



Preparation and Characterization of pH-Sensitive Hydrogels Based on Crosslinked Maleic Anhydride-Styrene-Methyl Methacrylate Terpolymer

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Abstract. In this study, the hydrogels have been synthesized by the crosslinking reactions maleic anhydride-styrene-methyl methacrylate terpolymer with *N, N'*-methylene-bis-acrylamide and glutaraldehyde in various crosslinker ratios. Crosslinking reactions were carried out in the presence of tetrahydrofuran as solvent at 25-50°C for different time period, and the resulting material properties compared. The best conditions for effective crosslinking, i.e., crosslinking temperature, time and crosslinker ratios were determined for each crosslinker type. The swelling behaviour of the hydrogels was examined in Tris-buffer solutions at various pH at 37°C. Swelling depending on pH was observed in the hydrogels. The pH-dependent swelling of hydrogels was strongly influenced by the functional group of crosslinker. The molecular structure of the hydrogels was studied by Fourier Transform Infrared Spectroscopy and their pore structure was investigated by using Scanning Electron Microscope.

Keywords: Maleic anhydride-styrene-methyl methacrylate terpolymer, crosslinking, *N, N'*-methylene-bis-acrylamide, glutaraldehyde, pH-sensitive hydrogels.

Çapraz Bağlı Maleik Anhidrit-Stiren-Metil Metakrilat Terpolimerine Dayalı pH-Duyarlı Hidrojellerin Hazırlanması ve Karakterizasyonu

Özet. Bu çalışmada; hidrojeller, maleik anhidrit-stiren-metil metakrilat terpolimerinin *N, N'*-metilenbisakrilamid ve glutaraldehitin farklı oranları ile çapraz bağlanmasıyla sentezlenmiştir. Çapraz bağlanma reaksiyonları çözücü olarak tetrahidrofuran varlığında farklı zaman periyodunda 25-50°C aralığında gerçekleştirilmiş ve malzeme özellikleri kıyaslanmıştır. Her bir çapraz bağlayıcı tipi için çapraz bağlanma sıcaklığı, zamanı ve çapraz bağlayıcı oranı gibi etkin çapraz-bağlanma koşulları belirlenmiştir. Hidrojellerin şişme davranışı Tris tampon ortamlarda farklı pH aralığında 37°C'de incelenmiştir. Hidrojellerin pH-duyarlı olduğu ve pH'ya bağlı şişmenin çapraz bağlayıcının fonksiyonel grubundan etkilendiği görülmüştür. Hidrojellerin moleküler yapısı Fourier Transform Infrared Spektroskopisi ile, gözenek yapısı da taramalı elektron mikroskobu ile incelenmiştir.

Anahtar Kelimeler: Maleik anhidrit stiren metil metakrilat terpolimer, çapraz bağlanma, *N, N'*-metilen-bis-akrilamid, glutaraldehit, pH-duyarlı hidrojel.

1. INTRODUCTION

Hydrogels are the three-dimensional, hydrophilic, polymeric network structures being able to absorb much more water or biological liquids than their own weight. They are non-soluble due to the existence of chemical or physical cross-links between main chains. Some hydrogels are stimuli-sensitive: they change their volume or shape in response to environmental changes such as temperature, pH, ionic strength and magnetic field[1-4]. Among these stimuli-sensitive hydrogels, pH-sensitive hydrogels have been widely used in specific applications such as drug delivery[5-9], biotechnology and waste water treatments[10, 11].

Terpolymers are polymeric structures that takes much interest in the studies relating to improving the properties of polymer blends[12, 13], polymeric biomaterials[14-18]and advanced separation systems[19, 20]due to the distribution of different functional groups. In addition terpolymers offer a great potential to develop to stimuli-sensitive hydrogels which combine two or more stimuli-sensitive mechanisms[4].

In literature many terpolymer formulations have been reported to form well-characterized stimuli-sensitive hydrogels. As examples: Bajpai and Dubey (2004) developed a pH-sensitive terpolymeric hydrogel system based on acrylamide (AAm), methacrylamide (MAm) and acrylic acid (AAc) by aqueous polymerization[21]. Gümüşderelioğlu and Topal (2005) synthesized pH-sensitive hydrogels by crosslinking of monomer mixtures containing ethylene glycol vinyl ether (EGVE), butyl vinyl ether (BVE) and acrylic acid (AA) in the presence of crosslinking agent diethylene glycol divinyl ether (DEGDVE)[22]. Paris et al. (2009) prepared terpolymeric hydrogels based on *N*-isopropylacrylamide (*N*-iPAAm), methacrylic acid (MAA) and poly(ethylene glycol) monomethyl ether monomethacrylate macro monomer (PEGMEMA) and investigated their pH-sensitivity[23]. Reinicke et al. (2009) synthesized double stimuli-sensitive poly(2-vinylpyridine)-*block*-poly(ethyleneoxide)-*block*-poly(glycidyl methyl ether-*co*-ethyl glycidyl ether) (P2VP-*b*-PEO-*b*-P(GME-*co*-EGE)) terpolymeric hydrogels by means of sequential anionic polymerization[24]. Akperov et al. (2009) modified maleic anhydride-allyl propionate-

