due to the high degree of polymerization aimed at in this assay (target DP = 200), preventing the maintenance of optimum control over the final material.

**Table 1:** Summary of the synthesis parameters and molecular weight data for the synthesis of the three poly(HEMA-random-FMA) via ATRP in methanol.

| Polymer ID | T (°C) | Theoretical composition (mol %) |     | NMR composition <sup>a</sup> (mol %) |     | Conversion <sup>a</sup> (%) | $M_n^b$ | $M_w/M_n^b$ |
|------------|--------|---------------------------------|-----|--------------------------------------|-----|-----------------------------|---------|-------------|
|            |        | HEMA                            | FMA | HEMA                                 | FMA |                             |         |             |
| Polymer 1  | 15     | 95                              | 5   | 94                                   | 6   | 58                          | 35000   | 1.17        |
| Polymer 2  | 25     | 90                              | 10  | 89                                   | 11  | 70                          | 61100   | 1.30        |
| Polymer 3  | 15     | 85                              | 15  | 85                                   | 15  | 31                          | 13750   | 1.17        |

Polym. Condit.: [M]<sub>0</sub> = 50% w/v, EBiB/CuBr/bpy (1:1:2.5); target DP = 200. <sup>a</sup>At 3 h. <sup>b</sup>Determined by GPC.

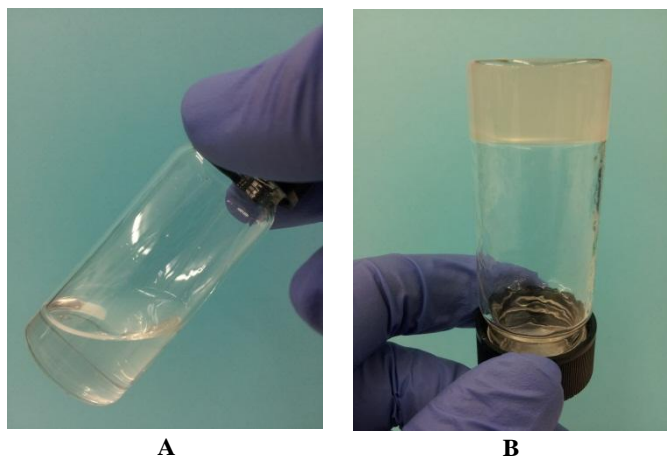




**Figure 4:** (A) Kinetic plot for the ATRP of HEMA-FMA copolymer in MeOH at 25 °C. (B) Evolution of molecular weight with conversion for the same experiment followed by GPC.  $[M]_0 = 50\%$  w/v, EBiB:Cu(I)Br:bpy 1:1:2.5. Target DP: 200.

#### Gelification of poly(HEMA-random-FMA) copolymers with DMDOO

The Diels-Alder reactions for the three copolymers with DMDOO were next examined. Liu *et al.*<sup>16</sup> described the formation of polymeric gels from the Diels-Alder reaction of maleimide and furan groups in *N,N*-dimethylacetamide (25 % w/v) at 30 °C. The observed gel times, monitored by eye, for their systems were 10-54 days, depending on the content of reactive groups. In contrast, our aqueous-based 7.8 % w/v solutions reached a gel-like viscosity above 1000 Pa s (shear rate  $0.1 \text{ s}^{-1}$ ) from within 20 hours up to 7 days, at 30 °C, indicating the increased rate of the Diels-Alder reaction in water (Figure 5). The gelification of poly(HEMA<sub>85%</sub>-random-FMA<sub>15%</sub>) led to an opaque material whose hydrophilic nature was diminished with the reduction of HEMA content.



