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Synthesis and characterization of degradable hydrogels formed from acrylate modified poly(vinyl alcohol) macromers

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Abstract

Poly(vinyl alcohol) was modified with pendant acrylate groups to create a multifunctional macromer that is crosslinkable via photopolymerization and degradable through hydrolytically cleavable ester groups within the crosslinks. The chemistry and functionality of the macromer, as well as the polymerization conditions, were varied to produce hydrogel networks with a wide range of physical properties and degradation behavior. The resulting networks were characterized by measuring the volumetric swelling ratio and mass loss profiles with degradation time. Experimental results show that the volumetric swelling ratio increases exponentially during degradation of these gels, and this increase can be predicted through a pseudo-first order reaction depending only on the kinetic constant for hydrolysis and the number of degradable links in the crosslinker. Coupled to the hydrolytic degradation, the network structure also influences the mass loss or erosion profile and, ultimately, the overall time for degradation. © 2002 Published by Elsevier Science Ltd.

Keywords: Biodegradable; Hydrogels; Poly(vinyl alcohol)

1. Introduction

Historically, hydrogel networks have been synthesized from a variety of hydrophilic polymers and crosslinking mechanisms. Crosslinked gels often have different properties based on the type of crosslinking method used (i.e. chemically, physically or ionically crosslinked), as well as the fact that each method brings with it its own limitations and benefits depending on the desired use and application of the gels. Because of their unique properties (e.g. high water content and elastic properties) and the ability to control and tailor these properties, hydrogels are useful for numerous applications. Non-degradable hydrogels have found widespread application as contact lenses, controlled release matrices, and bioadhesives [1–3], whereas degradable polymers have been studied widely for use in controlled release applications [4–6].

Of the three crosslinking methods mentioned previously, covalently crosslinked degradable networks, especially those formed via chain crosslinking polymerization of multifunctional monomers, are finding increased interest in biomaterial applications. For example, Sawhney et al. [4] formed degradable gels via the photopolymerization of a copolymer composed of a poly(ethylene glycol) (PEG) core and oligomeric α-hydroxy acids segments, in an A–B–A fashion, that were end-capped with acrylate functionalities. These researchers found that by coupling PEG and the relatively hydrophobic α-hydroxy esters together in varying ratios, the overall time for complete degradation was significantly altered. The erosion of the PEG based hydrogels was varied from less than one day up to 4 months and was shown to depend on the crosslinking density and the type of α-hydroxy esters that was used.

To provide additional flexibility in the resulting network structure, other research groups synthesized degradable gels from macromers of higher functionality. For example, Argade and Peppas [7] have used copolymerization or crosslinking techniques with PVA and acrylic acid to obtain biodegradable, superabsorbant polymers. The PVA used in these studies either had the functionality incorporated randomly into the backbone or the functionality was added as pendant groups. It was determined that the swelling and degradation of hydrogels made from these

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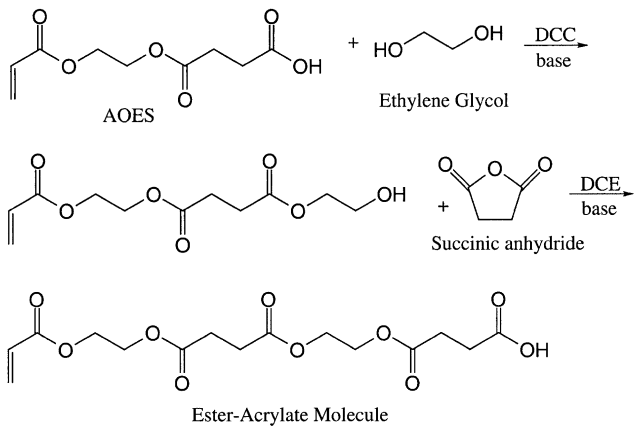

Fig. 1. Schematic of the degradable ester-acrylate molecule synthesis.

systems depended on the crosslinking ratios, the type and pH of the degrading medium and the type of PVA chemistry used. In another example of multifunctional macromers, van Dijk-Wolthuis et al. [8] synthesized and characterized a wide array of dextran macromers derivatized with crosslinkable methacrylate groups. In their approach, glycidyl methacrylate [9–12], hydroxyethyl methacrylate [13,14] and hydroxyethyl methacrylate–oligolactide groups were coupled to dextran [8]. The hydroxyethyl methacrylate and hydroxyethyl methacrylate–oligolactide derivatized dextran macromers incorporated a hydrolytically degradable spacer between the polymerizable group and the dextran backbone, similar to the PEG based macromers; however, the methacrylated-dextrans did not include a hydrolytically degradable spacer and, therefore, relied solely on enzymatic degradation of the dextran. The degradation time and drug release profiles of networks formed from the derivatized dextran molecules were controlled by varying the degree of substitution of dextran, as well as varying the amount of water that was present at the time of polymerization [8–14].