styrene terpolymer with tri-ethanolamine in order to prepare a new cross-linked functional polymer sorbent[10]. Ngadaonye et al. (2011) fabricated thermo-sensitive terpolymer hydrogels based on *N*-tert-butylacrylamide (NtBAAm), *N*-isopropylacrylamide (NIPAAm) and *N*-vinyl pyrrolidone (NVP) monomers via UV polymerization[25]. Micic et al. (2012) synthesized a series of dual (pH and thermo) sensitive terpolymeric hydrogels with different mole fractions of 2-hydroxyethyl methacrylate (HEMA), itaconic acid (IA) and oligo(ethylene glycol) acrylates (OEGA) by gamma radiation[26]. Yin et al. (2015) prepared slightly crosslinked monodisperse poly(maleic anhydride-cyclohexyl vinyl ether-divinylbenzene) (MA-CHVE-DVB) microspheres via precipitation polymerization using 2,2-azobisisobutyronitrile as an initiator in a mixture of methyl ethyl ketone and n-heptane[27]. However, there is a limited amount of research dealing with the preparation of terpolymer-hydrogels containing maleic anhydride (MA)[10,27]. Meanwhile, terpolymers and terpolymer based hydrogels continue to be important materials for drug delivery, biotechnology and medical applications. We studied the synthesis of maleic anhydride-styrene-methyl methacrylate (MA-St-MMA) terpolymer based hydrogels by direct crosslinking with *N*, *N'*-methylene-bis-acrylamide (MBAm) and glutaraldehyde (GA) to obtain a new type of pH-sensitive hydrogel.

2. EXPERIMENTAL

2.1. Materials

Methyl methacrylate (MMA, bp: 100°C) and Styrene (St, bp: 138°C) were purchased from Merck (Germany). Maleic Anhydride (MA, bp: 200°C) was obtained from Sigma-Aldrich (Germany). Azobisisobutyronitrile (AIBN) used as the free radical initiator was supplied by Sigma-Aldrich (Germany). *N*, *N'*-methylene-bis-acrylamide (MBAm) and glutaraldehyde (GA) were obtained from Sigma-Aldrich (Germany). Tetrahydrofuran (THF, bp: 67°C) used as the solvent was purchased from Prolabo (France). Hydrochloric acid (37%) and 2-amino-2-hydroxymethyl-1,3-propanediol (Tris) used in the swelling studies were supplied by Sigma-Aldrich (Germany). All chemicals were of analytical grade and were used as received.

2.2. Synthesis of the MA-St-MMA terpolymer hydrogels

Terpolymerization reaction of MA-St-MMA taking the mole proportions of 2: 1: 1 ternary systems was carried out in the presence of AIBN as initiator at 70°C for 1 hour. The terpolymer was precipitated in ethyl alcohol and then dried at 37°C in a vacuum and its composition was determined by FTIR[28]. In the second stage the terpolymer hydrogels were synthesized by crosslinking reaction of MA-St-MMA terpolymer in THF medium in the presence of MBAm or GA at 25-50°C. The crosslinking agent was added to the terpolymer solution in different crosslinker ratios (i.e., mass of crosslinker/mass of terpolymer), and stirred magnetically for 15 min. The polymer mixture was then poured into the Pyrex test tube (diameter = 6 mm) and placed into an incubator (Nüve FN 055, Turkey) with appropriate time-temperature program. The resulting hydrogels were carefully removed from the test tubes and washed with distilled water to remove any impurities. Washed hydrogels were dried until constant weight in vacuum at 25°C.

2.3. Swelling studies

In order to determine swelling ratio of hydrogels, each dried hydrogel sample was immersed in Tris buffer solutions of different pH (2.0-9.0, $I = 0.2$) at 37°C. The hydrogel was weighed every 30 min after drying the surface. Measurements were taken until a constant weight was reached. The swelling ratio, SR , was calculated by applying the following equation:

$$SR = \left[\frac{M_t - M_o}{M_o} \right] \quad (1)$$

where, M_t and M_o represent the weights of swollen and dry samples, respectively.

2.4. FTIR analysis

The FTIR analysis was performed to identify the molecular structure of the hydrogels. The vacuum-dried samples were mixed with KBr and pressed into pellets under hydraulic press force. The spectra were collected on a Mattson 1000 FTIR spectrophotometer at the wavelength range of 400-4000 cm^{-1} with a resolution of 4 cm^{-1} .

2.5. SEM analysis

The synthesized hydrogels were examined using a scanning electron microscope (SEM) (LEO 440) in order to characterize the morphology. The samples were freeze-dried and fractured. The fractured surface was coated with gold-palladium under vacuum.

3. RESULTS AND DISCUSSION

3.1. Preparation of MA-St-MMA terpolymer hydrogels

MA-St-MMA terpolymer hydrogels were prepared by crosslinking of MA-St-MMA terpolymer with organic functional crosslinking agents MBAm and GA. The ring-opening reaction of MA units with MBAm resulted in the formation of crosslinked polymer with carboxylic groups and ester bonds.

In order to study the effect of crosslinker ratios on hydrogel formation, MA-St-MMA terpolymer hydrogels with different crosslinker ratios were prepared and characterized. MA-St-MMA / crosslinker mixtures containing less than 10% crosslinker (wt %) do not lead to the stable hydrogel formation. This is why, MA-St-MMA terpolymer hydrogels were prepared by varying crosslinker ratios from 10 to 40%.

The curing time and step by step increase of reaction temperature are important for the completion of the crosslinking reaction[2]. In this study to establish crosslinking, rather drastic conditions (appropriate time-temperature program, crosslinker ratio) have to be applied. Our results showed that the reaction temperature has a strong effect on the completion of MA-St-MMA terpolymer/crosslinker reactions, and the applied time-temperature program increased the mechanical stability of the hydrogels. It was therefore decided to realize the crosslinking reactions with an appropriate time-temperature program by depending upon crosslinker type. For MBAm: 2 h at 25°C, 24 h at 37°C; for GA: 2 h at 25°C, 24 h at 37°C, and 24 h at 50°C.