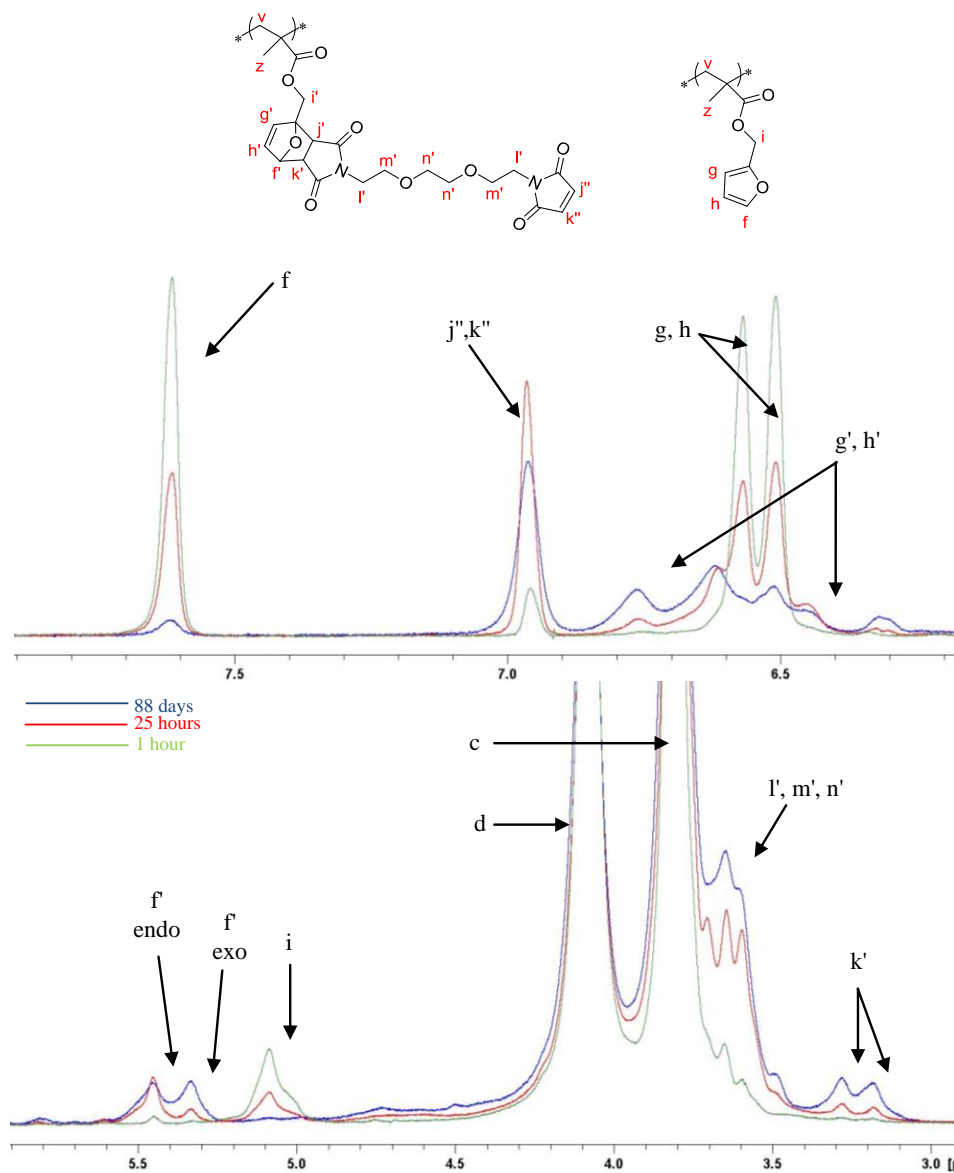
**Figure 5:** Photos illustrating cross-linking reaction of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) with DMDOO at  $t = 0$  hours (A) and at  $t = 20$  hours (B).

The gels developed in this study successfully demonstrated a proof of concept as well as the reproducibility of the method, although in other works a number of drawbacks associated to them was encountered, such as the low molecular weight of furfuryl acrylate-based oligomers synthesized and their relatively high polydispersities.<sup>33</sup>

#### Kinetic studies of the gelification “via” Diels-Alder of the poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) copolymer