To build on these efforts using radical chain polymerizations to form degradable hydrogels, we are interested in the chemical modification of PVA to produce photocrosslinkable and hydrolytically degradable macromers that enable a high degree of flexibility in the final hydrogel properties, especially as a function of degradation. PVA was chosen as the backbone for our macromers because of its many advantageous properties in biomedical applications, e.g. hydrophilic, naturally adhesive, and facile modification of its pendant hydroxyl groups [1,15–19]. Herein, we present techniques to modify chemically linear PVA chains to produce multifunctional macromolecular monomers that can be reacted via a photoinitiated polymerization to form degradable gels. Photopolymerization provides several advantages with respect to the gel fabrication including rapid polymerization rates under physiological conditions, and spatial and temporal control of the initiation process. These mild polymerization conditions are beneficial for many applications and allow in situ formation of gels (for tissue adhesives), polymerization in the presence of cells (for tissue engineering), and encapsulation of drugs (for controlled release matrices) [20]. The chemical modification technique presented here allows for a diverse range of final network properties to be achieved. Specifically, the functionality and number of degradable linkages in the macromer are readily altered, as well as the concentration of the macromer in solution at the time of polymerization. These modifications influence not only the overall time for degradation, but also the erosion profile and the volumetric swelling ratio throughout the degradation process.

2. Experimental

2.1. Materials

Poly(vinyl alcohol) (PVA) (14,000 g/mol, 83% hydrolysis and 31,000 g/mol, 88% hydrolysis, Clairant), mono-2-(acryloyloxy)ethyl succinate (AOES, Aldrich, 99%), ethylene glycol (Aldrich, 99 + %), 1,3-dicyclohexylcarbodiimide (DCC, Aldrich, 1 M in dichloromethane), hydrochloric acid (Mallinckrodt, 37%), sodium bicarbonate (Sigma, 100%), succinic anhydride (Aldrich, 97%), magnesium sulfate (Aldrich), and triethylamine (Aldrich, 99.5%) were used without further purification. The solvents used (dichloromethane, dichloroethane, dimethyl sulfoxide, acetone, and ethyl ether) were supplied by Fisher Scientific and used without further purification. The photoinitiator, 2-hydroxy-1-[4-(hydroxyethoxy)phenol]-2-methyl-1-propanone, (Irgacure 2959, I2959, Ciba-Geigy) was used as supplied at a 0.05 wt% concentration in all formulations.

2.2. Degradable ester-acrylate synthesis (Fig. 1)

A degradable ester-acrylate molecule with various numbers of degradable ester linkages terminated with a carboxylic acid group was synthesized and subsequently coupled to PVA. A simple 3-ester acrylate PVA macromer can be prepared by coupling mono-2-(acryloyloxy)ethyl succinate, AOES, directly to PVA [21]. To obtain a 5-ester degradable molecule, AOES (32.43 g, 0.15 mol) was dried in a 10–30% dichloromethane solution in a 500 ml, 3-neck round bottom flask with a five molar excess of ethylene glycol (relative to the AOES, 46.55 g, 0.75 mol) and a small amount of base. The solution was cooled in an ice bath, and a stoichiometric ratio of a 1 M DCC solution (150 ml, 0.15 mol) was slowly added over several minutes. The solution was allowed to react for at least one hour at room temperature, while maintaining a small positive pressure of nitrogen. Upon completion, the white precipitate was filtered off, and the remaining solution was extracted with 10% hydrochloric acid (2 × 100 ml), 1 M sodium bicarbonate (2 × 100 ml) and water (2 × 100 ml) to remove the base, AOES, and DCC salts, respectively. The organic phase was dried over magnesium sulfate, and the solvent was removed by evaporation [21]. The alcohol terminated

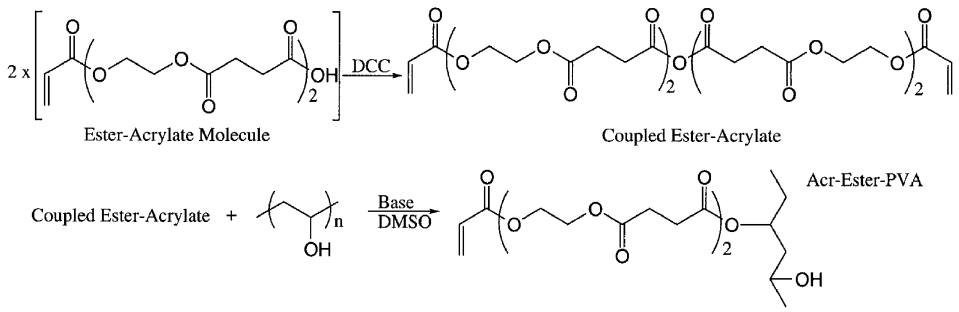

Fig. 2. Schematic of the Acr-ester–PVA synthesis.

