Swelling Properties of poly(AM-co-AA)/Chitosan pH Sensitive Superporous Hydrogels

Kwang-Won Seo, Duk-Joon Kim†, and Ki-Nam Park*

Department of Chemical Engineering, Sungkyunkwan University, Suwon 440-746, Korea
*School of Pharmacy, Purdue University, West Lafayette, IN 47907, USA

Received February 23, 2004; Accepted June 28, 2004

Abstract: Superporous hydrogels (SPHs) of poly(acrylamide-co-acrylic acid) [P(AM-co-AA)]/chitosan and P (AM-co-AA)/glycol chitosan interpenetrating polymer networks (IPNs) were prepared, and their swelling and mechanical properties were investigated. The introduction time of the blowing agent was determined from gelation reaction exotherms. For both SPH systems, equilibrium swelling ratios decreased in distilled water, but increased in simulated gastric fluid, as the chitosan concentration increased. Replacement of glycol chitosan for chitosan led to a significant increase in the swelling rate because of its high water affinity. Equilibrium swelling ratios were mostly governed by the ionic concentration difference between the gel and bulk phases, but the swelling rate depended upon the pore size and structure. The compressive strength of P(AM-co-AA)/chitosan IPN SPHs swollen in water was very weak, but that in simulated gastric fluid was over 60 kPa.

Keywords: superporous hydrogels, swelling, poly(acrylic acid), chitosan

Introduction

Studies on controlled release technologies have been pursued for decades to fulfill efficient medical treatment by releasing drugs at controlled rates. Polymeric materials often have been prepared as carriers for sustained release [1-5]. Oral administration is a convenient, safe, and economic way for drug delivery, but has a problem in that the gastric retention time, 6 to 8 h, is too short to complete sustained release in the stomach. Because of this short retention time, over 80% of an administrated drug is wasted before it can supply its function [6].

Among many endeavors to prolong gastric retention, the synthesis and applications of superporous hydrogels (SPHs) have been accepted recently as upcoming technologies [7-13]. The main ideas for applying SPHs are that the long-term retention can be achieved because they rapidly become highly swollen in the stomach such that they do not transport rapidly through the pylorus.

Several polymeric hydrogels have been synthesized and characterized for this purpose. Poly(acrylamide-co-acrylic acid) [P(AM-co-AA)] is one of the most promising materials because of its super absorbent properties and simple synthesis [14-17]. Despite these advantages, its application as a gastric retention device has not been accepted practically because of the de-swelling characteristics of poly(acrylic acid) (PAA) under acidic conditions. Even though longer gastric retention is required for more effective release, the swollen carriers cannot remain in the stomach forever: they must be degradable for excretion after sufficient release of the drugs. In this study, chitosan, a biodegradable polymer, was incorporated in the preparation of P(AM-co-AA) SPHs. High swelling at acidic condition was expected because of the presence of cationic charges in the molecular backbone. Degradation of the macromolecular chains is also expected because of its introduction [18-20]. Thus, semi-interpenetrating polymer network (SIPN) SPHs of P(AM-co-AA)/chitosan and P(AM-co-AA)/glycol chitosan were synthesized, and their swelling and mechanical properties were investigated.

Experimental

Materials

Materials and reagents for the synthesis of P(AM-co-
AA/chitosan and P(AM-co-AA)/glycol chitosan IPN SPHs are summarized in Table 1. They were used without prior treatment.