3.2. pH-sensitivity of the hydrogels

The chemical structure of the polymer affects the swelling ratio of the hydrogels which is directly related to hydrogel application. The chemical structure depended upon composition of the

polymeric matrix i.e. the crosslinker ratio. Highly crosslinked hydrogels that have a tighter structure will swell less as compared to the same hydrogels with lower crosslinking ratios[5]. This is why experiments to determine the pH-dependent swelling behaviour were performed by depending upon the nature and ratio of crosslinker in

Trisbuffer solutions which have various pHs between 2 and 9 at 37°C. The kinetic curves of swelling for the MA-St-MMA/MBAm and MA-St-MMA/GA hydrogels containing about 10-40% w/w crosslinker are illustrated respectively in Figures 1 and 2(a-d).

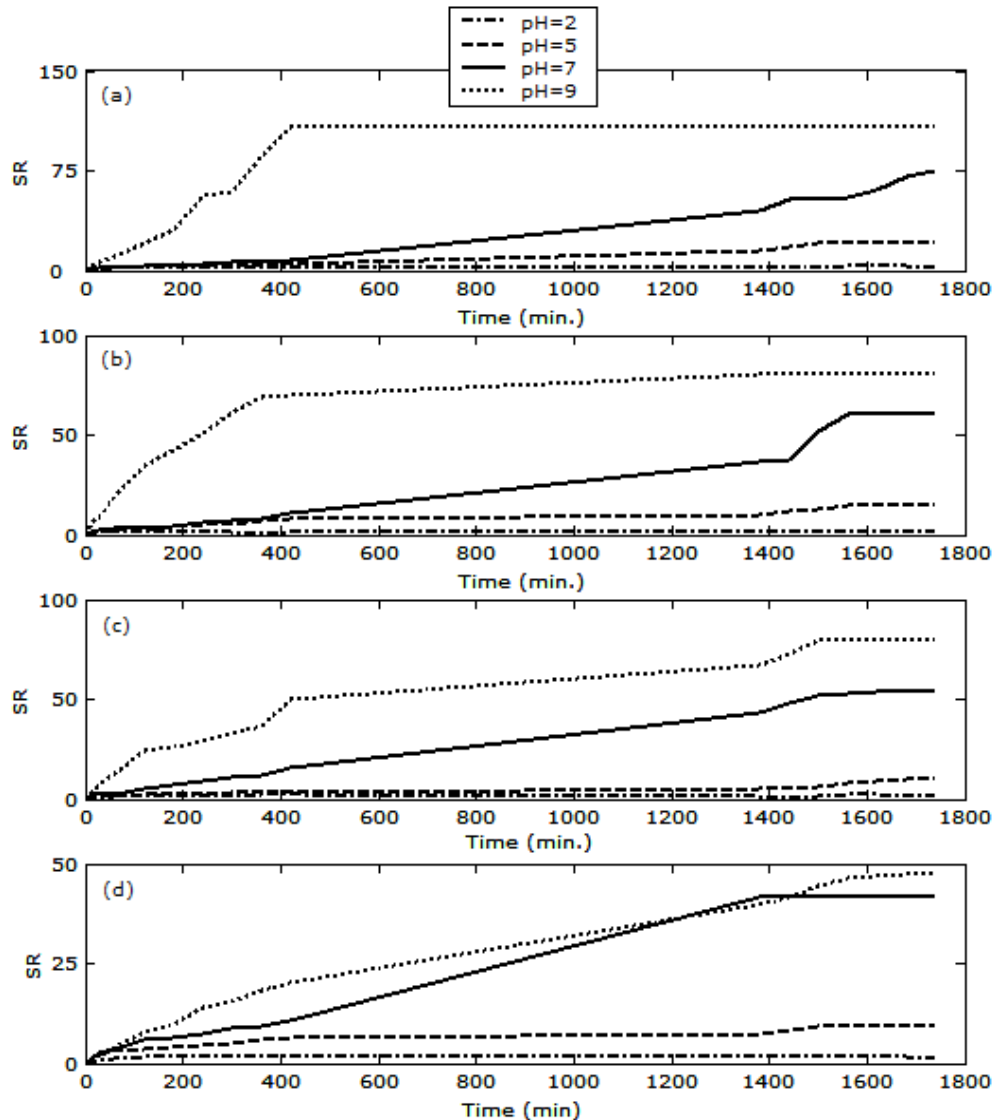


Figure 1. SR values of MA-St-MMA/MBAm hydrogels as a function of swelling medium pH. (a) MA-St-MMA/MBAm (10%) hydrogel, (b) MA-St-MMA/MBAm (20%) hydrogel, (c) MA-St-MMA/MBAm (30%) hydrogel, and (d) MA-St-MMA/MBAm (40%) hydrogel.