3-ester molecule was activated with base and then reacted with a molar equivalent of succinic anhydride (15.01 g, 0.15 mol) in a 25% dichloroethane solution and stirred at 65 °C for at least one hour to produce a carboxylic acid terminated 5-ester degradable molecule. The solution was subjected to extraction with 10% hydrochloric acid solution (2 × 75 ml) and water (2 × 75 ml), and then the organic layer was dried over magnesium sulfate. The solvent was removed by evaporation and the final product was dried under vacuum [21].

2.3. Acrylate-ester–PVA macromer synthesis (Fig. 2)

The attachment of the ester acrylate molecule to the PVA can be done in varying degrees, and the recipe that follows is for attaching 7 ester acrylate molecules per 14,000 g/mol PVA chain [21]. A 10% DCM solution of the 5-ester acrylate molecule (3.6 g, 0.01 mol) was dried over molecular sieves with a small positive pressure of nitrogen for at least one hour. The solution was then cooled in an ice bath, and DCC was slowly added (5 ml, 0.005 mol) to produce an anhydride linkage between two 5-ester acrylate molecules. After stirring at room temperature for 1 h under nitrogen, the precipitate was filtered off and the solvent was removed by evaporation [21].

An 18 wt% solution of a 14,000 g/mol PVA in dimethyl sulfoxide (DMSO) was prepared with heating at 60 °C. The 5-ester anhydride molecule was dissolved in a small amount of DMSO, and 55.55 g of the PVA solution was added along with 250 μl of triethylamine. The solution was stirred overnight at room temperature. The resulting Acr-ester–PVA macromer was then precipitated into a 10-fold excess of an 80/20 mixture of acetone and ether [21]. By controlling the degree of substitution and length of the degradable segment (e.g. 3-ester vs. 5-ester), the degradation time of the final network can be significantly altered [21].

2.4. Macromer characterization

^{1}H NMR (Varian VXR-500S) was used to follow and verify each step of the synthesis. For the ester-acrylate synthesis, the area under the integrals for the vinyl resonances ($\delta = 6.4$ ppm, d, $\delta = 6.1$ ppm, q, $\delta = 5.8$ ppm, d) were compared to that for the ester resonances ($\delta = 4.2$ ppm, $\delta = 2.6$ ppm). Substitution of the ester-acrylate onto the PVA was verified by noting the presence of resonances for the vinyl protons ($\delta = 6.4$ ppm, d, $\delta = 6.1$ ppm, q, $\delta = 5.8$ ppm, d), as well as the resonances for the PVA backbone (methylene protons, $\delta = 1.4$–1.8 ppm, methylene adjacent to the hydroxy, $\delta = 3.8$–4.1 ppm). The ester-acrylate spectra were collected in $CDCl_3$, and the PVA spectra were collected in D_2O.

2.5. Macromer polymerization

After functionalization and drying, the multifunctional Acr-ester–PVA was then re-dissolved in DI–H_2O at 80 °C at concentrations ranging from 10 to 50 wt%. The photoinitiator, I2959, was then dissolved in the solution at a concentration of 0.05 wt%. The final solution was photopolymerized using an ultraviolet light source (Novacure, EFOS, Inc.) at an intensity ranging from 5 to 20 mW/cm^2 for 5 min or less. These mild photoinitiating conditions were chosen since it was previously determined that these conditions are cytocompatible [20].

2.6. Hydrogel characterization

Immediately after polymerization and prior to degradation, the sol fraction was extracted from the gel. The sol fraction was approximately 40% in each of the gels and is likely a result of either unsubstituted PVA chains or PVA chains that have reacted completely upon themselves (i.e. formed cycles) and not with any other macromers in the system, and therefore, are not attached to the network. Upon calculation of the sol fraction, degradation of the polymerized hydrogel was carried out in a 7.4 pH phosphate-buffered saline solution at 37 °C. Disks (10 mm in diameter and 1 mm thick) were polymerized in molds and weighed immediately following polymerization, placed in a permeable, plastic tissue cassette, and degraded in buffer solution under sink conditions. At various time points, a tissue cassette was removed from the buffer solution, patted dry, and weighed to obtain the swollen wet weight of the disk (m_s). The disk was then thoroughly dried by

lyophilization and a final dry weight was obtained (m_{fd}). The initial dry polymer mass (m_{id}) was calculated by multiplying the initial wet weight of the disk with the weight fraction of macromer in that solution and then subtracting out the sol fraction. The percent mass loss of each sample was determined using the following equation:

$$\%\ \text{mass loss} = \frac{(m_{id} - m_{fd})}{m_{id}} \times 100\% \quad (1)$$

