Network Macromolecular Structures. The Crosslinker Effect

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***Abstract* — The study presents the possibility to prepare copolymers based on 2-hydroxyethyl methacrylate using two variants of comonomers: ethylene glycol dimethacrylate (1) and respectively 3, 9- divinyl -2, 4, 8, 10-tetraoxaspiro[5.5]-undecane (2) that act as crosslinkers for the methacrylate networks. All these monomers are well known for their use in the bio- and photodegradable polymers preparation as well as to generate gel structures. The chemical structure and composition of the copolymers – synthesized through redox polymerization process using ammonium persulfate and N,N,N', N' –tetramethylethylenediamine as initiator pair were confirmed by FT-IR spectroscopy. The transparent gel structures were prepared in ethylene glycol. The influence of the comonomers type upon gel copolymers formation was put into evidence by the swelling behavior of the polymeric structure. The swelling effected at 37°C differentiates the crosslinker comonomers, attributing a better performance to the 3, 9- divinyl -2, 4, 8, 10-tetraoxaspiro[5.5]-undecane. The morphological information concerning the studied polymeric compounds by SEM evidenced the differences between the hydrogels with respect to crosslinker type and its quantity in the monomer feed. Also the thermal stability is a function of the type and quantity of the crosslinker. The study underlines the possibility to optimize the network macromolecular structure using a properly crosslinker choice, taking into account the potential application in biomedical and sensors domain.**

***Index Terms* — biotechnological applications, crosslinker, hydrogel, network structures, poly(orthoesters)**

I. INTRODUCTION

Hydrogels are hydrophilic homopolymers or copolymers with three dimensional network structures that undergo extensive swelling in water and found a wide variety of applications in medical, pharmaceutical and related fields, e.g. artificial organs, contact lenses, wound dressings and drug delivery systems [1 - 3]. Because of the swelling capacity, their structure is similar to natural tissue [4, 5]. Also they found an extremely favorable field of applications in agriculture, food industry, photographic technology and others.

Hydrogels do not dissolve in water at physiological temperature and pH, but they swell considerably in an aqueous medium [6] and demonstrate extraordinary capacity (>20%) for imbibing water into the network structure. Gels exhibiting a phase transition in response to change in external conditions such as pH, ionic strength, temperature and electric currents are known as "stimuli-responsive" or "smart" gels [7]. Being insoluble, these three-dimensional hydrophilic networks can retain a large amount of water that not only contributes to their good blood compatibility but also maintains a certain degree of structural integrity and elasticity [8]. Thus, crosslinked polymer networks formed by free radical polymerization of ethylene glycol methacrylates and dimethacrylates have been found attractive as hydrogel matrices since they do swell in aqueous media to certain extend depending on the crosslinking density, but do not dissolve. 2-hydroxyethyl methacrylate (HEMA) based hydrogels are inert to normal biological processes, show resistance to degradation, are not absorbed by the body and can be prepared in a variety of shapes and forms. The crosslinked 2-hydroxyethyl methacrylate hydrogels because of their hydrophilic character and potential biocompatibility have been of great interest to biomaterial scientists for many years [9-11]. The presence of hydroxyl and carboxyl groups makes this polymer compatible with water, whereas the hydrophobic methyl groups and backbone impart hydrolytic stability and supports the mechanical strength of the polymer matrix. HEMA copolymers have also been investigated as carriers for enzyme and protein immobilization, as absorbents for chromatographic applications, and as scavengers for removing metal ions from solution [12–15]. HEMA can be polymerized and crosslinked easily and the properties of proper hydrogels are dependent upon their method of preparation, polymer volume fraction, degree of crosslinking, temperature and swelling agent.

Poly(orthoesters) have attracted considerable interest for the controlled delivery of therapeutic agents within biodegradable matrices. This interest is due primarily to poly(orthoesters) being susceptible to acid catalysed hydrolysis. Hydrolysis proceeds *via* the protonation of an alkoxy oxygen followed by bond cleavage, with pentaerythritol, aliphatic acid and the diol or mixture of diols as degradation products. As the hydrolysis of poly(orthoesters) requires an initial protonation, these polymers may be considered pH sensitive, being stable in basic conditions [16].

