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Research paper

Synthesis and characterization of cyclic acetal based degradable hydrogels

Sachiko Kaihara [a], Shuichi Matsumura [a], John P. Fisher [b,*]

[a] *Department of Applied Chemistry, Keio University, Yokohama, Japan*
[b] *Fischell Department of Bioengineering, University of Maryland, MD, USA*

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Abstract

While many synthetic, hydrolytically degradable hydrogels have been developed for biomedical applications, there are only a few examples whose polymer backbone does not form acidic products upon degradation. In order to address this concern, we proposed to develop a hydrogel based on a cyclic acetal unit that produces diols and propanals upon hydrolytic degradation. In particular, we proposed the fabrication of hydrogels formed by the free radical polymerization of two diacrylate monomers, 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1,3-dioxane-2-ethanol diacrylate (EHD), a cyclic acetal having two acryl groups, and poly(ethylene glycol)diacrylate (PEGDA). However, the hydrophobicity of the EHD monomer inhibits hydrogel fabrication. Therefore this work develops a strategy to form hydrogels with a co-monomer system, one of which is hydrophobic, and subsequently describes the properties of the resulting hydrogel. Using benzoyl peroxide as an initiator and *N*,*N*-dimethyl-*p*-toluidine as an accelerator, the EHD and PEGDA monomers were reacted in an acetone/water co-solvent system. The chemical structure of the resulting EH–PEG [5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1,3-dioxane-2-ethanol-*co*-PEG] hydrogel was then characterized by FT-IR. Physicochemical properties of the EH–PEG hydrogel, including swelling degree, sol fraction, and contact angle, were determined so as to characterize the properties of these materials and ultimately investigate their use in drug delivery and tissue engineering applications. Results showed that EH–PEG hydrogel may be formed using the co-solvent system. Further results indicated that swelling degree is dependent upon initiator concentration, monomer concentration, and molar ratios of monomers, while sol fraction significantly depended on initiator concentration and monomer concentration, only. These results demonstrate the ability to fabricate hydrogels using EHD and PEGDA system as well as to control the properties of the resulting hydrophilic networks.

Keywords: Cyclic acetal; Hydrogel; Biomaterial; Swelling; Hydrolytic degradation

1. Introduction

The development of biomaterials has been remarkable in recent years. While both naturally derived and synthetic biomaterials have advantageous features, synthetically obtained biomaterials have merits of reproducibility and control over physical properties. Therefore many researchers are engaged in synthesis of new biomaterials for applications such as implants, drug delivery constructs, or tissue engineering scaffolds. Hydrogels are polymeric networks which retain a large amount of water without dissolution due to their hydrophilic but crosslinked structure [1]. Tanaka was among the first to describe the preparation, hydrolysis, and swelling behavior of hydrogels [2]. Due to these properties, hydrogels have attracted considerable academic and industrial attention in the last decades. In particular, the utility of hydrogels for medical applications, including drug delivery vehicles and three-dimensional polymer scaffolds for tissue engineering, has been extensively developed [3,4]. The critical parameter for hydrogels

* Corresponding author. Fischell Department of Bioengineering, University of Maryland, 3238 Jeong H. Kim Engineering Building, College Park, MD 20742, USA. Tel.: +1 301 405 7475; fax: +1 301 405 0523.
E-mail address: jpfisher@umd.edu (J.P. Fisher).
URL: http://www.ench.umd.edu/~jpfisher (J.P. Fisher).

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is their water content, often described as their swelling degree. The swelling properties of hydrogels, for example, affect the release rate of entrapped drug substances as well as the osmotic behavior of components necessary for cell survival. The typically high water content of hydrogels allows for the high permeability to molecules such as water, oxygen, and nutrients that are necessary for encapsulated cell viability.