The volumetric swelling ratio (Q) was also calculated via the mass swelling ratio ($q = m_s/m_{fd}$) according to the following equation

$$Q = 1 + \frac{\rho_{polymer}}{\rho_{solvent}}(q - 1) \quad (2)$$

where $\rho_{polymer}$ is the macromer density, and was approximated by the density of PVA ($\rho_{PVA} = 1.2619$ g/ml). $\rho_{solvent}$ is the density of the buffer solution and was approximated as 1.0 g/ml. In all swelling and mass loss plots shown in this paper, the y-axis error bars were calculated from at least three samples taken at the same time point, and x-axis error bars are a result of variation in either the time the sample was taken, or the variation in the total time required for degradation (i.e. the last data point).

3. Results and discussion

Degradable hydrogels were formed from the multivinyl PVA macromers via a photoinitiated, radical chain polymerization. The initiating radicals propagate through the pendant acrylate groups to form kinetic chains, or polyacrylate chains, which react to form a relatively complex 3D network structure with hydrolyzable groups between the kinetic chains and the PVA chains. Thus, the network is comprised of PVA chains, kinetic chains, and small crosslinker segments that contain the degradable linkages (Fig. 3). Complete conversion of the double bonds to either form crosslinks or cycles is assumed, based on near-IR experiments done with similar multifunctional, non-degradable PVA networks [22]. Due to the network's hydrophilicity, these networks swell in water, and the ester bonds in the crosslinks are cleaved homogeneously at a rate dictated by the hydrolysis kinetic constant for the ester bond and the number of degradable ester linkages (i.e. pseudo-first order kinetics). Once a significant fraction of the ester bonds have been cleaved, the polymer chains (e.g. PVA chains or kinetic chains) are eroded from the network, which results in an overall mass loss from the network. These polymer chains are assumed to diffuse rapidly out of the network, as the degradation occurs much faster than the degradation of the bonds. The assumption was verified by using simple equations based on Fickian diffusion to estimate the initial diffusion coefficient (e.g. 6×10^{-11} mm^2/s), and the time required for the polymer chains to diffuse out of a 1 mm thick disk (<4 h). Once all

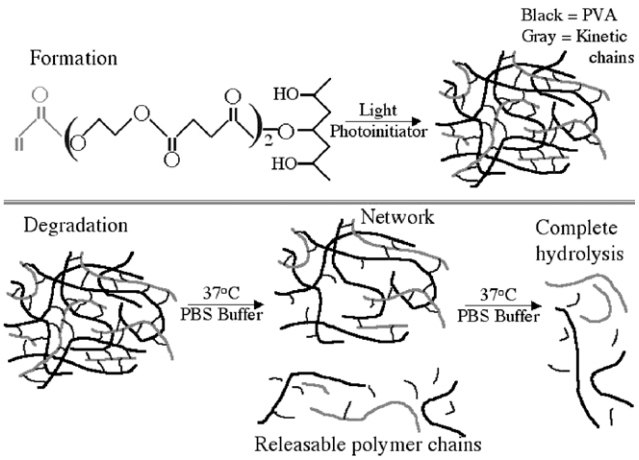

Fig. 3. Schematic of the formation of hydrogel networks from multifunctional PVA chains, and the subsequent degradation process and products.

of the degradable linkages are hydrolyzed, one is left with PVA chains, polyacrylate chains, and the small molecules used to form the ester bonds (i.e. ethylene glycol and succinic acid).

The general degradation behavior of hydrogel networks formed from the chain polymerization of divinyl PEG macromers was studied previously [4,23,24]; however, these macromers form a maximum of one crosslink in the network per PEG chain. The addition of more crosslinkable functionalities to the polymer backbone (e.g. PVA) significantly complicates the structure of the network and the subsequent mass loss from these networks during degradation. For example, each macromer can be connected to several kinetic chains in a range of conformations [25]. Both of these parameters lead to variations in the overall degradation profile and must be understood to control important parameters such as the time for complete degradation and the corresponding mass loss profile.

Previous work using multifunctional, *non-degradable* PVA macromers demonstrated that changing the functionality of the macromer and polymerization conditions, such as the percent macromer in solution prior to polymerization, results in variations in the subsequent network structure [22]. For example, the initial swelling ratio varied from 18 to 15 to 5.5 as the macromer solution concentration increased from 20 to 30 to 50 wt%. Similarly, changes in the functionality or polymerization conditions of multifunctional, *degradable* PVA macromers should lead to different initial network structures and subsequent changes in the degradation and erosion profiles.