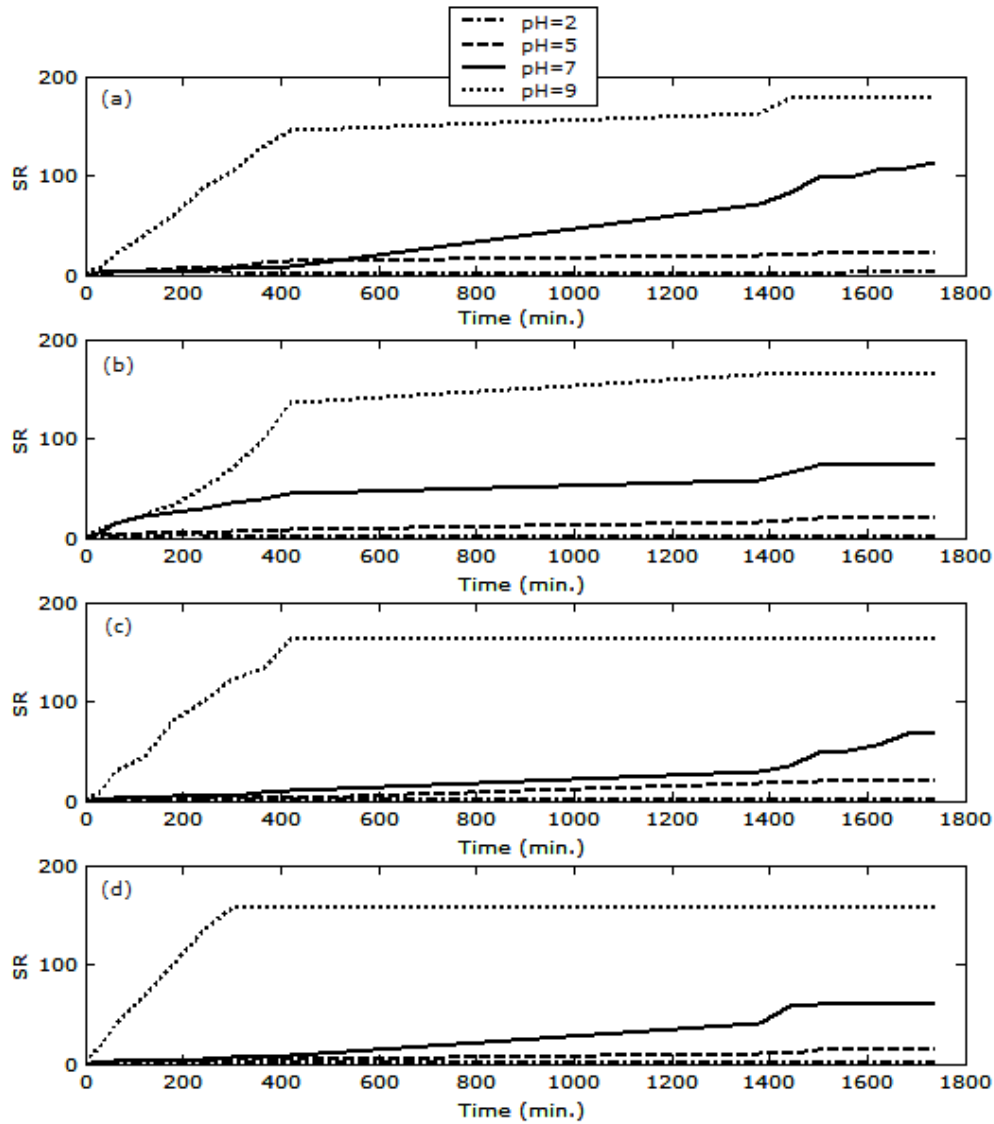


Figure 2. SR values of MA-St-MMA/GA hydrogels as a function of swelling medium pH. (a) MA-St-MMA/GA (10%) hydrogel, (b) MA-St-MMA/GA (20%) hydrogel, (c) MA-St-MMA/GA (30%) hydrogel, and (d) MA-St-MMA/GA (40%) hydrogel.

As clearly seen in Figures 1 and 2 (a) - (d), the SR values of MA-St-MMA hydrogels were higher at basic medium than acidic medium, and there was a change swelling behavior of the hydrogels in response to pH change. These observations were taken as an indicator of that hydrogels exhibit pH-sensitive swelling behavior.

It is also shown that the SRs of all hydrogels were increased by time, but after a certain period they show constant swelling (Figures 1 and 2(a)-(d)). This constant value may be called equilibrium swelling ratio (ESR). The determination of ESR has great practical significance and it was realized by eq. (1). The ESR values were given in Table I together with the crosslinker ratios.

Table 1. Equilibrium swelling ratios of the MA-St-MMA-crosslinker systems in different pHs at 37°C.

Hydrogel Type	Crosslinker Ratio % (w/w)	ESR Values			
		pH 2	pH 5	pH 7	pH 9
MA-St-MMA/MBAm	10	1.92	20.71	75.45	107.98
MA-St-MMA/MBAm	20	1.60	14.59	61.41	80.90
MA-St-MMA/MBAm	30	1.56	10.14	53.40	79.15
MA-St-MMA/MBAm	40	1.38	9.43	41.47	47.29
MA-St-MMA/GA	10	1.95	22.71	112.67	177.70
MA-St-MMA/GA	20	1.68	19.49	73.50	165.00
MA-St-MMA/GA	30	1.59	19.14	67.61	163.17
MA-St-MMA/GA	40	1.43	13.57	61.20	157.46

As seen in Table 1, the ESR values of MA-St-MMA hydrogels containing 10% crosslinker were higher than those with crosslinker ratios of 20%, 30%, and 40% in all pH values. For example for pH 9, the ESR values of MA-St-MMA/MBAm hydrogels containing 10 and 40% MBAm crosslinker were respectively 108 ± 1 and 47 ± 1 . However the ESR values of MA-St-MMA/GA hydrogels are higher than MA-St-MMA/MBAm in all studied pH values. These differences among the swelling properties of MA-St-MMA hydrogels might be attributed to the different functional groups of crosslinkers.

These results clearly demonstrate that the maximum water uptake was observed at 10% crosslinker ratio then it begins to decrease with further increase in crosslinker content. This is probably due to the reduction in the mesh size of the gel on raising the crosslinker content, which slows down the diffusion rate of water molecules out of the gel phase.

The results obtained allow to simply reflect the possibility of the formation of terpolymeric hydrogel with different swelling properties and functionality in the MA-St-MMA/crosslinker systems.