**Table 1. Reagents used for the Synthesis of P(AM-co-AA)/Chitosan (or Glycol Chitosan) IPN SPHs**

<table>
<thead>
<tr>
<th>Use</th>
<th>Reagent</th>
<th>Source</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomer</td>
<td>Acrylic acid (AA)</td>
<td>Daejung, Korea</td>
<td>99+%</td>
</tr>
<tr>
<td></td>
<td>Acrylamide (AM)</td>
<td>Daejung, Korea</td>
<td>-</td>
</tr>
<tr>
<td>Crosslinker</td>
<td>N,N'-Methylenebisacrylamide (BIS)</td>
<td>Aldrich, USA</td>
<td>-</td>
</tr>
<tr>
<td>Initiator</td>
<td>Ammonium persulfate (APS)</td>
<td>Aldrich, USA</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>N,N,N'-Tetramethylenebisacrylamide (TEMED)</td>
<td>Aldrich, USA</td>
<td>99%</td>
</tr>
<tr>
<td>Neutralization agent</td>
<td>Sodium hydroxide</td>
<td>Daejung, Korea</td>
<td>-</td>
</tr>
<tr>
<td>Blowing agent</td>
<td>Sodium bicarbonate</td>
<td>Aldrich, USA</td>
<td>-</td>
</tr>
<tr>
<td>Foam stabilizer</td>
<td>Pluronic F127 (PF127)</td>
<td>Sigma, USA</td>
<td>-</td>
</tr>
<tr>
<td>Polymer</td>
<td>Low-molecular-weight chitosan (Mv: 50,000-190,000)</td>
<td>Aldrich, USA</td>
<td>Degree of deacetylation: 86%</td>
</tr>
<tr>
<td></td>
<td>Glycol chitosan (DP:2500)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Synthesis of Superporous Hydrogels**

Aqueous solutions of AM (50 w/v\%) and AA (50 v/v\%) were mixed in a variety of compositions. To 50 mL of the monomer aqueous solution were added 10 mL of BIS, 3 mL of PF127 (10 w/v\%), 2 mL of TEMED (20 v/v\%), and 33 mL of distilled water. Chitosan (M<sub>v</sub> 50000-190000 g/mol) was dissolved in this mixture to prepare final concentrations of 5, 10, and 20 wt\%, respectively. After the pH of the stock solution was adjusted to 5.1 by adding sodium hydroxide, 1.5 mL of the reactant solution was placed in a glass tube having an OD of 18 mm and a length of 100 mm. Addition of 60 \( \mu \)L of APS initiated the gelation reaction and 90 mg of sodium carbonate initiated the foaming reaction. Adequate polymerization and foaming reaction kinetics made it possible to synthesize superporous P(AM-co-AA)/chitosan SPHs having semi-IPN structures. The products were removed from the tubes and placed in the drying oven to eliminate residual solvents and monomers.

**Measurement of Gelation Kinetics**

Gelation and foaming reactions must take place simultaneously to produce large and rigid pores. If the gelation reaction is much faster or slower than the foaming reaction, bubbles cannot maintain their initial shapes at the completion of the reaction. Because the gelation reaction was exothermic, the reaction rate was predicted by monitoring the temperature change during the reaction. A K-type thermocouple was positioned in a glass tube to measure the reaction temperature, and the detected signal was transferred to a personal computer via a thermocontroller (Center 305 datalogger, Taiwan).

**Characterization**

A scanning electron microscope (SEM, XL-30 Philips, Netherlands) was used to analyze the microstructures of the pores. Dry samples were quenched using liquid nitrogen, and then fractured before the microphotographs were taken. Samples were palladium gold-coated using an ion coater (Eiko IB-3, Japan) before measurements.

Dry samples were placed in distilled water or simulated gastric fluid (SGF, pH 1.2). Samples were periodically weighed until no weight change was observed. The SGF was prepared by dissolving 2 g of sodium chloride in 7 mL of hydrochloric acid. The pH of the mixture was adjusted to 1.2 by adding water [21]. The swelling ratio, \( Q \), was determined by equation (1):

\[
Q = \frac{W_s}{W_d}
\]

Here, \( W_s \) and \( W_d \) indicate the weights of the swollen and dry polymer samples, respectively.

A Universal Testing Machine (UTM, Strograph V-C, Toyoseiki, Japan) was used to measure the compressive strengths of the swollen SPH samples. The crosshead speed was 20 mm/min. The compressive strength was determined as the average value of five measurements.

**Results and Discussion**

**Gelation Reaction Kinetics**

Because heat was released during polymerization and gelation reactions, the temperature of the reactant system increased until no further reaction proceeded. The temperature change during the polymerization reaction is shown in Figure 1 for the case where the AM-to-AA weight ratios of the reactant systems were 0.6:0.4, 0.8:0.2, and 1:0, respectively. Regardless of the monomer concentration, a higher chitosan concentration lowered the polymerization and gelation rates as a result of the reduced molecular mobility associated with high viscosity. Introduction times of the blowing agent were
determined from the reaction exotherms in Figure 1; it was added at the moment when the reaction temperature first increased. The results are shown in Figure 2. The gelation rate was delayed upon increasing the AA concentration. There was almost a linear relationship between the gelation time and the AA concentration when the chitosan concentration was fixed.

