pH-Responsive Hydrogel with Controlled Swelling and Degradation Rate

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ABSTRACT

A range of hydrogels were prepared by solution polymerization of methacrylic acid, poly(ethyleneglycol) methyl ether methacrylate (M.W. 475 g/mol) and poly(ethyleneglycol) dimethacrylate (as the cross-linking, M.W. 550 or 875 g/mol) in various proportions. The effects of methacrylic acid/ poly(ethyleneglycol) methyl ether methacylate concentration ratios as well as cross-linking concentration in the degree of swelling as a function of the media pH were studied. Reversibility of the swelling process was confirmed. Degradation in the system described previously was introduced using a hydrolytically labile diacrylate cross-linker (A-PLA-PEG-PLA-A) instead of the poly(ethyleneglyco) dimethacrylates. The degrees of swelling and degradation rates at different pH were studied. Hydrolytically degradable polymers that respond to pH stimuli to activate the swelling and decomposition process were developed. Multiple interrelated control parameters dictated by the synthetic recipe were studied and are available to separately control swelling and degradation rates of these novel polymers.

Keywords: hydrogel, pH-responsive, swelling, degradation

1 INTRODUCTION

"Smart" hydrogels as drug delivery vehicles, which once introduced in the body, controllably release the right amount of drug, protein or peptide in response to internal or external stimuli, e.g., temperature [1], pH [2],[3] glucose [4], electric field [5], ultrasound [6], etc have received considerable attention in the last past years. However, the development of polymeric systems that couple stimuli response with degradability in hydrogels for controlled release is much more limited [7], [8]. Nevertheless, a biodegradable hydrogel system can present very important advantages since it contributes an additional degree of control over the release of drug or other bioactive component while on the other hand, once implanted in the body, it can be cleared readily after depletion of the agent.

For a novel drug delivery application, a polymeric material was required that could serve as a stable matrix for prolonged periods of aqueous media storage without undergoing degradation or allowing release. Following introduction into the body controlled swelling, degradation and release was desired. Since modest alterations in pH can be temporarily tolerated and moderated in the body, a pH-responsive, degradable hydrogel material was developed.

Hydrogels capable of response to a pH-based stimulus are typically reliant on polymeric structures containing ionizable groups of a week acid (carboxylic or sulfonic acid) or a week base (amino group). Amine substitution results in swelling in acidic pH solutions due to formation of an ammonium polyelectrolyte. Conversely, carboxylic acid substituents form ionized salts at neutral or basic pH resulting in increased network swelling. So, it is possible to produce stable complexes under acidic or basic conditions depending of the target applications.

Typically, polymer networks containing poly (methacrylic acid) or poly (acrylic acid) can form hydrogen-bonding complexes that are stable under acidic conditions [9]. More stable complexes tend to be formed with the more rigid methacrylate acid backbone structures. Klier and Peppas first studied copolymers [10] formed from (methacrylic acid) and poly(ethylene glycol) monomethacrylate, which is the basic approach selected in our investigation. Intra- and inter- molecular complexes in this system are formed due to the cumulative strong hydrogen bonding interactions between the carboxylic acid groups along the polymer backbone and the poly(ethylene glycol) (PEG) ether oxygen located in the side chains. Under acid conditions, the P(MAA-g-PEGMEMA) hydrogels assume a collapsed , hydrophobic structure with low degrees of swelling and permeability. In the current study, cross- linking in the pH-responsive system is introduced using the hydrolytically labile A-PLA-b-PEG-b-PLA-A originally described by Sawhney et al. [11].

In the present work, we describe the synthesis of pH-responsive hydrogel with potential use for delivery of drugs or other biomedical applications. The goal is to better understand the parameters that control the interrelated swelling and degradation behavior of the hydrogels. To accomplish this, pH-dependent swelling of non-degradable model systems is studied along with investigations of the swelling and mass loss profiles of the fully degradable hydrogels.