Figs. 4 and 5 show typical changes in the volumetric swelling ratio and mass loss as a function of time from these degradable PVA gels. This particular gel was synthesized from a 20 wt% solution of a 31,000 g/mol, 88% hydrolyzed PVA macromer that had seven acrylate functionalities per PVA chain. Several important characteristics of the volumetric swelling ratio are shown in Fig. 4. First, the

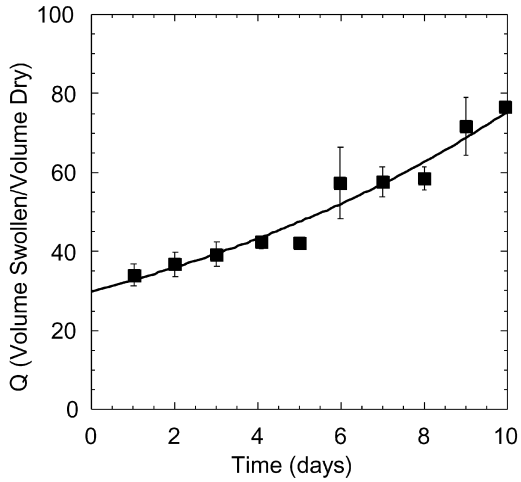

Fig. 4. Typical volumetric swelling ratio (Q) as a function of degradation time for a hydrogel synthesized from multifunctional, degradable PVA macromers. Data (■) are shown for a gel synthesized from a 20 wt% solution of a 31,000 g/mol PVA macromer with 88% hydrolysis and 7 acrylate functionalities per PVA chain. The solid line is an exponential fit of the data.

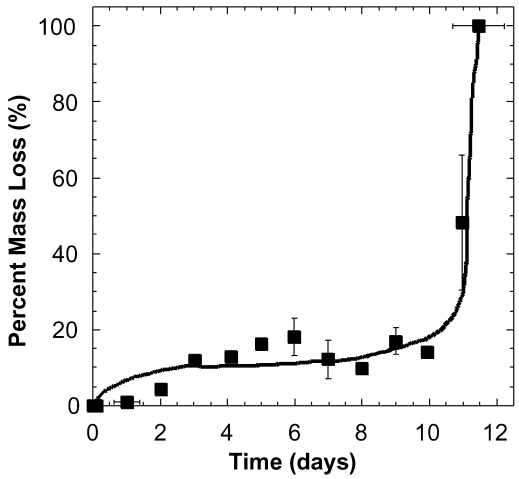

Fig. 5. Typical percent mass loss as a function of degradation time for a hydrogel synthesized from multifunctional, degradable PVA macromers. Data (■) are shown for a gel synthesized from a 20 wt% solution of a 31,000 g/mol PVA macromer with 88% hydrolysis and 7 acrylate functionalities per PVA chain. The line is meant to guide the eye in observing the trends of the data.

equilibrium water content of these networks is very high ($Q > 20$ for most systems), corresponding to a water content >95%. Since the degradation of these hydrogels is facilitated through hydrolytic cleavage of the ester bonds in the crosslinking functionality, the network crosslinking density decreases with degradation, resulting in an increase in the swelling ratio. Specifically, the rate of hydrolysis of the ester linkages is given by

$$\frac{-\mathrm{d}n_{\mathrm{E}}}{\mathrm{d}t} = k n_{\mathrm{E}} n_{\mathrm{H_2O}} \tag{3}$$

where k is the kinetic constant for hydrolysis of the ester linkages, $n_{\mathrm{H_2O}}$ is the moles of water with the swollen network; t is degradation time, and n_{E} is the moles of undegraded ester blocks (i.e. the number of undegraded crosslinkable functionalities). Although there is more than one cleavable ester bond in each crosslink, once a single ester linkage is degraded, the entire crosslink is broken. Thus, for simplicity, one can examine the entire ester block instead of each individual ester linkage. Since the networks are all highly swollen, the water concentration is essentially constant throughout the degradation process and the specie balance can be rewritten as $-\mathrm{d}n_{\mathrm{E}}/\mathrm{d}t = k' n_{\mathrm{E}}$. Upon integration

$$\frac{n_{\mathrm{E}}}{n_{\mathrm{E_0}}} = \mathrm{e}^{-k't} \tag{4}$$

where $n_{\mathrm{E_0}}$ is the initial moles of ester blocks. Thus, $n_{\mathrm{E}}/n_{\mathrm{E_0}}$ represents the fraction of undegraded ester blocks and is proportional to the number of crosslinks that remain in the network or the crosslinking density (ρ_{xl}).