Poly(ethylene glycol) (PEG) is a hydrophilic polymer that is extensively used as a biomaterial and hydrogel because of its ease of use and mild tissue response [5]. PEG has been studied for uses including preparation of biologically relevant conjugates [6], surface modification of biomaterials [7], and induction of cell membrane fusion [8]. In addition, PEG may be easily modified so that it can be crosslinked into a hydrophilic polymer network. Examples of PEG based polymers that may be formed into hydrogels include PEGDA and PEG dimethacrylate (PEGDMA), both of which are thought to be biocompatible and available as a tissue scaffolding material. PEG has also been fabricated as semi-interpenetrating network hydrogels by utilizing both PEGDMA and PEG, with results demonstrating that the formulation of PEG-based hydrogels affects tissue-engineered cartilage construct characteristics [9]. Furthermore, PEGDA has been utilized to encapsulate several cell types. For example, mesenchymal stem cells (MSCs) were encapsulated within a PEG gel and it was demonstrated that a PEG based hydrogel could be used to form a cartilage-like tissue [10]. Similarly, osteoblasts have also been encapsulated in a PEG hydrogel modified with the arginine–glycine–aspartic acid adhesion peptide to facilitate cell adhesion [11].

An additional strategy is to form degradable hydrogels fabricated from copolymers of PEG and another degradable segment, as PEG itself is mostly stable in water. Degradable segments include water labile polyesters such as poly(lactic acid) [12,13], poly(glycolic acid) [14], and poly(propylene fumarate) [15], as well as enzymatically labile polymers such as peptide [16]. For example, photopolymerizable, biodegradable block copolymers between PEG and poly(lactic acid) have been synthesized, with results indicating that degradation rate and permeability were controllable by changing the length and composition of the degradable segments of the copolymer [12]. Similarly, copolymers of PEG with poly(propylene fumarate) have also been synthesized and characterized [15]. Enzymatically degradable photopolymerized hydrogels have also been investigated, with results demonstrating that those hydrogels were degradable in the presence of targeted enzymes and stable in the presence of not targeted enzymes [16].

The significant disadvantage of designing hydrogels with polyesters, as well as many other hydrolytically labile units, is the formation of carboxylic acid degradation products. The rise of local acidity of the surrounding tissue has been implicated in both the autocatalysis of further scaffold degradation and the elicitation of pronounced inflammatory response [17–20]. For example, it has been reported that scaffolds prepared from poly(lactic acid) and poly(glycolic acid) have led to autocatalysis of the degradation reaction [17]. In order to address this concern, we propose the use of a cyclic acetal unit to impart hydrolytic degradation to a PEG network. Cyclic acetals produce alcohol and carbonyl terminals as primary degradation products, and thus may not affect local acidity. The potential acidity of hydrogel degradation products may be a concern considering the potential use as cell transplantation and drug delivery vehicles. Our laboratory has recently reported the utility of a hydrolytically degradable, crosslinked material based on cyclic acetal monomer alone [21]. Here, we propose to extend this work by using the cyclic acetal monomer 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1,3-dioxane-2-ethanol diacrylate (EHD) and PEGDA to form an amphiphilic degradable EH–PEG [5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1,3-dioxane-2-ethanol-*co*-PEG] hydrogel. Amphiphilic conetworks (APCNs) have been widely studied and their utility for medical application has been successful due to their unique characteristics, such as swelling both in water and organic solvent. Indeed, APCNs play important roles in applications for contact lenses, implantable drug delivery devices and bioartificial pancreas [22].

Therefore, the objective of this work is to develop and characterize novel cyclic acetal hydrogels based upon an EHD monomer. We are particularly interested in the effects of a hydrophobic monomer, such as the EHD monomer, on the ability to fabricate hydrogels as well as the resulting properties of these hydrogels. To this end, cyclic acetal based hydrogels were formed from an EHD and PEGDA system. To the best of our knowledge, this is the first demonstration of hydrogels fabricated using the EHD monomer as well as cyclic acetal based hydrogels for biomedical applications. Physicochemical properties including swelling degree, sol fraction and contact angles were then evaluated. The specific objectives of this work were to (1) determine the effect of the EHD to PEGDA ratio as well as initiator content on the extent of hydrogel fabrication reaction and (2) determine the effect of the EHD to PEGDA ratio as well as initiator content on the hydrophilicity of the resulting hydrogel.