In this study, the effects of the two crosslinking agents : ethylene glycol dimethacrylate and an orthoester type named 3, 9-divinyl-2, 4, 8, 10 - tetraoxaspiro[5.5]-undecane) on the structure, water absorption, morphology of the network and thermal stability of the HEMA – based hydrogels were investigated. The hydrogels are aimed to be matrices for bioactive compounds entrapment or for sensor applications.

II. EXPERIMENTAL

Materials

2-hydroxyethyl methacrylate (HEMA) from Aldrich (purity 97%) was purified by passing it through an inhibitor removal column (for removing hydroquinone and

hydroquinone monomethyl ether). 3,9 – divinyl -2,4,8,10 - tetraoxaspiro[5.5]-undecane (U) (purity 98%) and ethylene glycol dimethacrylate (EGDMA) (purity 99%) as crosslinking comonomers were purchased from Aldrich.

Ammonium peroxodisulfate (APS, Merck) and N,N,N', N' –tetramethylethylenediamine (Sigma Aldrich, TEMED) were used as the redox initiator pair. Ethylene glycol was used as reaction medium and distilled water was used in the swelling studies.

Hydrogel preparation

The hydrogels based on hydroxyethyl methacrylate were prepared by simultaneous redox polymerization and crosslinking in solution of ethylene glycol. The monomers HEMA, EGDMA or U concentration in ethylene glycol as reaction medium is 8%. EGDMA or U as a crosslinking agent was used at two concentrations 1 and 5 wt % with respect to HEMA content. APS and TEMED were used as initiators in a 1:1 wt ratio, at concentrations of 0.6 wt % each of them with respect to the total amount of monomers.

A typical procedure for the copolymerization can be described as follows: HEMA 1 ml and EGDMA (0.02 mL) or U (0.02 g) were dissolved in 22 mL of ethylene glycol, then APS (1.2 mL water solution of 1%) and TEMED (0.016 mL) were added into the monomer solution mixture, respectively. The solution was stirred until thoroughly mixed. The samples of about 2 mL were polymerized stationary in 5 mL glass tubes (7 mm I.D) as the polymerization reactors, for 24 hr at room temperature to ensure complete polymerization.

The copolymers samples obtained in the form of long cylinders were removed from the tubes and placed in 60 mL glass sample bottles filled with deionized water. Then they were washed within distilled water at room temperature for 24 hours to remove any unreacted monomers and physically entrapped reaction components and the purity is verified by UV spectroscopy of the washing waters.

Finally the samples were dried by lyophilization. The dried samples were stored in desiccator at room temperature until tested in experiments of swelling, spectroscopy, SEM and thermal stability analyses.

Fourier Transform Infra-Red Spectroscopy

FTIR spectra were recorded on a Vertex Brucker Spectrometer in the absorption mode ranging from 400 to 4000 cm^{-1}, at 4 cm^{-1} resolution, as an average of 64 scans.

Equilibrium swelling experiments

The equilibrium swelling degree SR of the hydrogels was determined by the gravimetric method, in the buffer solutions: Na_2HPO_4 / CH_3COOH for pH 5.5 and 7.4, at 22 and 37°C, by applying the equation (1) :

$$SR = \frac{W_t - W_O}{W_O} X100 \qquad (1)$$

where Wt is the weight of the swollen gel at time t and Wo is the weight of the dried gel at time 0.

Scanning electron microscopy

SEM microphotographs were obtained by using Quanta 200 with EDAX - Elemental Analysis System. The samples have been cross-sectioned and the morphological structure was investigated in an accelerating voltage of 10.60 kV and high vacuum.

Thermal analysis

The thermal behavior of the polymers was evidenced by using a STA 449F1 Jupiter model (Netzsch-Germany) system at heating rate of 10 °C/min. Experiments under non-isothermal condition were following in nitrogen atmosphere with a 50 ml/min flow rate. 7.5-8 mg of polymeric mass were heated from 30 to 600º C.

II. RESULTS AND DISCUSSION

Polymerization techniques based on addition, such as free radical chain growth crosslinking copolymerization of HEMA and EGDM, are usually used for the preparation of polymers, which are subsequently converted into hydrogels, by moderate crosslinking of the polymeric chains in fairly concentrated solutions.