To monitor the Diels-Alder reaction, diffusion-filtered NMR experiments were made on a solution of poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>) / DMDOO (0.5 molar equivalents based on the moles of furan in the copolymer, see Experimental Section). The gel was formed through the reaction of bismaleimide DMDOO with the copolymer in the presence of a suitable solvent system (D<sub>2</sub>O, CD<sub>3</sub>OD, DMSO-*d*<sub>6</sub>, 44:44:12). An efficient way to discriminate between polymer signals and those belonging to other smaller molecules present in the solution is to use diffusion-filtered NMR spectroscopy.<sup>34-36</sup> This technique takes advantage of the differences in translational diffusion between molecules of diverse sizes in solution. Signals from fast-diffusing molecules can be dramatically attenuated, so that they are filtered out from the NMR spectrum, while the signals of the species with slower translational diffusion, such as the polymer, are retained. This allows monitoring the changes in the NMR spectrum of the polymer without interference from other species.

Several diffusion-filtered <sup>1</sup>H NMR spectra were acquired at different times (from 0 to 25 h) during the kinetic study of the cross-linking process of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) with DMDOO. A final spectrum after 88 days was also acquired to obtain information about the system after such a long period of time (Figure 6). The experimental parameters were optimized



**Figure 6:** Diffusion-filtered  $^1\text{H}$  NMR spectra of the gelification process of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) with DMDOO at  $t = 1$  hour (green),  $t = 25$  hours (red), and  $t = 88$  days (blue).

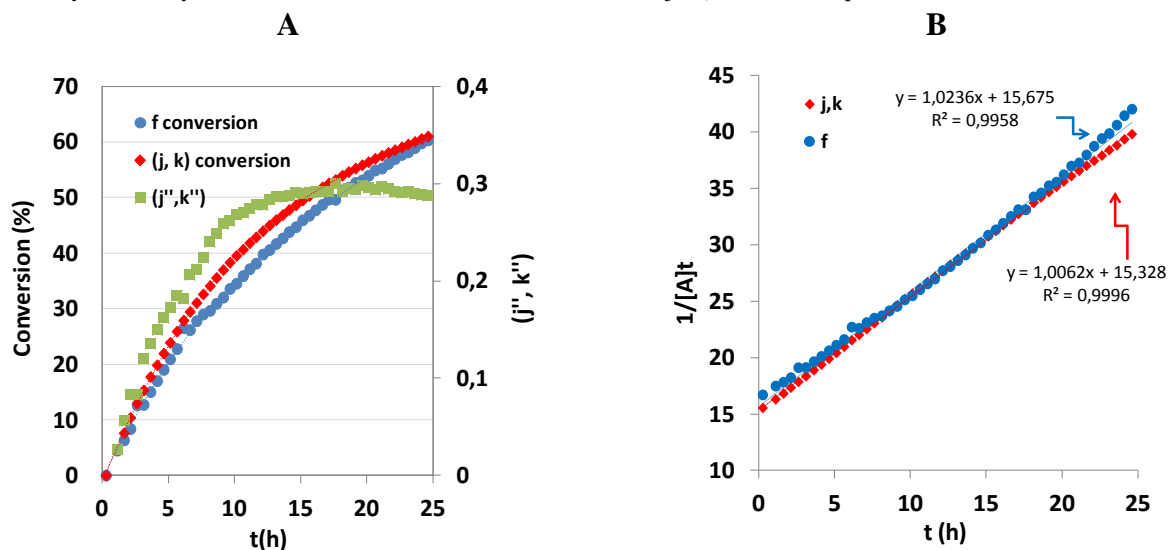
to observe exclusively the signals of the polymer (see Experimental Section). These spectra unequivocally showed the reaction between the two species. In particular, a continuous decrease was observed in the intensity of the signals corresponding to the furfuryl moiety (f, g, h, and i), together with an increase in intensity of new signals which correspond to the Diels-Alder cyclic-adduct (f', g' and h'). Most important was the observation of new signals in these spectra corresponding to protons of the DMDOO molecule (k', l', m', n', j'' and k''). Taking into account that the experimental conditions were adjusted to filter out the free DMDOO signals, these observations demonstrate that the small DMDOO molecule was incorporated into the polymer. Two further noteworthy considerations arose from the study of these spectra. First, the

new signal at 6.95 ppm, corresponding to the unsaturated protons of the pendant maleimide moiety (j'' and k''), increased during the first hours, remained stable for a time, and finally decreased, indicating that the free maleimide ring later cross-linked with unreacted furan moieties left over in the polymer. Secondly, for longer times, a new signal with  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts similar to those of the proton f' appeared and increased in intensity, suggesting that, at shorter times, the kinetically controlled *endo* cyclic-adduct was formed, whereas the thermodynamically more stable *exo* product was generated at longer times.