2 MATERIALS AND METHODS

2.1 Synthesis of non-degradable hydrogels

Hydrogels were synthesized by free radical copolymerization of poly(ethyleneglycol)methyl ether methacrylate 475(PEGMEMA-475) with methacrylic acid

(MAA) in the presence of poly(ethyleneglycol) dimethacrylate molecular weight 550 and 875 g/mol (PEGDMA-550, PEGDMA-875) as the cross-linker agent. All monomers were used as received (Aldrich, Milwaukee, WI). The molar ratio of PEGMEMA-475 to methacrylic acid (MAA) was varied at either 1:8 or 1:10. Based on the PEGMEMA structure used, the 1:8 molar feed composition represent a slight excess of hydrogen bond acceptor PEG-ether functionality relative to the hydrogen bond donor methacrylate acids groups. The 1:10 ratio inverts this with a slight excess of the carboxylic acid functionality relative to PEG-ether group. The ratio of PEGDMA cross-linker was varied among 1, 2, 3 and 10 wt % based on the total monomer weight. The reaction was thermally initiated by 0.2 wt% (based on total monomer mass) azobis(isobutyronitrile) (AIBN). The polymerization was carried out in a solution of 1:1 (by volume) of distilled water and DMSO. In all cases, the mass to volume ratio of monomer to solvent during solution copolymerization was 1:9 to ensure complete miscibility. Each reaction mixture was placed between two glasses plates with Mylar release films and a 3.4mm (thick) x 100 mm (high) x82 mm (wide) rubber spacer. The mold assembly was held together by multiple spring clamps. Air in the cavity and in the reaction mixture was removed by passing a steam of nitrogen through the empty assembly. The monomer solution was purged by bubbling nitrogen through the mixture for 15 min. The monomer was introduced into the mold via syringe and the clamped mold was placed in an oven at 65 °C for 18 hours. Each sheet of the resulting gels was removed and placed in a separate container with distilled water for 18 h; during the first 8 h the water was changed every 2 h. Approximately 25 disc-shaped specimens (12 mm diameter) were punch-cut from the large sheet and these were dried first at 37 °C for 24 h and then at 65 °C under vacuum until constant weight.

2.2 Synthesis of degradable hydrogels

In an analogous manner, degradable gels were synthesized by polymerizing MAA with PEGMEMA-475 in the presence of a macromer degradable crosslinker A-PLA-b-PEG-b-PLA-A (Figure 1), which was prepared according to the procedure described by Sawhney et al. [11]. The ratio of degradable cross-linker was varied between 3, 10 and 15 % based on total monomer weight.

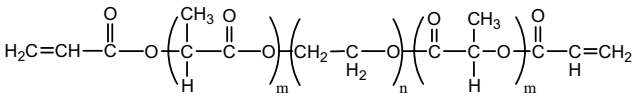

Figure 1.Degradable A-PLA-b-PEG-b-PLA-A macromer (m = 5.3 and n = 18.7)

2.3 Swelling studies

Swelling studies were carried out at pH 3.0, 5.0, 7.4 and in distilled water at room temperature. Each hydrogel disc was weighted and placed in a container with 20 mL of buffer solution at a given pH. Changes in mass were monitored at various time intervals until equilibrium swelling was reached for the non-degradable system and before significant degradation for the degradable samples. The pH in the swelling studies in the buffer solutions remained unchanged during the experiments. The degree of swelling is expressed as Q = (Ws-Wd)/Wd, where Ws and Wd are the weight of swollen disc and dried disc respectively.

2.4 De-swelling studies

De-swelling studies were carried out on the non-degradable gels that had previously reached equilibrium swelling in a buffer solution at pH = 7.4 during 4 days. The swollen discs were weighted and the degree of swelling was calculated as indicated. The swollen disc specimens were transferred to a buffer solution either pH = 3 or 5. The changes in specimen mass were monitored as a function of time until constant weight was reached. Triplicate samples were monitored.

2.5 Degradation studies

Mass loss of the A-PLA-PEG-PLA-A cross-linked hydrogels were carried out in a 0.05 M phosphate-buffered saline solution at pH = 5.0 or 7.4 at room temperature. Each degradable hydrogel previously weighed was place in 20 mL of PBS buffer. At specified time points, one to two specimens were removed from the degradation medium, washed with HCL 1M solution; washed with water three times and dried until constant weight. The percent mass loss of each specimen was then determined using the following equation: % mass loss = (Wi – Wb)/Wi x 100, where Wi and Wb are the initial weight and the final dried mass of the disc after degradation, respectively.