3.3. FTIR characterization

The ring-opening reaction of MA units with crosslinkers (MBAm and GA) resulted in the formation of crosslinked polymers with carboxylic groups and ester bonds. FTIR spectra of MA-St-MMA

terpolymer and MA-St-MMA hydrogels were presented in Figure 3. Peaks related to O=C-O-C=O ring stretching vibrations of a saturated cyclic five membered anhydride (at $952-909\text{cm}^{-1}$) were clearly seen in the IR spectrum of MA-St-MMA terpolymer. As expected, the conversion of cyclic anhydride to carboxylic and ester groups after the cross-linking reactions, increased the carboxyl and ester group absorption intensities in a range of $1700-1727\text{ cm}^{-1}$ (for MA-St-MMA/MBAm and MA-St-MMA/GA hydrogels). The absorption band at 1735 cm^{-1} can be assigned to MMA groups in the terpolymer. It is important to notice that when the MMA amount is decreased (for the hydrogels), the intensity of the absorption band is also decreased. These FTIR studies indicated that crosslinking occurs through the ring opening reaction of MA units with crosslinkers (MBAm and GA).

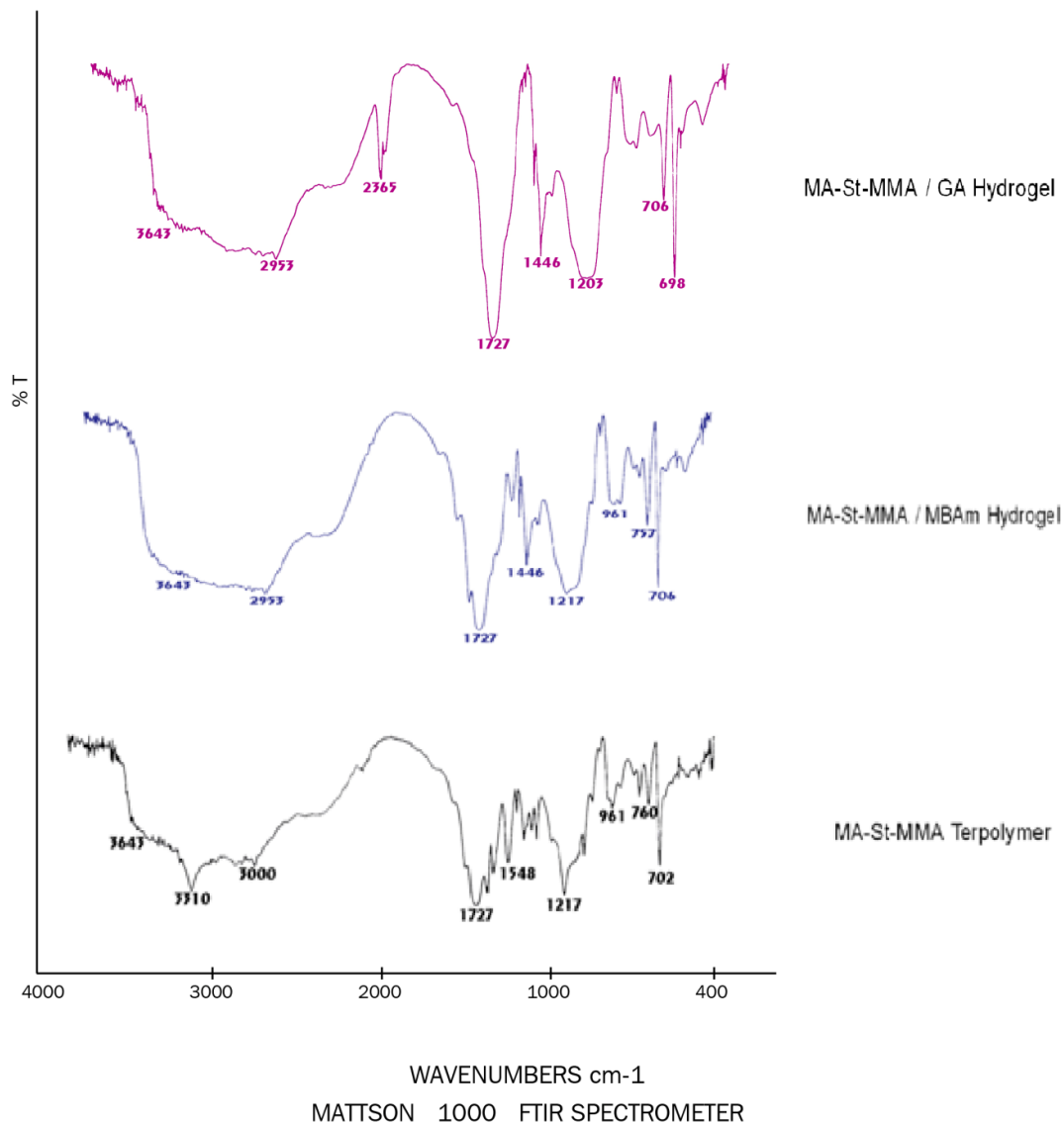
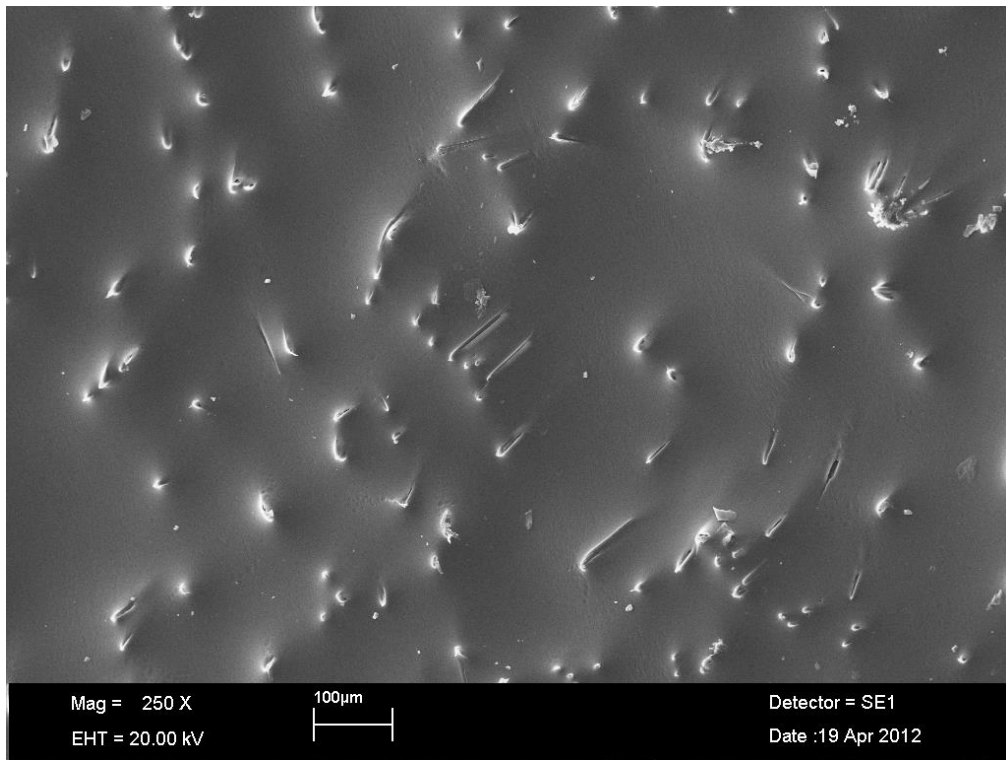