Simultaneously,  $^1\text{H}$  NMR quantitative kinetic studies of the gelification process of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) via

the Diels-Alder coupling reaction were carried out over 24 h [Figure 7, furfuryl methacrylate: DMDOO molar ratio 2:1.05

at time zero, are  $15.68 \text{ dm}^3 \text{ mol}^{-1}$  for  $1/[f]_0$ , and  $15.33 \text{ dm}^3 \text{ mol}^{-1}$  for  $1/[j,k]_0$ , which compare well with the real values ( $1/[f]_0 =$



**Figure 7:** Kinetic studies of the gelification process of poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) with DMDOO based on <sup>1</sup>H NMR spectra. **7A:** Conversion vs. time; **7B:**  $1/[A]_t$  (where A is either FMA or 1,8-dimaleimide-3,6-dioxaoctane) vs. time plot for the Diels-Alder reaction.

(diene:dienophile 1:1.1), furfuryl methacrylate initial concentration 0.06 M] in CD<sub>3</sub>OD-D<sub>2</sub>O-DMSO-d<sub>6</sub> (44:44:12).

The conversions were calculated by comparing the changes in the integral values of the signals at 7.61 ppm (f, due to the furan ring), 6.96 ppm (j'' and k'', due to the pendant maleimide moiety joined to the polymer chain), and 6.91 ppm (j and k corresponding to the dienophile in DMDOO) (for assignment, see Figure 6). The conversions of the Diels-Alder reaction were plotted against time for the chosen solvent system, as shown in Figure 7A. This demonstrates a conversion of about 60% (59.8% or 60.6%, depending on the data studied) after 24 h. The high concordance of data obtained integrating different peaks of the spectrum is remarkable: peak f corresponding to the furan ring and peak j,k, associated to the bisdienophile DMDOO. Furthermore, an increase in the values from the integrals of the new peaks j'' and k'' in the plot can be observed at low conversions, as well as a plateau region when 50% conversion of the Diels-Alder reaction was reached. The decreasing trend of those values was intuited at longer times, indicating that free maleimide rings pending from polymer chains reacted with remaining unreacted furan moieties in the polymer.

In this gelification process, the initial concentration of furan groups (diene) in poly(HEMA<sub>90%</sub>-random-FMA<sub>10%</sub>) and maleimide groups (dienophile) in DMDOO were 0.06 M and 0.066 M, respectively. Mathematical treatment of the data was similar to that described above for the coupling reaction between furfuryl isobutyrate and DMDOO. Figure 7B shows plots of inverse concentration of unreacted maleimide groups at time  $t$  ( $1/[j,k]_t$ ) and unreacted furan group ( $1/[f]_t$ ) against time. Linear least-squares analysis gave values for R<sup>2</sup> of 0.9996 and 0.9958 for the first-order plots of  $1/[j,k]_t$  and unreacted  $1/[f]_t$  vs. time, respectively. The intercepts of the linear plots, measured

$16.67 \text{ dm}^3 \text{ mol}^{-1}$  and  $1/[j,k]_0 = 15.15 \text{ dm}^3 \text{ mol}^{-1}$ , respectively). As in the case of the model compound furfuryl isobutyrate, all these data support the second-order kinetics mechanism.

The rate constant  $k$  was calculated from both plots in Figure 7B. The experimental values were very close to each other ( $2.843 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  and  $2.795 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , respectively), and higher than the rate constant  $k$  ( $1.223 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ) found in the coupling reaction of the model compound with DMDOO in D<sub>2</sub>O:d<sub>6</sub>-DMSO (1:4) (see *Results and Discussion: Kinetic studies of the Diels-Alder reaction of furfuryl isobutyrate with DMDOO*).