2. Materials and methods

2.1. Materials

The significant materials used in this work, including 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1,3-dioxane-2-ethanol diacrylate (326 g/mol), PEGDA (average molecular weight of 700 g/mol), benzoyl peroxide (BPO) and *N*,*N*-dimethyl-*p*-toluidine (DMT), were purchased from Sigma–Aldrich (St. Louis, MO). All reagents were used without further purification.

2.2. Synthesis of EH–PEG hydrogel

A series of EH–PEG hydrogels were synthesized with BPO as an initiator and DMT as an accelerator. Three fabrication parameters were utilized to control the properties of EH–PEG hydrogels: molar ratio of monomers, monomer concentration, and initiator concentration. For the case of a 1.0 molar ratio of EHD to PEGDA, EHD (318 mg) and PEGDA (682 mg) were weighed in glass vial. An initiator solution was prepared by dissolving BPO (50 mg) in acetone (4 mL), to give a BPO concentration of 5 wt% relative to the total weight of both monomers. W_i was defined as the total weight of monomers and initiator. Water (2 mL) and initiator solution (4 mL) were added into the vial, so that the monomer to solvent ratio was 0.167 g/mL and the acetone to water volume ratio was 2.0. After stirring thoroughly, DMT (7 μL) was added to the monomer solution. An EH–PEG hydrogel was formed within 10 min at room temperature.

For the case of EHD/PEGDA = 10.0, EHD (823 mg) and PEGDA (176 mg) were weighed and dissolved in acetone and water (volume ratio = 7.0). For the case of EHD/PEGDA = 0.1, EHD (46 mg) and PEGDA (954 mg) were weighed and dissolved in acetone and water (volume ratio = 1.5). A series of samples were then prepared by changing the initiator concentration (1, 5, or 10 wt%) and the solvent content (1–7 mL).

2.3. Characterization of EH–PEG hydrogel

The chemical structure and the conversion of acrylate functional groups during free radical polymerization were measured by using Fourier transform infrared spectroscopy (FT-IR) (FTS-60A, Bio-Rad, Digilab Division, Cambridge, MA). Both PEGDA and EHD were analyzed as a liquid film. EH–PEG hydrogels were dried, embedded within KBr pellets, and analyzed within the pellets.

2.4. Swelling degree and sol fraction

Phosphate-buffered saline (PBS: pH 7.4, 8 g/L of NaCl, 0.2 g/L of KCl, 1.44 g/L of Na_2HPO_4, 0.24 g/L of KH_2PO_4) was first prepared. PBS (15 mL) was added to hydrogels, which were allowed to swell overnight. Swollen hydrogels were then weighed, W_s. The swollen hydrogels were dried in oven until the weights were stabilized and then weighed, W_d. The swelling degree was calculated using the following formula, swelling degree $(q) = W_s/W_d$. As the initial weight of the gel (W_i) was determined during fabrication (see above), sol fraction could then be calculated using the following formula: sol fraction $= (W_i - W_d)/W_i \times 100\%$. Each sample type was run three times; the reported values are the mean values, and the associated errors are the standard deviations.

2.5. Contact angle

EH–PEG hydrogels were prepared on glass plates. Briefly, a total 1 g of PEGDA and EHD was measured. Next, 50 mg of BPO was dissolved in toluene and mixed with the monomer. The solution was poured into glass plates and placed in the oven (70 °C) for 5 h. After thin films were formed, they were washed with acetone to remove the residual toluene and water for three times, soaked in water overnight, and then the surface of the hydrogels was wiped briefly. Water contact angles of those synthesized hydrogels were then measured (Master 500, Kyowa Interface Science Co. Ltd., Japan). Each sample type was run five times; the reported values are the mean values, and the associated errors are the standard deviations.

2.6. Statistical analysis

All experiments were conducted in triplicate. Data from all studies were analyzed using one-way analysis of variance (ANOVA) and Tukey's multiple-comparison test ($p = 0.01$). All results were reported as means ± standard deviation.