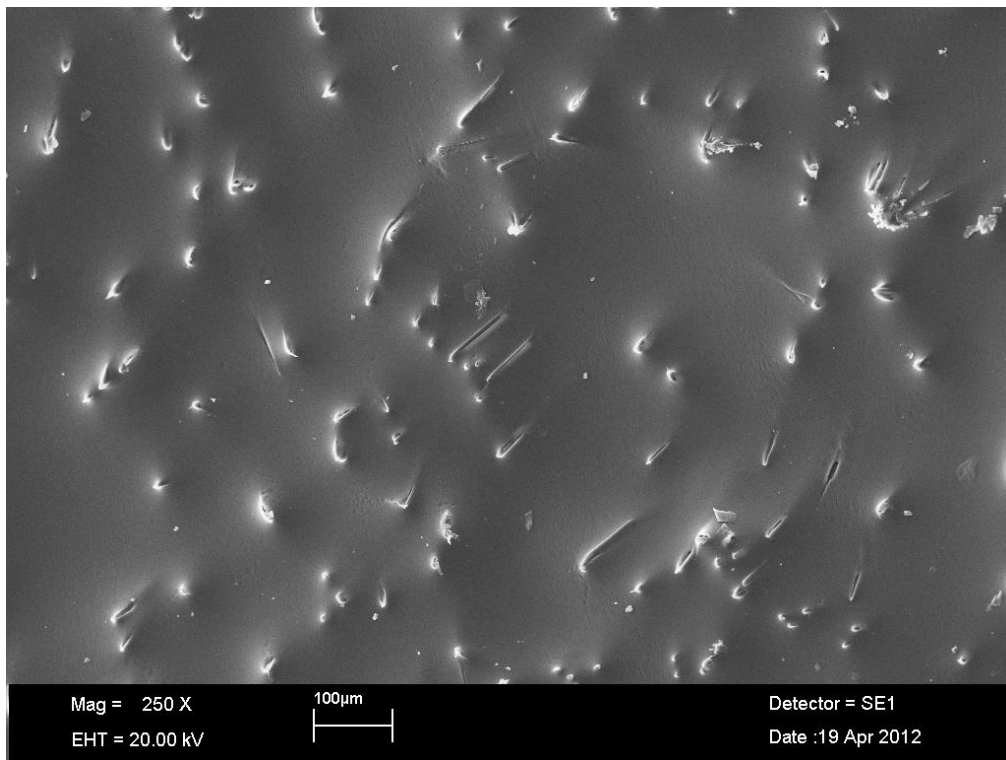
Figure 3. FTIR spectra of MA-St-MMA terpolymer, MA-St-MMA/MBAm and MA-St-MMA/GA hydrogels (40%).