In summary, solution <sup>1</sup>H NMR spectroscopy is an excellent and reliable technique for following the gelification process of synthesized HEMA-FMA copolymers with DMDOO. It can be observed that the consumption of FMA and DMDOO match well, due to the absence of side reactions which would alter the molar ratio between them.

#### MTDSC studies of gels based on poly(HEMA-random-FMA) copolymers

Modulated temperature differential scanning calorimetry (MTDSC) is the general term for DSC techniques where a non-linear heating or cooling rate is applied to the sample to separate the kinetic data from the thermodynamic ones. This technique finds multiple applications in the polymer field: for instance, Higginbotham *et al.*<sup>37</sup> developed some thermosensitive polymer matrices based on *N*-isopropylacrylamide (NIPAAm) photo-polymerized with 1-vinyl-2-pyrrolidinone (NVP). The thermosensitive hydrogels synthesized belong to the negative temperature-sensitive hydrogels category, with a lower critical solution temperature (LCST), and contract upon heating above the LCST. In general terms, the reversing heat-flow signal provided great sensitivity

in the determination of LCST when compared with conventional DSC. Also, Nazzal and Wang<sup>38</sup> studied soft gelatin capsules by thermal analysis. They investigated the transition gel-sol by MTDSC and focused on the reversible heat-flow plot corresponding to transitions where the gelatin systems underwent a transformation from an arrangement with a higher heat capacity to one with a lower heat capacity. As the phase transition temperature is a completely reversible transition,<sup>39,40</sup> the reversible heat-flow curves reflect true gel-sol transitions and are, therefore, a better measurement of physical changes in polymeric gels. It should be noted that several researchers have differed in their interpretation of the phase transition endotherm. Thus, Otake *et al.*<sup>40</sup> define the phase transition temperature as the onset of the transition endotherm (the interaction of the baseline and the leading edge of the endotherm), while Schild *et al.*<sup>41</sup> define it as the temperature at the peak of the thermogram. This aspect should be taken into account when analyzing transition temperatures by calorimetry, since peak and onset values may differ by a number of degrees Celsius. We investigated herein the phase transition temperature of the prepared gels by modulated differential scanning calorimetry (MDSC), and both peak onset and peak maximum values were recorded.

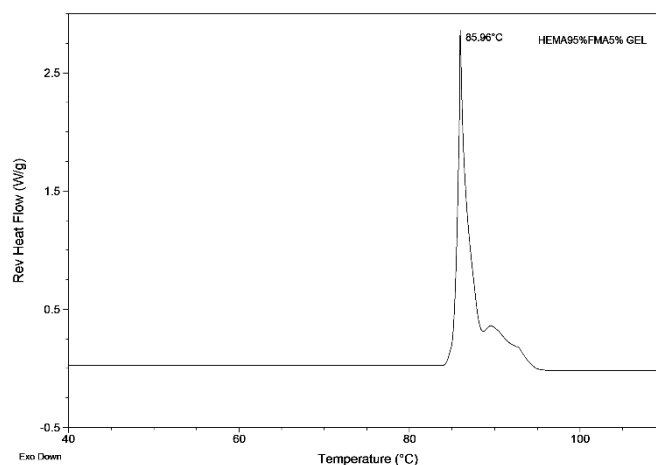
Table 2 records the phase transition temperatures (°C) obtained at the peak of the transition endotherm and from the onset of the transition endotherm for the three hydrogels prepared. All the values encountered were in a very narrow range (from 86 °C to 94 °C) for the hydrogels synthesized, and the differences in the values for the same network system were less significant at lower cross-linking degrees (for poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>), those values were 85.96 °C and 85.68 °C, respectively).