The crosslinking density of the network is related to the volumetric swelling ratio by the Flory–Rehner equation [26]. Neglecting the effects of chain ends and assuming a high swelling ratio ($Q > 10$), the Flory–Rehner equation reduces to the following:

$$Q \sim \rho_{\mathrm{xl}}^{-3/5} \tag{5}$$

Eqs. (4) and (5) can then be combined to demonstrate that as the crosslinking density decreases, the volumetric swelling ratio should increase exponentially and is directly related to the degradation kinetic constant by the following equation:

$$Q \sim \mathrm{e}^{3/5k't} \tag{6}$$

For the data shown in Fig. 3, good agreement is observed between the data and an exponential fit, and the kinetic constant is approximately equal to 0.15 day^{-1}. The ester bonds being degraded in these gels are similar, although slightly modified, from the more characterized ester bond in the lactide chemistry. Past researchers have found that hydrolysis rate constants for poly(lactic acid) range anywhere from 2.45×10^{-3} to 3.17 day^{-1} [27,28], and the calculated degradation constant for the degradable PVA macromers is within this broad range.

Similar to the volumetric swelling behavior, there are several characteristic features of the mass loss behavior for multifunctional, degradable PVA hydrogels, and these are illustrated by the data shown in Fig. 5. There are three main sections of the mass loss profile; first, an initial delay is seen where no significant mass loss occurs. This delay results from the large number of crosslinks that must be degraded before even a single chain is released from the gel. The next section of the mass loss profile is a slow release of unattached polymer chains. In this region, the crosslinking density is continually decreasing as the ester bonds are being cleaved, and eventually the fraction of degraded ester blocks (i.e. crosslinks) is high enough, so that the kinetic and PVA chains are unattached from the network and are releasable. Whether these chains are PVA chains or kinetic

chains is dependant on how the two types of chains are attached to the network. If the PVA chains are moderately substituted (e.g. 7 crosslinkable functionalities) and the kinetic chains are relatively long (e.g. 100 repeat units), then the PVA chains will be released first. However, if the opposite is true and the kinetic chains are quite short, then the kinetic chains will be released first. The substitution of the PVA chains is controlled during the synthesis of the macromers; whereas, the kinetic chains evolve during the radical chain polymerization and are not as easily controlled. The relative length of the kinetic chains is primarily manipulated by controlling the initiation conditions, such as the concentration of photoinitiator that is present or the intensity of the light that is used to initiate the polymerization.

The third and final region of the mass loss profile is reverse gelation [23,29]. After the slow release of polymer chains, a critical crosslinking density is reached where the entire network becomes soluble (i.e. the reverse gelation point). Reverse gelation occurs when the weighted average number of crosslinks per chain is less than two and is the opposite of the gel point that Flory derived for the formation of networks [26]. At this point, the 3D hydrogel becomes a highly branched, soluble polymer, and a burst is seen in the mass loss profile.

Once the typical degradation and mass loss behavior of hydrogels formed from these multifunctional macromers was understood, then gels synthesized from systematic variations in the macromer structure were compared. In particular, Fig. 6 demonstrates how changes in the hydrogel crosslinking density influence the degradation profiles. The crosslinking density of these networks was varied by keeping the number of acrylate functionalities on the PVA chain constant at seven, while varying the molecular weight of the PVA chain from 31,000 to 14,000 g/mol ($\rho_{xl} = 0.3$ mol/l vs. $\rho_{xl} = 0.64$ mol/l). Both systems are highly swollen ($Q > 20$); however, their initial swelling values are quite different. The gel synthesized from the 31,000 g/mol PVA macromer had an initial Q of $\sim$30, whereas the gel from the 14,000 g/mol PVA macromer only had an initial Q of $\sim$20. This difference in the initial swelling of the two different macromer systems is further proof of significant differences in their initial network structure, because a more tightly crosslinked system will swell less than a more loosely crosslinked network of a similar chemistry. Furthermore, based on Eq. (5), one would predict a 1.5 times increase in Q based on the changes in ρ_{xl}. Both curves were fit with exponential functions and result in significantly different kinetic constants. The sample with the faster erosion profile (i.e. 31,000 g/mol PVA) had a degradation rate constant, k', of $\sim$0.15 day^{-1}, whereas for the 14,000 g/mol PVA sample, a degradation time constant of $\sim$0.025 day^{-1} was calculated. While the equilibrium water content in both of these gels is high, the difference in the kinetic constants may be related to differences in the local concentration and accessibility of the degradable blocks to the water. This same effect has been observed in other systems (e.g. degradable PEG-based hydrogels) [24].