It was evidenced in the literature that the incorporation of spiroacetal groups in the polymer structures improves the solubility and the adhesive properties [17]. More than that, the polymers which include these moieties are stable in base, hydrolyze at very slow rates at the physiological pH of 7.4, and become progressively more labile as the pH is lowered. Also, these kinds of comonomers induce good oxidative and thermal stability, are good fiber formers, and the prepared films present good flexibility and tensile strength [18]. These characteristics are attributed to the properties inherent into the spiroacetal ring: stiffness, which is higher than cycloaliphatic rings but lower than aromatic rings; interactions on ether oxygen such as hydrogen bonds or coordinate bonds with other functional groups, and bulkiness. Different researchers described the developments in synthesis of alternating poly(ester–ether)s from spiroortho-esters, which were also considered biodegradable and useful for biomedical applications [19, 20].

Fig. 1 presents the FTIR spectra for the samples oh hydrogels based on HEMA crosslinked with EGDMA (1 and 5 wt % in the monomer phase) and U (1 and 5% in the monomer phase). Firstly, from the FTIR spectrum depicted in Fig. 1, the presence of the main comonomer in the hydrogel structure is confirmed by the hydroxyl and strong carbonyl bands appearing at 3500 cm^{-1} (O-H stretching) and 1730 cm^{-1} (C=O stretching), respectively. Also, there are evidently the bands at 1172 cm^{-1} (O-C-C stretching), 2951 cm^{-1} (asymmetric stretching of methylene group) and 1454 cm^{-1} (O-H bending).

The FTIR spectra are used to confirm the consumption of C=C bonds in HEMA, EGDMA and U. In the spectra, the absorbance change of the peak at 1635 cm^{-1} (C=C stretching) estimates the conversion of vinyl bonds in the samples and their consumption during the polymerization.

The absorbance of the peak at 1730 cm^{-1} (C=O stretching) was picked as standard. The spiroacetal moieties inclusion is also confirmed by the new strong bands in the region of 1000 – 1200 cm-1 (due to ether C-O-C stretching and C-H in plane bending) and at ~ 1715 cm-1 (due to C=O stretching of conjugated ether). The supplementary absorption at 2887 cm^{-1} is attributed to the -CH - CH_2 -symmetric stretching from U. The carbonyl peak of the acrylate of EGDMA appears at 1730 cm^{-1} and the lactone carbonyl at 1764 cm^{-1}.

Secondly, in a general view, the spectra of HEMA based gels are almost similarly, but with the exception of a peak at about 1573 cm -1 which can be assigned to the stretching of the COO- group [21]. As it can be seen for both crosslinking comonomer EGDMA and U, the intensity of this peak increases comparative to p(HEMA) as a function of crosslinking density, respectively the increase of cross-linker concentration from 1 to 5% in the monomer phase. The aspect is more evidenced for the sample hydrogel with EGDMA.

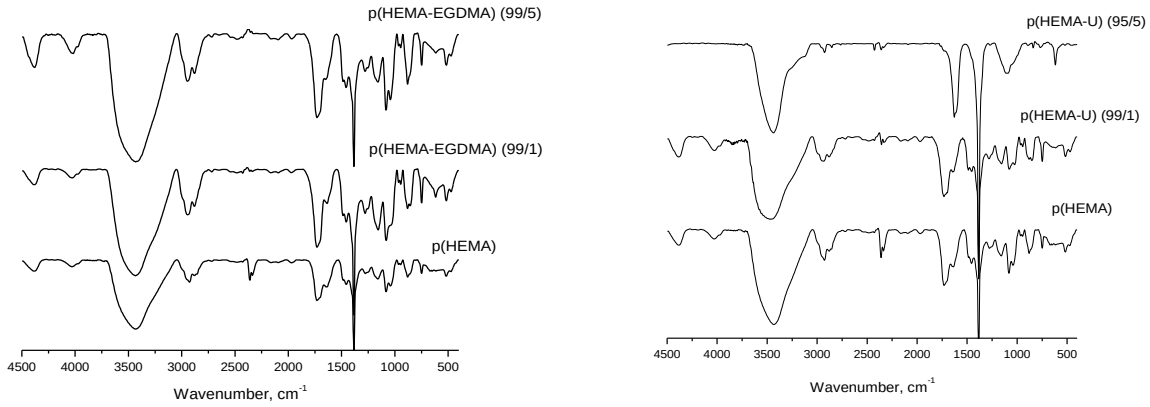

Fig. 1. FTIR spectra for the hydrogel samples based on HEMA crosslinked with EGDMA and U