**Table 2:** Thermal properties of synthesized poly(HEMA-FMA)-based hydrogels from modulated temperature differential scanning calorimetry (MTDSC).

| Gel   | MTDSC                   |                          |                             |
|---|-------------------------|--------------------------|-----------------------------|
|   | Peak Temp. <sup>a</sup> | Onset Temp. <sup>b</sup> | Rev. Heat Flow <sup>c</sup> |
| p(HEMA <sub>95%</sub> -FMA <sub>5%</sub> )  | 85.96                   | 85.68                    | 209.9                       |
| p(HEMA <sub>90%</sub> -FMA <sub>10%</sub> ) | 92.49                   | 91.17                    | 81.21                       |
| p(HEMA <sub>85%</sub> -FMA <sub>15%</sub> ) | 94.46                   | 91.44                    | 134.2                       |

<sup>a</sup> Peak Temp.: Phase transition temperature from the temperature at the peak of the transition endotherm (°C); <sup>b</sup> Onset Temp.: Phase transition temperature from the onset of the transition endotherm (°C); <sup>c</sup> Rev. Heat Flow: Reversible heat flow (J/g).

Du Prez and co-workers<sup>26</sup> prepared some furan-based thermoset polyurethanes in which maleimide rings were the dienophile used for the cross-linking reaction. They demonstrated that, at temperatures higher than 90 °C, the retro Diels-Alder reaction was favored, leading to the starting diene and dienophile (furan and maleimide groups, respectively). In the present study, the findings showed that the reversing heat-flow signal yielded a well-defined endotherm and was close to 90 °C (Figure 8). These results suggest the thermo-reversibility of the covalent



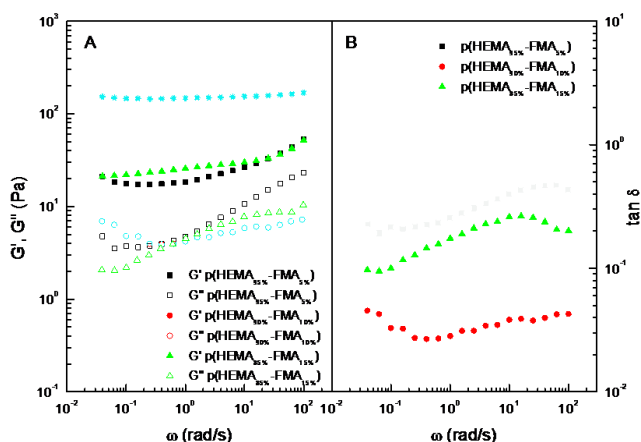
**Figure 8:** Reversible heat-flow plot and phase transition temperature from the temperature at the peak of the transition endotherm (°C) of poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>)-based hydrogel established using modulated temperature DSC (MTDSC).

bonds generated when furan and maleimide moieties self-assembled into the tricyclic system.

#### Rheological characterization of HEMA-FMA copolymer-based gels in methanol-water

Figure 9 shows the mechanical spectra obtained from small-amplitude oscillatory shear (SAOS) measurements inside the linear viscoelastic range, for gels prepared with poly(HEMA-random-FMA) in methanol-water, differing in HEMA and FMA composition. All the formulations contain the same total copolymer concentration in the homogeneous mixture (7.8% w/v). For the gel prepared with poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>), the values of storage modulus,  $G'$ , are significantly higher than those found for the loss modulus,  $G''$ , over the whole frequency range studied. The so-called “plateau region” was noticed, where  $G'$  increases slightly with frequency, and  $G''$  displays a clear minimum at intermediate frequencies. This mechanical spectrum corresponds with the traditional description given for solid-like gels,<sup>42</sup> and is typically found in highly entangled polymeric systems.<sup>43</sup> However, lower  $G'$  values and a tendency to a crossover between  $G'$  and  $G''$  at high frequencies, *i.e.* the beginning of the transition region, were obtained for the gel containing poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>) copolymer. Moreover, the values of  $G''$  were similar at low frequencies and increased at high frequencies for the poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>) copolymer. Therefore, it is clear that the values of  $G'$  for poly(HEMA-co-FMA) copolymer-based gels increase when the HEMA content decreases and FMA content increases from 5% to 10%. As is well known,<sup>44</sup> the gel strength of copolymer dispersed systems, from dilute solutions to completely cross-linked gels, can be quantified from SAOS measurements as a function of the  $G'$  and  $G''$  frequency dependence, *i.e.* the slopes in plots of  $G'$  and  $G''$  vs. frequency, and the relative values of both viscoelastic functions, *i.e.* the relative elasticity, expressed in terms of the loss tangent ( $\tan \delta = G''/G'$ ). Thus, the poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>) copolymer seems to induce a more developed plateau region, with lower slopes in plots of  $G'$  and  $G''$  vs. frequency