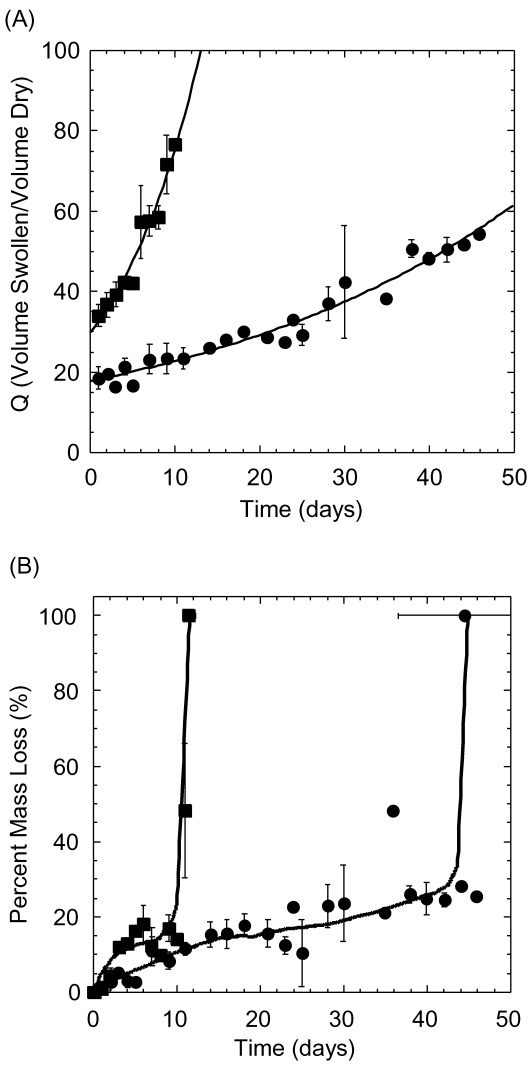

Fig. 6. Comparison of the volumetric swelling (A) and percent mass loss (B) profiles as a function of degradation time for gels synthesized from 31,000 g/mol PVA macromer (■) and 14,000 g/mol PVA macromer (●). Both macromers have 7 acrylate functionalities per PVA chain. The lines drawn in (A) are exponential fits of the data and the lines in (B) are meant to guide the eye in observing the trends of the data.

A higher crosslinking density results in more crosslinks that need to be degraded before a PVA chain can be released and, therefore, should take longer to degrade. From the mass loss profiles in Fig. 6B, the network with the lower crosslinking density erodes at a faster rate, with complete degradation being reached in approximately 12 days, while the higher crosslinking density network does not reach complete degradation until approximately 45 days. The erosion profiles of these two samples are also different, with the faster degrading system (31,000 g/mol PVA) transitioning between the three sections (i.e. initial release, slow release, and reverse gelation) relatively quickly and reaching approximately 20% mass loss before reverse gelation

occurs. Whereas, the slower degrading system has a much longer slow release section, where very few chains are released and only reaches about 30% mass loss before it goes through reverse gelation. The percent mass loss at reverse gelation is an indication of how much of the network can be eroded before the entire network solubilizes. For a given number of crosslinkable functionalities on the PVA chain, as the number of crosslinks in the kinetic chain is increased, the percent mass loss at the time of reverse gelation is increased. In addition, the reverse gelation point and the kinetic chain length also depend on the extent of cylcization in the network. Overall, the differences observed in the erosion profiles are highly indicative of significant changes in the network structure, where the chains are attached to the two different networks in different ways. In the 31,000 g/mol macromer there are fewer crosslinks to degrade on a whole and less of the network mass is contained in the kinetic chains (7.5%), as compared to the more tightly crosslinked system (14,000 g/mol macromer), which has more crosslinks and more of the network mass contained in the kinetic chains (15%). In addition, differences in the initial macromer structure and concentration of crosslinkable functionalities can influence the kinetic chain lengths and final network structure.

Changes in the polymerization conditions can also result in the formation of different network structures. Fig. 7 is a comparison of one macromer (31,000 g/mol PVA with 7 acrylate functionalities) that was polymerized under different conditions, i.e. the percent macromer in solution at the time of polymerization varied from 10 to 20 to 30 wt%. Therefore, gels were created with the exact same chemistry, but with differences in their initial crosslinking density. The differences in the network structure are easily observed in the initial volumetric swelling ratios (Fig. 7A), and each gel exhibited the exponential increase in swelling with time, but at varying rates (i.e. 20% macromer, $k' = 0.15$ day^{-1} and 30% macromer, $k' = 0.06$ day^{-1}). One explanation for the differences in the network structure, and therefore the kinetic constants, is that in a more concentrated sample, the chains have a higher likelihood of becoming entangled during polymerization, which changes the overall structure of the network that is being formed.