3.4. Morphological analysis by SEM

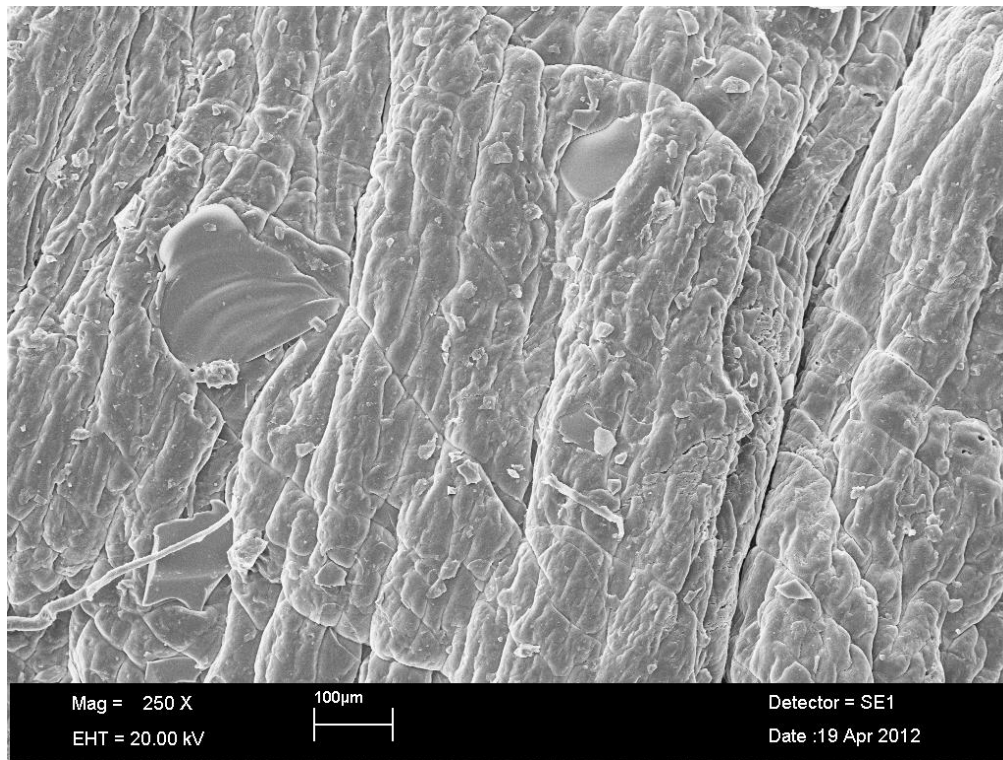
SEM provides information about morphology of the hydrogel network. SEM pictures were taken at the surfaces and cross sections of the MA-St-MMA hydrogels for this purpose. These pictures were presented in Figures 4(a-c) and 5(a-c) for MA-St-MMA/MBAm and MA-St-MMA/GA hydrogels, respectively.



(a)

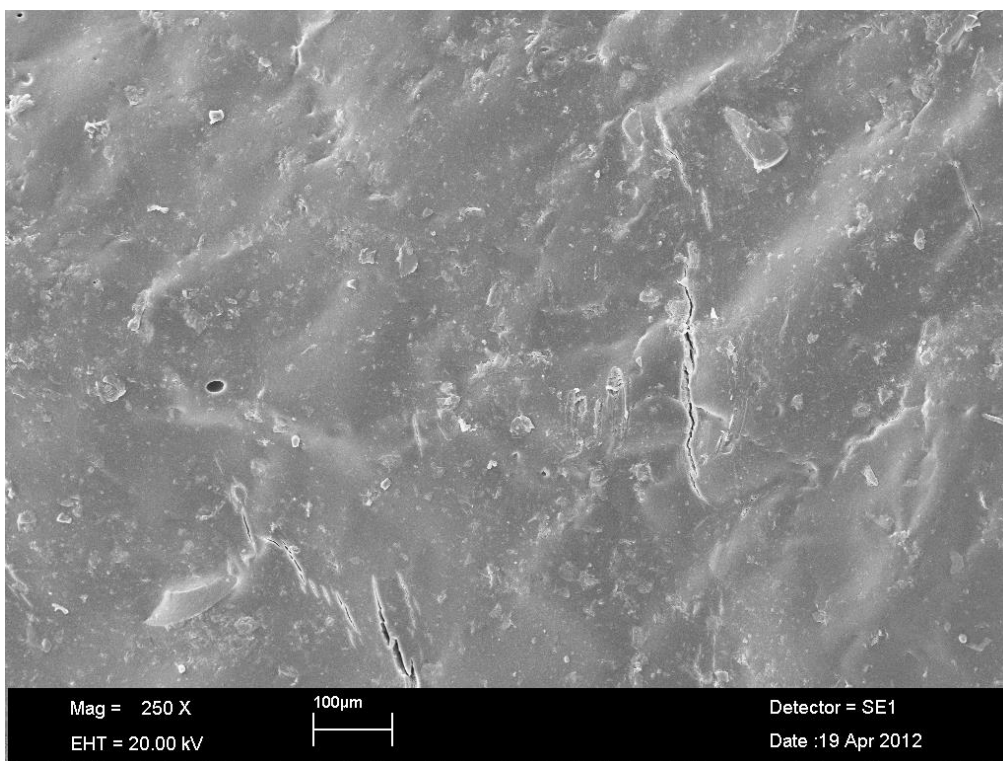


(b)