3. Results

3.1. Synthesis of EH–PEG hydrogels

Hydrogels based on EHD and PEGDA were synthesized by free radical polymerization to crosslink unsaturated double bonds of acryl groups of both components (Fig. 1). In order to investigate the conversion of the monomers, the crosslinking density and the chemical structure of the EH–PEG hydrogels were analyzed by FT-IR. In particular, the conversion of acryl groups was monitored. Hydrogels were prepared by using initiator concentration of 5.0 wt% and monomer concentration of 0.33 g/mL for

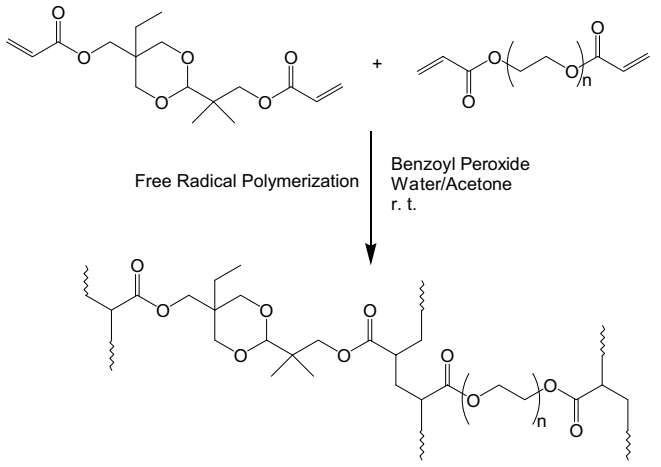

Fig. 1. Reaction scheme for synthesis of EH–PEG hydrogels from EHD and PEGDA.

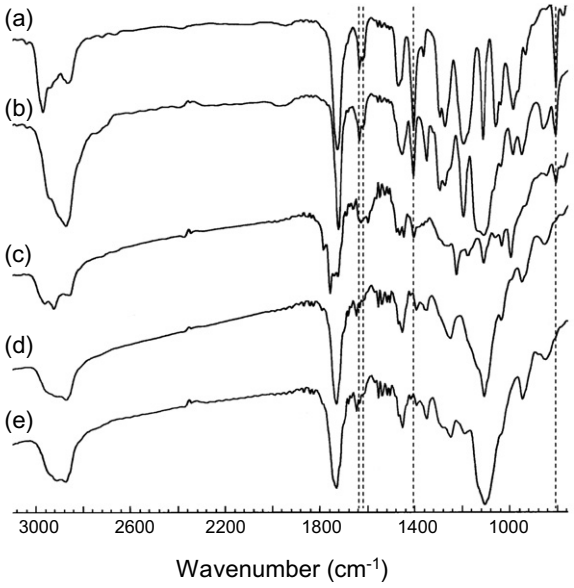

Fig. 2. FT-IR spectra of pure EHD (a), pure PEGDA (b), and an EH–PEG hydrogel containing an EHD/PEGDA = 10.0 ratio (c), an EH–PEG hydrogel containing an EHD/PEGDA = 1.0 ratio (d), and an EH–PEG hydrogel containing an EHD/PEGDA = 0.1 ratio (e).

all the monomer molar ratios. As depicted in Fig. 2, FT-IR indicated that spectroscopic peaks at 1635, 1621, 1409 and 810 cm^{-1}, corresponding to the main C=C bond signals of acryl groups, diminished significantly after the reaction for all the samples investigated.