Figure 2. Blowing agent introduction time as a function of polymer composition when chitosan concentrations were (▲) 5, (●) 10, and (■) 20 wt%.

Pore Size and Structure

Figure 3 shows microphotographs of IPN SPHs having an AM:AA ratio of 0.6:0.4 for different chitosan concentrations (0, 10, and 20 wt%, respectively). All of the pores were distributed uniformly and their diameters ranged from 50 to 600 μm. They were connected to form a capillary structure. The pore size and porosity decreased upon increasing the chitosan concentration, because the gelation reaction was slower at higher chitosan concentrations. The bubbles that developed at the initial stage were no longer stable when the gelation took a much longer time than did the foaming (refer to Figure 2). The increase of the solution viscosity was another reason for the pore size to be reduced.

Swelling Behavior of SPHs in Distilled Water

Figures 4 and 5 show the equilibrium and dynamic swelling behavior, respectively, of P(AM-co-AA)/chitosan IPN SPHs in distilled water of pH 6.7. As shown in Figure 4, equilibrium swelling ratios increased monotonically upon increasing the AA concentration because the neutralized does PAA absorbs more water than does PAM. Increase of the chitosan concentration led to decrease of the swelling ratio because it has lower swelling capacity than does P(AM-co-AA). Figure 5 shows the chitosan concentration effect on the dynamic swelling behavior of P(AM-co-AA)/chitosan IPN SPHs at various AM:AA ratios (0.6:0.4, 0.8:0.2, 1.0). The swelling rate decreased as the chitosan concentration increased because smaller pores were developed at higher chitosan concentrations (see Figure 3).

Figure 6 shows the dynamic swelling behavior of P(AM-co-AA)/glycol chitosan IPN SPHs in distilled water. Comparing Figure 6 with Figure 5 indicates that the swelling kinetics increased considerably when glycol chitosan was replaced for chitosan. The equilibrium swelling
Figure 3. SEM microphotographs of P(AM-co-AA)/chitosan IPN SPHs having AM-to-AA weight ratios of 0.6:0.4 when the chitosan concentrations were (a) 0, (b) 10, and (c) 20 wt%.

was obtained within 10 min when the glycol chitosan was incorporated, even up to 20 wt%. This situation occurred because glycol chitosan is much more hydrophilic than is chitosan. The concentration effect of glycol chitosan on the equilibrium swelling ratio was similar to that of chitosan, except for its absolute value.

Swelling Behavior of SPHs in SGF

As shown in Figure 7, the equilibrium swelling ratios of P(AM-co-AA)/chitosan IPN SPHs in SGF are much lower than they are in distilled water. This situation arises because PAA molecules do not fully extend under acidic conditions because the sodium ions attached to the carboxylic group become partially exchanged with protons in the acidic environment. This effect was more significant at higher AA concentration. Equilibriums welling ratios increased upon increasing the chitosan concentration in this acidic environment, because ionization of amino groups extended the distance between chitosan molecules through cationic repulsion. Introduction of too high a concentration of chitosan, in this case 20 wt%, however, resulted in reduction of the swelling ratios. This situation arises because too great a molecular interaction between AA and chitosan molecules suppresses ionic repulsion between the chitosan molecules.

Figure 4. Equilibrium swelling ratios of P(AM-co-AA)/chitosan IPN SPHs in distilled water when the chitosan concentrations were (■) 0, (○) 5, (▲) 10, and (◆) 20 wt%.