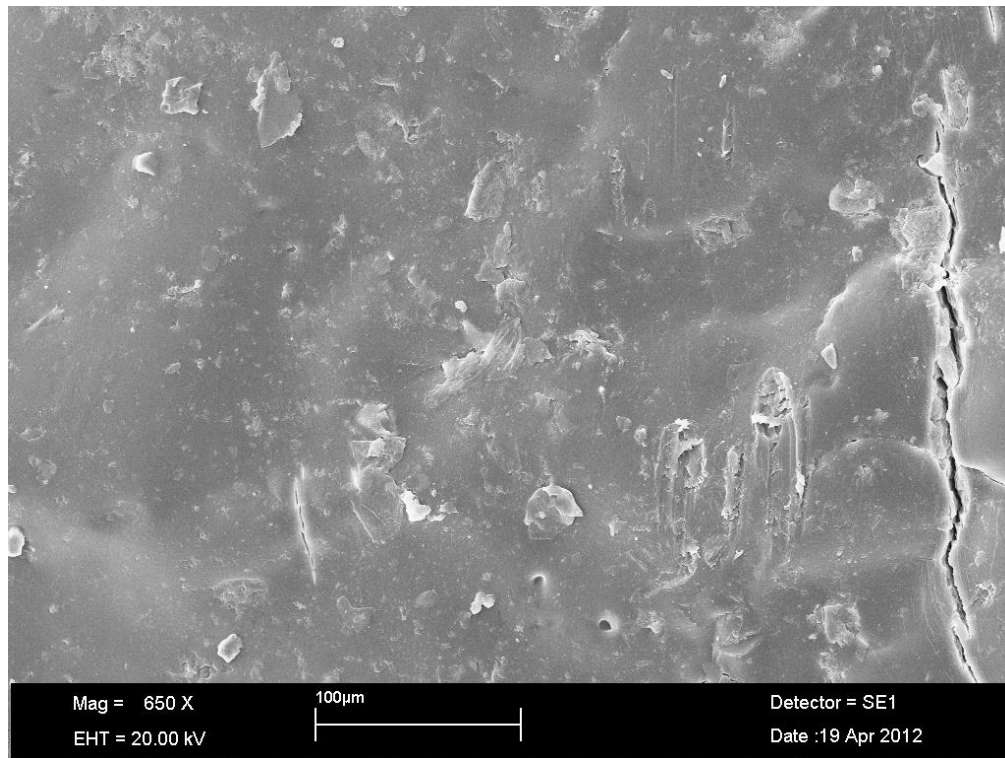


(c)

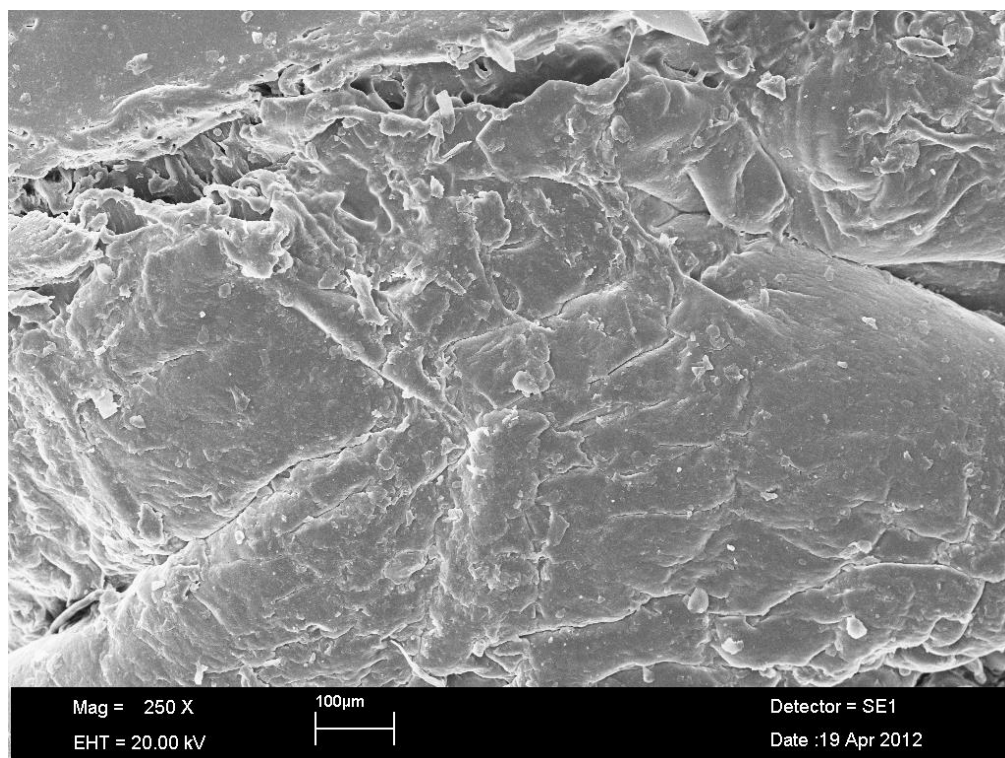
Figure 4. SEM images of MA-St-MMA/MBAm(40%) hydrogel: (a) a general view from surface (magnification = 250x), (b) a general view from surface of the same hydrogel (magnification = 650x), and (c) a cross section of the same hydrogel (magnification = 250x).



(a)



(b)



(c)

Figure 5. SEM images of MA-St-MMA/GA (40%) hydrogel: (a) a general view from surface (magnification = 250x), (b) a general view from surface of the same hydrogel (magnification = 650x), and (c) a cross section of the same hydrogel (magnification = 250x).

Figures 4 (a-b) and 5(a-b) show surface images from hydrogels with different crosslinkers (MBAm and GA, respectively). In the case of MA-St-MMA/GA hydrogels, the structure becomes less ordered and more porous (Figures 5 (a-b)). Figures 4 (c) and 5 (c) present cross-sectional view of the MA-St-MMA/MBAm and MA-St-MMA/GA hydrogels, respectively at a magnification of 250x. It is possible to see that MA-St-MMA/GA hydrogels are covered by irregular pores with size ranging 5-10 μ m (Figure 5 (c)) by using imageJ software.

4. CONCLUSION

In this study, MA-St-MMA terpolymer based hydrogels were prepared by crosslinking of MA-St-MMA terpolymer with organic functional crosslinking agents MBAm and GA. The appropriate time-temperature program was found to realize the crosslinking reactions for all studied MA-St-MMA/crosslinker systems. From the swelling studies of the hydrogels as a function of crosslinker ratio and pH, it is concluded that the hydrogels exhibit significantly pH-sensitive swelling behaviour. The proposed hydrogel system bears the potential to be used for specific applications such as drug delivery, biotechnology and waste water treatments.

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