3.2. Swelling degree

The swelling degrees of the various EH–PEG hydrogels were investigated by weight changes before and after drying. Fig. 3 shows the effect of monomer molar ratio (EHD/PEGDA) and monomer concentration on swelling degree of EH–PEG hydrogels, using initiator concentrations of 0.5 wt% (Fig. 3a), 1.0 wt% (Fig. 3b), and 5.0 wt% (Fig. 3c). The results show that the degree of swelling increased as monomer concentration decreased for any initiator concentration. Considering an initiator concentration of 5.0 wt% (Fig. 3c), swelling increased significantly from 1.5 ± 0.1 to 2.8 ± 0.1 as monomer concentration fell for the EHD/PEGDA = 10.0 group ($p < 0.01$). Similarly, swelling increased significantly from 1.7 ± 0.0 to 6.0 ± 0.3 for EHD/PEGDA = 1.0 ($p < 0.01$) and from 2.2 ± 0.1 to 3.5 ± 0.5 for EHD/PEGDA = 0.1 ($p < 0.01$) (Fig. 3c). A trend of increasing swelling with decreasing EHD/PEGDA ratio was also observed. For example in Fig. 3c, with a 5 wt% initiator concentration and 1 g/mL monomer concentration, swelling degree increased from 1.5 ± 0.1 to 2.2 ± 0.1 as ratio of EHD to PEGDA fell from 10.0 to 0.1 ($p < 0.01$). Finally, for EH–PEG hydrogels fabricated from 0.5 wt% initiator (Fig. 3a) and 1.0 wt% initiator (Fig. 3b), there was no significant difference in swelling degree at monomer concentrations greater than 0.5 g/mL ($p = 0.1$). Hydrogels could not be fabricated using the

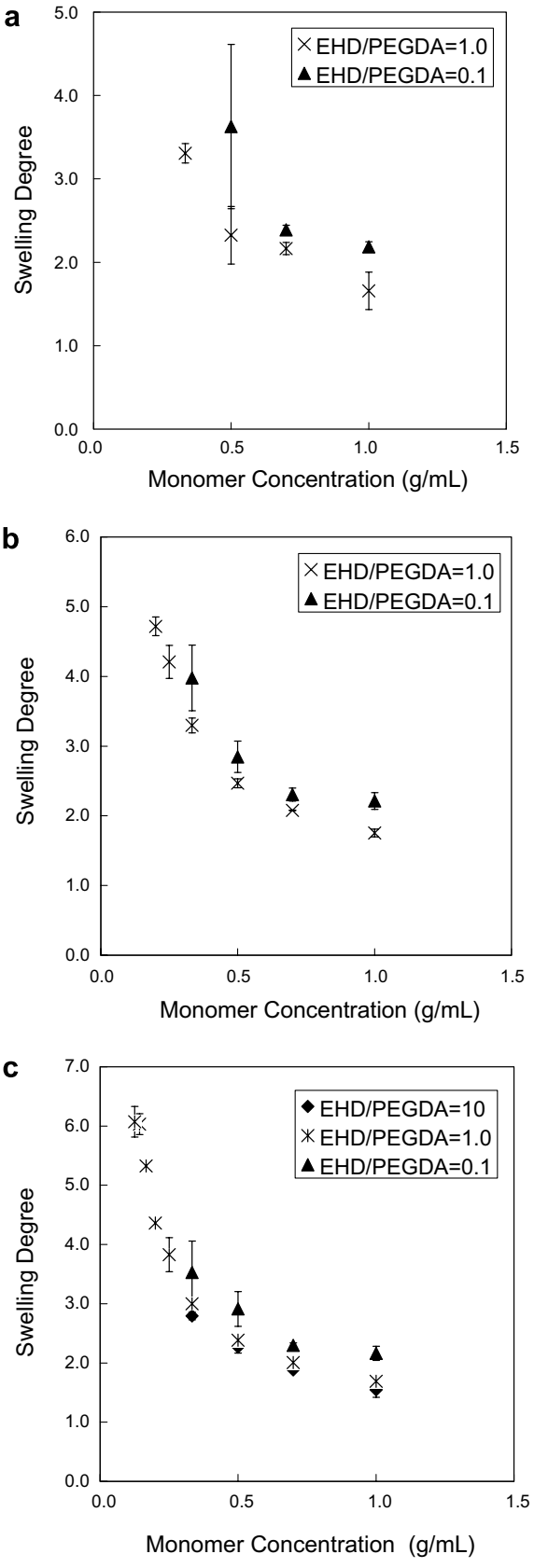

Fig. 3. The effect of total monomer concentration, EHD/PEGDA ratio, and initiator concentration on the swelling degree of EH–PEG hydrogels in PBS buffer. Initiator concentration was varied between 0.5 wt% (a), 1.0 wt% (b), and 5.0 wt% (c). The mean and standard deviation ($n = 3$) are reported.