The crosslinkers have pronounced effect on the swelling ratio. In the swelling behavior of the hydrogels, the percentage swelling increases with time but after a while constant percentage swelling is observed. This value of swelling percentage represents the equilibrium swelling.

The effect of the degree of crosslinking on the swelling was investigated by varying the concentration of EGDMA and U in the feed mixture of the polymerization recipe. In this study we have chosen two values for the crosslinker amount: 1 and 5 % from the monomer mixture. In Table 1 there were presented the equilibrium swelling degrees SR determined at 22 and 37 ^{o}C, for pH 5.5 and 7.4, taking into account the potential applicability for the sensitive materials at the environmental parameters (temperature and pH).

TABLE 1 EQUILIBRIUM SWELLING DEGREE SR FOR THE HYDROGEL SAMPLES

Temperature, ^{o}C	1% EGDMA		5% EGDMA		1% U		5% U	
	pH 7.4	pH 5.5	pH 7.4	pH 5.5	pH 7.4	pH 5.5	pH 7.4	pH 5.5
22 ^{o}	35.68	28.57	39.64	36.40	38.40	39.33	40.02	38
37^{o}	29.65	17.53	34.22	39.38	46.01	33.01	47.96	45

From the data presented in Table 1 it is observed that the equilibrium swelling degree SR determined in buffer solution increases as the extent of crosslinking grows, and its values demonstrate the temperature and pH sensitivity of the hydrogel samples. Also, the spiroacetal moieties in U induce higher swelling degree than the hydrogel with 5 % EGDMA. Usually the swelling degree is expected to decrease with increasing crosslinking. Surprisingly, in an inherent contradiction the water absorption is more significant for the relatively high degree of crosslinking (with 5% of EGDMA or U) than for the hydrogel with a low degree of crosslinking (with 1% of EDGMA or U). These results reflect the existence of two absorption mechanisms in the HEMA based hydrogel: absorption within the pHEMA walls through interaction with the hydrophilic polymer and absorption within the porous structure through capillary action. The literature also [22, 23] describes three different diffusion mechanisms for the transport of water through crosslinked pHEMA gels, which depend on the crosslinker content: a pore flow mechanism for low
crosslinking content, a water-matrix interaction mechanism for higher crosslinking content and an intermediate mechanism at intermediate crosslinker concentration. Our study on the pHEMA gels fulfills these aspects. At the same time, the synthesis of hydrogels that combine the water absorption through hydrophilic interactions and through capillary action can be used to synthesize better water-absorbent materials for different biotechnological applications, such as drug delivery or tissue engineering.

Fig. 2 presents the SEM images of the pHEMA based hydrogel (a), crosslinked with 5%EGDMA (b) and crosslinked with (5%) U (c). In detail are the SEM micrographs for hydrogels crosslinked with 1% EGDMA (b) and 1% U (c).

As it is observed in the SEM images, the hydrogels porous structure consists of distorted interconnected spherical voids separated by walls. These walls themselves have an unusual nanoscale porous structure with voids from the evacuated droplets of the organic phase (ethylene glycol).

The SEM images reflect two main conclusions: firstly, the crosslinked hydrogel with 5% EGDMA and 5% U have structures that are reminiscent of a typical pHEMA hydrogel. Secondly, the morphology of the hydrogels with higher degree of crosslinking (samples with 5% of EDGMA or U) is a porous structure completely different comparative to pHEMA hydrogels with EGDMA 1% or U 1%.

These hydrogels are able also to swell with greater amount of water, as it is reflected by the SR values in the swelling experiment (Table 1). The more porous structures and high surface area enhance capillary action and yield the large amount of water absorbed.

In Table 2 are presented the main characteristic temperatures in the decomposition process of the dried hydrogel samples.