3 RESULTS AND DISCUSSION

3.1 Non-degradable system

The initial work in this study dealt with the synthesis of soluble copolymers base on PEGMEMA-475 and MAA. Different reaction conditions and solvents were tested. It was found that under neutral pH conditions, soluble copolymers of PEGMEMA-475 and MAA in either 1:8 or 1:10 molar ratios could be prepared by free radical polymerization using AIBN (0.2w%) as initiator if a 1:1 mixture of DMSO/H_2O and a ratio of monomer weight to solvent of 1:9 were used.

3.2 Swelling in non-degradable systems

To study the effect of chemical cross-linking on the time-dependent swelling behavior of pH-responsive hydrogels polymeric networks were synthesized by the inclusion of varied concentrations of PEGDMA with the monometacrylate monomers. PEGDMA-550 and PEGDMA-885 were used as cross-linkers to probe the effect of different spacer group lengths on hydrogel swelling behavior. Figure 2 shows the pH-dependent swelling plot of non-degradable hydrogel composed of 1:8 ratios of acid group functionalities. It is apparent that either distilled water or buffer at pH 3.5 as the storage media, the polymers are hydrophobic and exhibit negligible swelling. As is discussed in the work of Peppas [12] the pK_A of poly(methacrylic acid) is around 5. As a result, an increase in the storage pH to 5.0 yields modestly increased equilibrium swelling. With storage under neutral pH conditions, the fully deprotonated state of the hydrogel produces rapid, extensive swelling.

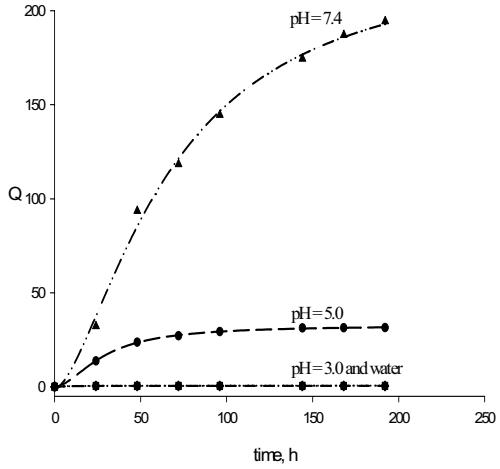

Figure 2. Swelling at different pH for hydrogel P(MAA-co-PEGMEMA) ratio 1:8 and 1% of PEGDMA-550.

3.3 De-swelling at different pH

To study the reversibility of the swelling process, dry discs of no degradable hydrogel (10w% PEGDMA) previously weighted, were placed in pH 7.4 buffer solution at room temperature until equilibrium swelling was reached. The swollen disc were weighed, washed with distilled water and placed in buffer solution at either pH 3.0 or 5.0. The mass loss over the time profile are shown in Figure 3, where each data point is the average value between three independent specimens and the error bars represent the one standard deviation. The results demonstrate the reversibility swelling nature of the polymer network synthesized, which depend on external pH changes.

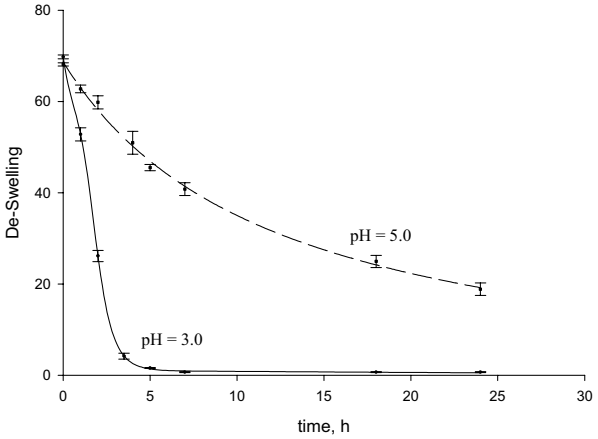

Figure 3. De-Swelling at different pH for no degradable system P(MAA-co-PEGMEMA) 1:10 with 10% of PEGDMA-875.