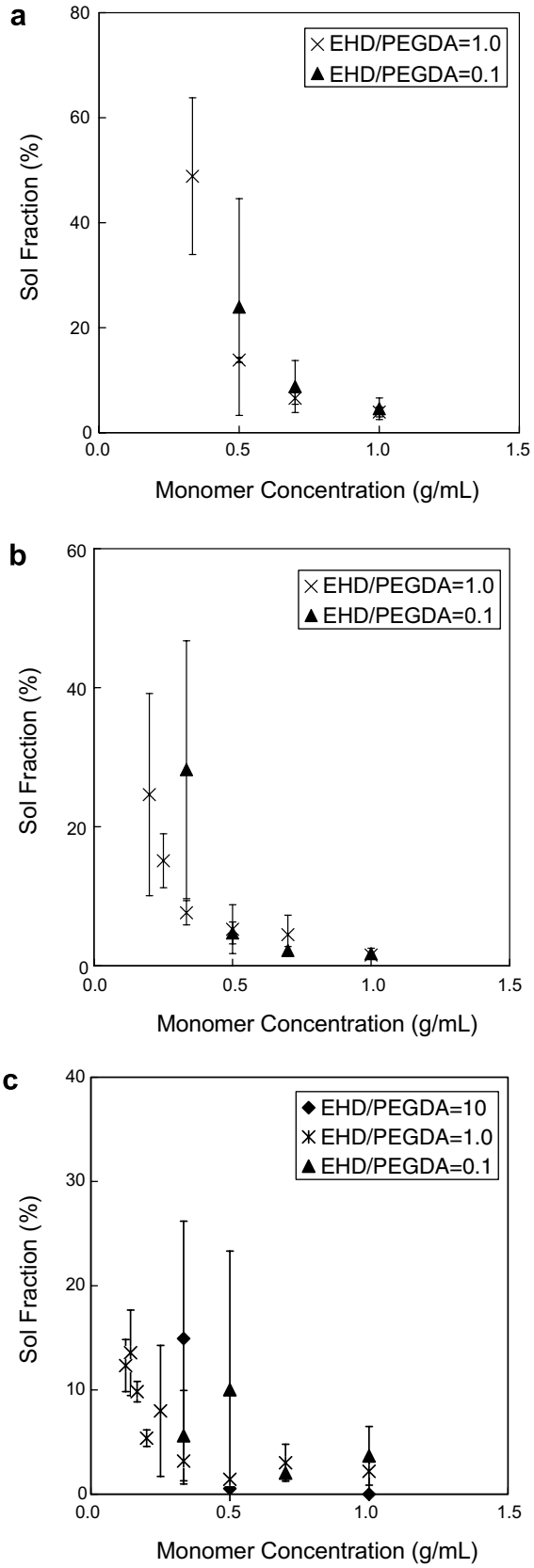

Fig. 4. The effect of total monomer concentration, EHD/PEGDA ratio, and initiator concentration on the sol fraction of EH–PEG hydrogels in PBS buffer. Initiator concentration was varied between 0.5 wt% (a), 1.0 wt% (b), and 5.0 wt% (c). The mean and standard deviation ($n = 3$) are reported.

described approach when initiator concentration was lower than 5 wt% for EHD/PEGDA = 10.0.

3.3. Sol fraction

The sol fraction of the EH–PEG hydrogels was examined by water sorption experiments. Fig. 4 shows the effect of monomer molar ratio (EHD/PEGDA) and monomer concentration on sol fraction of EH–PEG hydrogels, using initiator concentrations 0.5 wt% (Fig. 4a), 1.0 wt% (Fig. 4b), and 5.0 wt% (Fig. 4c). The results indicated that sol fraction generally increased as the monomer concentration decreased regardless of EHD/PEGDA ratio and initiator concentration. For example, sol fraction increased significantly from 4.0% ± 1.0% to 48.9% ± 14.9% as monomer concentration fell from 1.0 to 0.3 g/mL for EHD/PEGDA = 1.0 and an initiator concentration of 0.5 wt% ($p < 0.01$) (Fig. 4a). Similar trends are observed in other experimental groups studied here, although this trend appears to diminish as initiator concentration is increased to 5.0 wt%. Furthermore, as initiator concentration is increased to 5.0 wt%, sol fraction is almost negligible at high monomer concentration (Fig. 4c). As mentioned previously, hydrogels could not be fabricated when initiator concentration was lower than 5.0 wt% for EHD/PEGDA = 10.0.