As it can be seen from the listed results there were found differences between the thermal behaviors

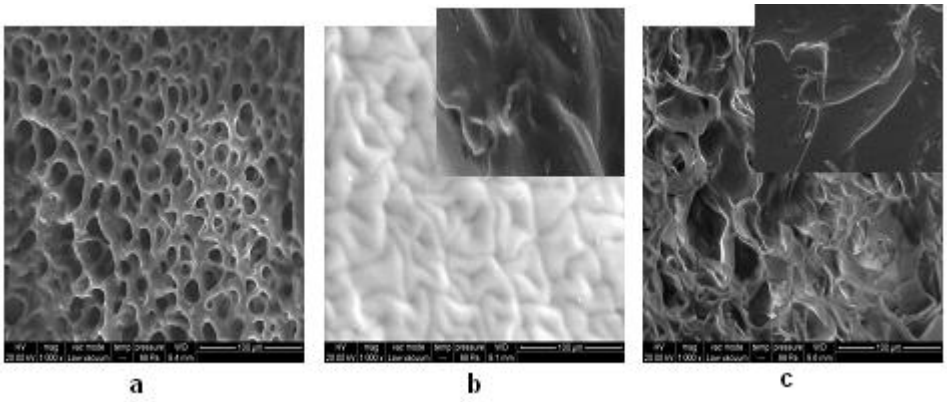

Fig. 2. SEM micrographs of the pHEMA based hydrogel (a), crosslinked with 5%EGDMA (b) and crosslinked with (5%) U (c). In detail are the SEM micrographs for hydrogels crosslinked with 1% EGDMA (b) and 1% U (c).Magnification: 1000X.

TABLE 2. THE MAIN CHARACTERISTIC TEMPERATURES IN THE DECOMPOSITION PROCESS OF THE HYDROGEL SAMPLES

Sample	First process			Second process			Residual mass. %
	Ti ^{o}C	Tmax ^{o}C	Tf ^{o}C	Ti ^{o}C	Tmax ^{o}C	Tf ^{o}C	
pHEMA	-	-	-	332	362	415	0.1
p(HEMA-EGDMA 1%)	218	238	275	335	366	454	0.09
p(HEMA-EGDMA 5%)	141	208.6	242.5	335.5	368	434.3	0.76
p(HEMA-U 1%)	-	-	-	345	372	426	0.83
p(HEMA-U 5%)	318.5	348.9	352.3	391	407	446	1.94

Ti, Tf—onset and final temperature of the thermal decomposition step, Tmax—maximum temperature of decomposition

P(HEMA) hydrogels crosslinked with 1 and 5 % EGDMA and with 5% U present a thermal decomposition process in two stages comparative with P(HEMA) and P(HEMA-U 1%) that have only one process of decomposition. As it is expected, the presence of the crosslinking comonomer 3,9 – divinyl -2,4,8,10 - tetraoxaspiro[5.5]-undecane (U) positively affects the thermal stability of the copolymers, because of the spiro acetal ring that controls the thermal properties. Thus, it is observed for P(HEMA-U 5%) Tmax registered an increase with about 40 ^{o} comparative to P(HEMA) and P(HEMA-EGDMA 1 or 5%). No significant thermal stability results were obtained by crosslinking with EDGMA comparative to P(HEMA).

III. CONCLUSIONS

The study presents the synthesis of 2-hydroxyethyl methacrylate based hydrogels by crosslinking with one of the two crosslinkers: ethylene glycol dimethacrylate and 3,9 – divinyl -2,4,8,10 - tetraoxaspiro[5.5]-undecane. The hydrogels were prepared by simultaneous redox polymerization and crosslinking in solution of ethylene glycol, by using ammonium peroxodisulfate and N,N,N', N' –tetramethylethylenediamine as the redox initiator pair. The transparent gel structures were prepared in ethylene glycol.

The influence of the crosslinker type is estimated and the hydrogels are characterized from the viewpoint of chemical structure, swelling behavior, morphology and thermal stability, by FTIR spectroscopy, equilibrium swelling degree SR determination, SEM and TGA.

The study underlines the possibility to optimize the network macromolecular structure using a properly crosslinker choice.

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