Figure 8 shows the dynamic swelling behavior of P(AM-co-AA)/chitosan IPN SPHs in SGF. Similar to the swelling behavior in water, the swelling rate decreased as the chitosan concentration increased because of the reduced pore size. In Figure 8(a) overshoot phenomena are observed when the chitosan concentrations were 5 and 10 wt%, respectively. This overshoot phenomenon occurs when the rate of molecular relaxation is much lower than that of diffusion. Initially, the anions in the polymer gel phase were not fully protonated and, thus, water molecules were imbibed by the ionic concentration difference between the polymer and bulk phases. Soon there after, however, the polymer gels were elastically contracted by the loss of anionic repulsion associated with the protonation. This elastic contraction led to molecular rearrangement of the polymeric systems, and repelled the water molecules from the polymer and to the bulk phases. This overshoot phenomenon was more prominent at higher AA concentration because more ions were present at the initial stage. A high chitosan concen-
Figure 6. Dynamic swelling behavior in distilled water for P(AM-co-AA)/glycol chitosan IPN SPHs having AM-to-AA weight ratios of 0.8:0.2 when the glycol chitosan concentrations were (■) 5, (○) 10, (▲) 15, and (◆) 20 wt%.

Figure 7. Equilibrium swelling ratios of P(AM-co-AA)/chitosan IPN SPHs in SGF (pH 1.2) when the chitosan concentrations were (■) 0, (○) 5, (▲) 10, and (◆) 20 wt%.

Figure 5. Dynamic swelling behavior in distilled water for P(AM-co-AA)/chitosan IPN SPHs having different AM-to-AA weight ratios: (a) 0.6:0.4, (b) 0.8:0.2, and (c) 1:0. Chitosan concentrations were (■) 5, (○) 10, and (▲) 20 wt%.

charge concentration in the polymer systems, but the dynamic swelling behavior was governed by the pore sizes. Figure 9 shows the dynamic swelling behavior of P(AM-co-AA)/glycol chitosan IPN SPHs in SGF. The swelling rate increased considerably when glycol chitosan was introduced in place of chitosan for the same reason as described above. Equilibrium swelling was obtained within 2 min when glycol chitosan was incorporated at 20 wt%.

Compressive Strength
In Figure 10, the compressive strengths of the P(AM-co-AA)/chitosan IPN SPHs are represented. P(AM-co-
AA)/chitosan IPN SPHs swollen in water were mechanically very weak, but the compressive strength of P(AM-co-AA)/chitosan IPN SPHs swollen in SGF was over 60 KPa. This situation arises because the swelling ratios in SGF solution were much lower than those in distilled water. The increase of compressive strength at a chitosan concentration of 20 wt% was due to the high entanglement of IPN molecules.

Conclusions

Swelling and mechanical properties were investigated for SPHs of prepared P(AM-co-AA)/chitosan and P(AM-co-AA)/glycol chitosan IPNs. The introduction time of the blowing agent was determined from the gelation rate associated with the polymerization reaction.
exotherms. The gelation rate decreased upon increasing the AA and chitosan concentrations. Pores were quite-uniformly distributed, and their diameters were in the range from 50 to 500 μm. For both IPN SPHs, the equilibrium swelling ratios in SGF increased upon increasing the chitosan concentrations to 10% because of the presence of positive ions, but they decreased at chitosan concentrations higher than 10% because of the formation of a high degree of molecular entanglement. In distilled water, the equilibrium swelling ratios decreased monotonically upon increasing the chitosan concentrations, because tighter network structures and higher degrees of molecular entanglement were developed by the presence of the increased number of chitosan molecules. Swelling rates of P(AM-co-AA)/chitosan IPN SPHs were low at high chitosan and AA concentrations because of the relatively small pores that developed. In SGF medium, the overshoot phenomenon was observed especially for SPHs composed of high AA concentrations. Water molecules initially imbibed in the gels because of the ion concentration difference were soon repelled by the elastic contraction associated with protonation. The swelling rate increased considerably when glycol chitosan was introduced in place of chitosan because of its higher water affinity. The equilibrium swelling behavior was governed mostly by the fixed charge concentrations in the polymer systems, but the dynamic swelling behavior was governed mostly by the pore sizes. P(AM-co-AA)/chitosan SPHs swollen in water were mechanically very weak, but the compressive strength of P(AM-co-AA)/chitosan SPH IPNs swollen in SGF was over 60 KPa.

Acknowledgement

This study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (02-PJ3-PG3-31402-0008).

References