Similar differences are apparent in the mass loss data (Fig. 7B), wherein the gel synthesized from a 10% macromer solution degraded in less than a day; the gel synthesized from a 20% macromer solution degraded in ~12 days; and the gel synthesized from a 30% macromer solution degraded in ~35 days. In the 10% hydrogel, a very loosely crosslinked system is formed with most of the chains connected into the network by only a few linkages; therefore, this network lacks much structural integrity and fully degrades in a very short time period (less than a day). In the 20 and 30% hydrogels, the chains are much more connected into the network and take longer to degrade. In addition to changes in the total degradation time, the mass loss profiles of the 20 and 30% hydrogels were significantly influenced by the variations in the network structure. The 20% hydrogel transitions quickly through the three stages of degradation, and in the second stage (i.e. the slow release of chains), a more significant fraction of the network is lost, as 50% mass loss is reached before reverse gelation occurs. The 30% hydrogel follows a similar erosion profile as the 20% hydrogel for the first few days of degradation; however, the 30% hydrogel goes through an extended period of slow release where a minimal amount of mass loss is observed, and the network only reaches approximately 30% mass loss before reverse gelation occurs. These differences in the erosion profiles again provide evidence that the network structure in these hydrogels is varied and is strongly influenced by the conditions under which the network was formed.

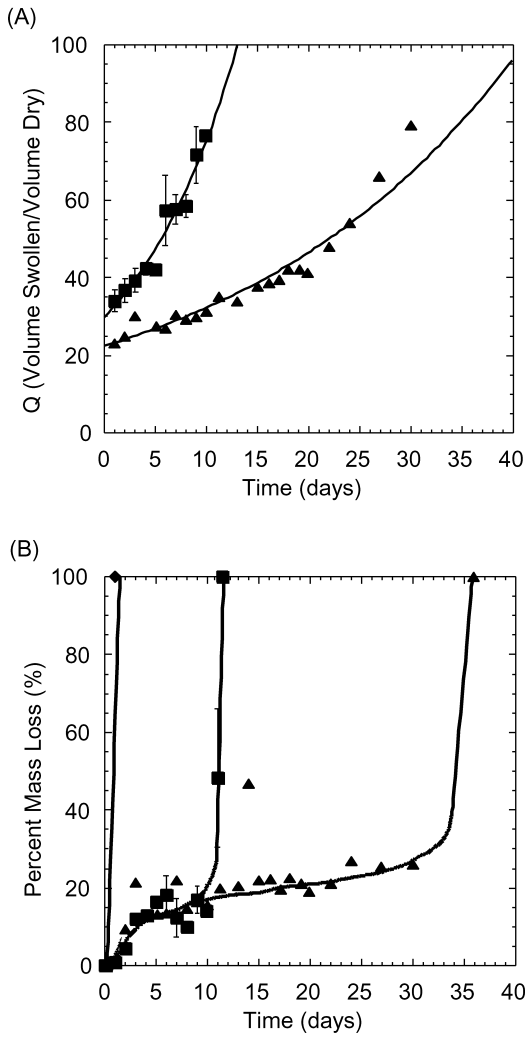

Fig. 7. (A) Volumetric swelling ratio and (B) percent mass loss of degradable PVA hydrogels as a function of degradation time. The exact same macromer is used in all three studies, and only the percent macromer in solution at the time of polymerization is changed from 10 (◆) to 20 (■) to 30 wt% (▲) (10 wt% volumetric swelling ratio data is unavailable). The lines drawn in (A) are exponential fits of the data and the lines in (B) are meant to guide the eye in observing the trends of the data.

4. Conclusions

Linear PVA was chemically modified with functional groups that enabled the macromer to be crosslinked with a photoinitiation mechanism to form a gel that degrades via hydrolysis of the crosslinks. This synthetic route was shown to have a large degree of flexibility, enabling variations in the molecular weight of the linear PVA chain or the number of functional groups that are attached to the macromolecular monomer. Combined with the fact that the polymerization conditions can also be varied, such as the amount of water present during polymerization, this macromer system allows for making simple changes in the formulation preparation that result in significant differences in the final hydrogel network. These network differences were characterized through the volumetric swelling behavior, as well as mass loss profiles during degradation. The swelling of the hydrogel networks was shown to increase exponentially for all networks studied; however, the degree of swelling was influenced by the initial network structure. The temporal swelling behavior was predicted by pseudo-first order hydrolysis kinetics, which led to exponential increases in the volumetric swelling ratio with degradation. However, the erosion of the hydrogels, measured by the mass loss profiles, exemplifies more of the complexities of the network structure. Simple changes in the macromer chemistry, as well as the polymerization conditions, were shown to result in substantial differences in the degradation of these hydrogel networks, including volumetric swelling, overall time for degradation, and the overall erosion profile. It was shown that by increasing the crosslinking density from 0.3 to 0.64 mol/L the overall degradation time for the hydrogels was increased from approximately 12 to 45 days. Likewise, a change in macromer concentration at the time of polymerization from 10 to 20 to 30% resulted in overall degradation times ranging from less than one to approximately 35 days. With the ability to tailor the hydrogel network to fit a wide range of degradation times and mass loss profiles, this class of crosslinked materials may be attractive for a wide range of biomedical applications.

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