(Figure 9A) and lower values of the loss tangent over a wide frequency range (Figure 9B), indicating a higher relative



**Figure 9:** Frequency dependence of the storage ( $G'$ ) and loss ( $G''$ ) moduli and the loss tangent for poly(HEMA-co-FMA) copolymer-based gels in methanol-water.

elasticity.

When the polymer poly(HEMA<sub>85%</sub>-FMA<sub>15%</sub>) is used in the Diels-Alder cross-linking reaction, a gel-like dispersion is developed. This dispersion shows similar  $G'$  values to those exhibited by poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>) copolymer-based gel, although with a different slope and slightly increased  $G''$  values at high frequencies compared with those presented by poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>) copolymer-based gel. Moreover, that dispersion shows a higher relative elasticity than the gel based on poly(HEMA<sub>95%</sub>-FMA<sub>5%</sub>) and lower than that of poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>).

## Conclusions

Well-defined HEMA-FMA copolymers with low polydispersities have been successfully synthesized using ATRP under very mild conditions. The molar percentage of HEMA and FMA in the copolymers was readily controlled simply by adjusting the HEMA/FMA molar ratio in the feed. The reactions proceeded with high conversions within 5 hours, and these copolymers showed an excellent agreement between the theoretical and actual compositions. Next, a model compound, namely furfuryl isobutyrate, was synthesized and used to examine the Diels-Alder reaction with 1,8-dimaleimide-3,6-dioxoctane. A kinetic experiment was carried out by  $^1\text{H}$  NMR for the reaction in both (1:4)  $\text{D}_2\text{O}:\text{d}_6\text{-DMSO}$  and  $\text{CDCl}_3$ . The results showed that the Diels-Alder reaction in (1:4)  $\text{D}_2\text{O}:\text{d}_6\text{-DMSO}$  proceeded one order of magnitude faster than that in  $\text{CDCl}_3$ . The procedure investigated was further applied to HEMA-FMA copolymers at 25 °C. It resulted in a robust synthetic strategy for the preparation of HEMA-based hydrogels where those copolymers react through aqueous-based Diels-Alder chemistry without the participation of catalysts in relatively short times (from 24 hours to 7 days, depending on the FMA ratio of the polymer). For monitoring the gelification processes, diffusion-filtered NMR spectroscopy proved an

excellent method to unequivocally confirm the reaction between the polymer and the cross-linking agent. Furthermore, solution  $^1\text{H}$  NMR spectroscopy was demonstrated to be an excellent and reliable technique for studying the kinetics of the cross-linking reaction, and corroborated the absence of side reactions in which furan and maleimide rings might be involved. The two techniques constitute a reliable tandem procedure to monitor the gelification process, since these strong hydrogels, with high elasticity, led to well-resolved solution  $^1\text{H}$  NMR spectra. Modulated temperature differential scanning calorimetry (MTDSC) revealed that the reversing heat-flow signal yielded well-defined endotherms close to 90 °C, suggesting the thermo-reversibility of the Diels-Alder coupling reaction. This is significant as it is the first account of thermally reversible HEMA polymeric networks in aqueous media *via* Diels-Alder chemistry. The linear viscoelasticity functions of hydrogels are influenced by the chemical composition. Thus, the values of the storage modulus ( $G'$ ) for poly(HEMA-random-FMA) copolymer-based gels increase when the HEMA content decreases from 95% to 90% and FMA increases from 5% to 10%. Moreover, the poly(HEMA<sub>90%</sub>-FMA<sub>10%</sub>) copolymer seems to induce a more developed plateau region and lower values of loss tangent, indicating a higher relative elasticity.

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## Notes and references

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