3.4. Contact angle

Water contact angles of EH–PEG hydrogels containing an EHD/PEGDA = 0.1, 1.0, and 10.0 ratio were measured to investigate the hydrophilicity of the synthesized hydrogels (Fig. 5). The results of the study indicated that the addition of PEGDA decreased the water contact angle of the surface of the hydrogels. Contact angles were found

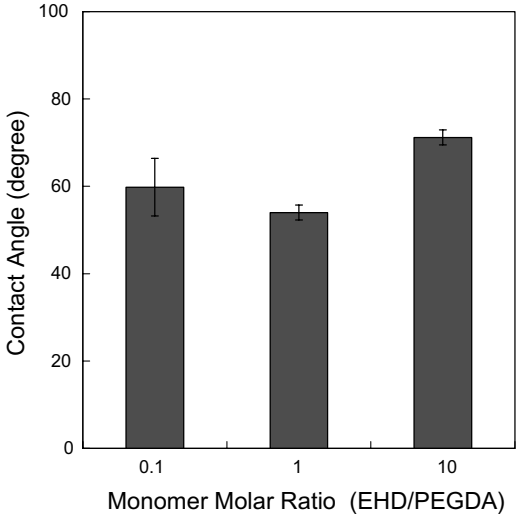

Fig. 5. Contact angle of an EH–PEG hydrogels containing a EHD/PEGDA = 0.1, 1.0, and 10.0 ratio. The mean and standard deviation ($n = 5$) are reported.

to be 59.8° ± 6.6° for EHD/PEGDA = 0.1 and 54.0° ± 1.7° for EHD/PEGDA = 1.0, but increase significantly to 71.2° ± 1.7° for EHD/PEGDA = 10.0 ($p < 0.01$).

4. Discussion

The objectives of this work were to synthesize and characterize a novel degradable hydrogel based upon hydrophobic degradable segments of EHD and hydrophilic segments of PEGDA. As the mass solubility of EHD in water is fairly low (0.055 g/L), those hydrogels which contain greater amounts of hydrophilic PEG segments should have a larger water content. Therefore, we hypothesized that the ratio of hydrophilic segments and hydrophobic segments will significantly affect the swelling properties of the hydrogels, with swelling degree increasing as the ratio of hydrophilic segments increases. Secondly, we investigated the effect of initiator concentration upon swelling degree and sol fraction. We hypothesize here that the sol fraction of the hydrogel will increase as the initiator concentration decreases, due to the decrease in crosslinking reaction.

In order to evaluate the physicochemical properties of the hydrogels, mass swelling degree was measured. The results showed that the swelling degree was notably influenced by the monomer concentration (see Fig. 3a–c), with swelling degree increasing as monomer concentration decreased. This tendency was especially significant when EHD/PEGDA = 1.0 and initiator concentration was 5.0 wt% (Fig. 3c), where swelling degree was lowest at 1.0 g/mL ($q = 1.7 \pm 0.0$) and rose to a high at 0.125 g/mL ($q = 6.0 \pm 0.3$). The results indicated that a solution with low monomer concentration contained a large amount of solvent, allowing the monomers to form a loosely crosslinked network with an increased swelling degree. Initiator concentration did not appear to significantly influence the swelling degree of these constructs, as shown in Fig. 3a–c. Swelling degree was also found to slightly increase as the ratio of EHD/PEGDA decreased and the monomer concentration was held constant, as expected. This result is due to the hydrophilicity of PEGDA. In particular, hydrogels with a large amount of PEGDA have a larger affinity for water; and therefore contain more water within the polymer network. This result corresponds to the report by Tan et al. that the swelling degree of amphiphilic gels is significantly influenced by the composition of the network [23]. In addition, the longer PEGDA chain length (700 g/mol, with approximately 38 atoms in one repeating unit), when compared to the EHD monomer (326 g/mol, with 9 atoms in one repeating unit), likely facilitates the retention of a larger volume of solvent due to the increase of crosslinking density. Interestingly, when a large excess of one of the two monomers exists, a hydrogel cannot be fabricated at low monomer concentrations under the conditions utilized in this work. Therefore, these results indicated that the random order of two monomers, as occurs when their molar contents are similar, allows the formation of a loosely crosslinked network capable of retaining increased amounts of water.