3.4 Swelling degradable system

To achieve the goal of designing hydrolytically degradable polymers that respond to pH stimuli, a degradable crosslinker was introduced to the well known (PMAA-co-PEGMEMA) system. After polymerization to form degradable cross-linked networks, disks were exposed to pH 3.0, 5.0 and 7.4 buffer solutions. Importantly, just as in the non-degradable system, the degradable disc specimens remain in a hydrophobic, complexed state at low pH. For storage at pH 3, only a minimum amount of water was taken up (Q = 4). IN this case, no longer-term additional swelling or degradation was observed upon storage for as long as 6 month. At pH 5.0, the specimens absorbed a moderated amount of water (Q =20) with swelling reaching an intermediate plateau before undergoing a gradual degradation over approximately 2 month period. However swelling in specimens at pH 7.4 begins very rapidly (Q = 99 after 46 hours). After 46 hours, the significant network degradation makes continued swelling measurements impractical.

3.5 Effect of degradable macromer concentration

The degradation behavior of hydrogels polymerized in solution with concentrations of the degradable macromer at 3, 10 and 15w% (adjusted to account for the actual functionality of the degradable macromer) was monitored. In Figure 4 the swelling ratio (Q) of the three-hydrogel set polymerized with various concentrations of macromer are plotted versus degradation time. As indicated by the best-fit exponential function, the swelling of these hydrogels is observed to increase exponentially with the degradation time. Samples with the lowest macromer concentration 3% experience the fastest growth in its swelling ratio. Here, as in the non-degradable hydrogels described previously, an increase in the cross-linking density induced restriction to the expansion of the polymer network leading to reduced water absorption and

as is shown in the next section a decrease in degradation rates.

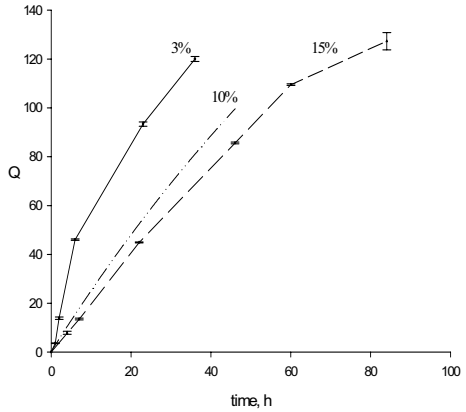

Figure 4. Swelling for degradable hydrogels P(MAA-co-PEGMEMA) ratio 1:10 and 1, 3 and 10% of A-PLA-PEG-PLA-A.

3.6 Degradation studies

Degradation studies were carried out for the three different degradable materials with varied cross-link densities as described in the previous section. Beginning with a large umber of disc specimens placed in a buffer solution at pH 7.4, triplicate subsets were removed at various storage time intervals. These specimens were washed with distilled water and then dried under vacuum until constant weight. As is shown in the figure 5, during the first phase, during which significant swelling has already been demonstrated, no mass loss is observed. After this time lag, which varies with the concentration of cross-linker in the network, the onset of mass loss is observed and the kinetics of the degradation are also clearly linked to the cross-link density. The rate of mass loss for the system with only 3 % of cross-linker is approximately 5 times faster than that of the polymer with 15% of degradable macromer.

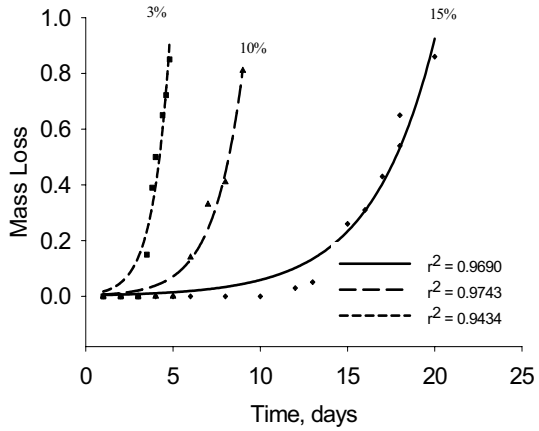

Figure 5. Mass loss as a function of time for degradable hydrogels with different ratios of degradable crosslinker

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