The results of the sol fraction studies largely reflect the trends observed in the swelling degree studies. Sol fraction gradually increased as the monomer concentration decreased in any monomer molar ratio, as shown in Fig. 4a–c. In addition, the FT-IR spectra (Fig. 2) showed the completion of crosslinking at high monomer concentration by the disappearance or significant reduction of acrylic C=C peaks at 1635, 1621, 1409, and 810 cm^{-1} by both PEGDA and EHD. As the C=C were consumed, reaction extent increased and therefore sol fraction decreased. These results indicated that in low monomer concentration, the crosslinking density of the network structure was significantly low, inhibiting some of the chains to form a three-dimensional network structure. As a result, increasing numbers of monomers remained either unreacted or as soluble, short primary polymer chains. The results also showed that the sol fraction increased as initiator concentration decreased (Fig. 4a–c). In addition, the minimal initiator concentration required for gelation was influenced by both the monomer ratio and concentration. For example, gelation of EHD/PEGDA = 10.0 required a monomer concentration of 0.33 g/mL and 5 wt% initiator, while the gelation of EHD/PEGDA = 1.0 was possible with a monomer concentration of 0.33 g/mL and 0.5 wt% initiator as well as 0.20 g/mL and 1.0 wt% initiator. These results indicated the expected result that a low initiator concentration does not produce a sufficient amount of radicals to propagate thorough crosslinking reaction, leaving many monomers unreacted.

Finally, a study of water contact angle was performed to examine the hydrophilicity of the surface of synthesized hydrogels. The contact angles of the EH–PEG hydrogels were relatively high when the ratio of EHD was high (71.2° ± 1.7° for EHD/PEGDA = 10.0). However the contact angles decreased as the ratio of EHD decreased (54.0° ± 1.7° for EHD/PEGDA = 1.0 and 59.8° ± 6.6° for EHD/PEGDA = 0.1). These results followed the expectation that the water contact angle would increase as the ratio of PEGDA increases, indicating that the addition of PEGDA strongly influenced the hydrophilicity of the material because of its hydrophilic polymer main chain. These results correspond to previous results, where the contact angles of the EH crosslinked material, without any PEG content, were mainly between 77.0 ± 4.9 °C and 74.6 ± 6.4 °C [20]. Also, these results imply that the previously observed relationship of increasing swelling degree with increasing ratio of PEGDA is likely due to the hydrophilicity of PEGDA as well as longer polymer chain of PEGDA when compared to EHD. Finally, the range of contact angles values is within the range of 50°–75° where cell adhesion is generally thought to be promoted [13,24].

5. Conclusions

The originally designed EH–PEG hydrogel was synthesized by free radical copolymerization of two diacrylate monomers. Crosslinking occurred because of the difunctionality of the monomers. The swelling degree and sol fraction were influenced by reaction conditions such as monomer concentration, initiator concentration, and monomer ratios. Contact angles of the hydrogels were high when fabricated with excess amount of EHD. It was confirmed that these physicochemical properties of the synthesized hydrogels were controllable. Therefore, the addition of hydrophobic EHD segments provided the conventional PEG hydrogels with unique characteristics. As a result, hydrolytically degradable EH–PEG hydrogels may be a promising biomaterial option for applications including drug delivery and tissue engineering.

Acknowledgments

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