Synthesis of Acrylic Acid Hydrogel by γ-Irradiation Cross-linking of Polyacrylic Acid in Aqueous Solution

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ABSTRACT

Polyacrylic acid (PAA) hydrogels are used extensively as a matrix in gastro-intestinal drug delivery systems. In this research, cross-linked PAA hydrogel was synthesized using a two step method. First, uncross-linked PAA was synthesized by free radical precipitation polymerization of acrylic acid in benzene. In the second step, PAA was dissolved in aqueous solution and it was cross-linked with γ-irradiation. The swelling behaviour of the gels was studied in pH 4 and 7 to simulate gastric and enteric pH, respectively. In buffered pH 4 solution, the degree of swelling ranged from 30 to 300 for irradiation doses of 5 to 25 kGy and swelling was Fickian. On the other hand, in buffered pH 7 solution, the degree of swelling ranged from 80 to 500 depending on the irradiation dose and swelling was non-Fickian.

Key Words: hydrogel, polyacrylic acid, γ-irradiation, cross-linking, swelling

INTRODUCTION

Hydrogels are three-dimensional cross-linked polymeric structures, which are able to swell in aqueous environment [1, 2]. Hydrogels are used extensively in medicine and pharmacy as drug delivery systems, contact lenses, catheters, wound dressings, and biosensors [3—6]. One of the most powerful applications of hydrogels is in controlled release systems for targeted delivery to specific areas of the body [7, 8].

More specifically, ionic hydrogels are used to immobilize a drug delivery device on a specific site for targeted release and optimal drug delivery due to intimacy and extended duration of contact [9—15]. After intimate contact is established, the rate and duration of drug release depend on swelling behaviour of the hydrogel [16, 17].

Because of the presence of carboxylic acid side groups, swelling behaviour of polyacrylic acid (PAA) hydrogel is highly dependent on pH of the surrounding medium [9, 18—22]. For example, since pKa of acrylic acid lies in the range of 4.5—5.0, PAA hydrogels swell significantly above pH 5, which is the pH of the small intestine. However, they do not swell significantly below pH 4, which is the pH of the stomach [19]. Therefore, one of the major applications of acrylic acid gels is in sustained gastro-intestinal drug delivery systems [7, 8].

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Hydrogels can be prepared by simultaneous copolymerization and cross-linking of one or more monofunctionals with one multifunctional monomer or by cross-linking of a homopolymer or copolymer in solution [23, 24]. The latter involves two steps in which, in the first step, the linear polymer is synthesized in the absence of a cross-linking agent and, in the second step, the synthesized polymer is cross-linked using either chemical reagents or irradiation.

In recent years, considerable research is done on characterization and swelling behaviour of hydrogels prepared by simultaneous free radical copolymerization and cross-linking in the presence of an initiator and a cross-linking agent. For example, Peppas and coworkers have worked extensively on characterization of anionic hydrogels synthesized by copolymerization of acrylic acid or methacrylic acid with hydroxyethyl methacrylate or chemically grafted with polyethylene glycol [9, 16-22].

Hydrogels can also be synthesized by cross-linking with electron beam or gamma (γ)-irradiation [25, 26]. However, little work is done on characterization of hydrogels prepared by cross-linking of a homo-polymer or copolymer in solution with γ-irradiation [27]. It is well known that the presence of initiator and cross-linking agent affects the macromolecular structure and phase behaviour of hydrophilic polymers in solution and contributes to the inhomogeneity of the network structure [24, 28]. It is argued that more homogeneous network structures can be synthesized if cross-linking is accomplished with γ-irradiation in the absence of initiator and cross-linking agent. The structural homogeneity of the network affects the swelling behaviour and mechanical properties of the hydrogel. The objective of this work was to investigate the swelling behaviour of acrylic acid hydrogels synthesized by γ-irradiation cross-linking of uncross-linked polyacrylic acid in aqueous solution. The uncross-linked PAA was prepared by precipitation polymerization of acrylic acid in benzene.

**EXPERIMENTAL**

All reagents were obtained from Merck Chemical Co., Germany. Acrylic acid monomer was distilled under reduced pressure of 5 mm Hg at 30 °C to remove the inhibitor, hydroquinone monomethyl ether. PAA was synthesized from the acrylic acid monomer by free radical precipitation polymerization [29, 30]. Benzene and 2,2'-azobis-2-methyl propionitrile (AIBN) were used as the solvent and initiator, respectively, without further purification.

The following procedure was used for the precipitation polymerization. In a dry reaction flask, 233 mL of benzene (2.61 mol), 0.0638 g of AIBN (0.39 mmol), and 20 mL of acrylic acid (0.29 mol) were mixed. The molar ratio of initiator to monomer was 1 to 750. The mixture was allowed to react for 1 h at 70 °C in a constant temperature bath until the mixture became opaque. The reaction was stopped by reducing the temperature to 25 °C and the solvent was evaporated using a rotary evaporator. To remove the residual monomer and unreacted initiator, the polymer was dissolved in methanol and precipitated in diethyl ether twice. After purification, the PAA was dried in vacuo at 46 °C for 12 h and stored in a desiccator.

The glass transition temperature, T_g, of the synthesized PAA was measured with differential scanning calorimeter (TA Instruments). The T_g of the PAA was 105 °C. The intrinsic viscosity of the synthesized PAA in 1 M aqueous NaCl solution was measured with a capillary viscometer at a constant temperature of 25 °C and the viscosity averaged molecular weight (M_v) of the sample was determined using the Mark-Houwink-Sakurada (MHS) equation. The intrinsic viscosity of the synthesized PAA was 0.897. The constants K and a in MHS equation were obtained from reference 31 and they were equal to 15.47×10^-3 mL/g and 0.90, respectively. M_v of PAA was 1.6×10^3 g/mol which was close to the values reported in the literature [30].

Two solutions of the synthesized PAA in deionized water with concentrations of 2.5% and 10.0% w/w PAA were prepared. Approximately 2 mL of each solution was poured in a 10 mL glass vial, which was sealed with a plastic top and each vial was exposed to γ-radiation. Each PAA solution was exposed to 5 different doses of radiation including 5, 10, 15, 20, and 25, kGy. The source of γ-radiation was
cobalt Co-60. It should be noted that the radiation doses chosen was in the range used for decontamination in the pharmaceutical and medical practice.

After irradiation, the disk-shaped samples were washed twice at ambient conditions for 24 h by swelling in deionized water to remove most of the uncross-linked polymer (sol fraction), dried in vacuo at 40 °C for 12 h and stored in a desiccator. The swelling measurements were carried out at buffered pH 4 and 7, to simulate the pH of the gastric and enteric cavities, respectively. Citrate and phosphate buffer was used to prepare buffered pH 4 and 7, respectively. Weight swelling ratio, defined as the difference between the weight of sample after swelling and the dry weight divided by the weight of dry sample, was determined as a function of time. For each sample, three measurement of swelling was performed and the average of the three values was reported.

RESULTS AND DISCUSSION

The mechanism of the cross-linking of polymers in solution by γ-irradiation is studied by Chapiro [32, 33], Saito [34–36] and others [37–39]. The subject is also reviewed by Peppas [24]. The mechanism is discussed here briefly for γ-irradiation of aqueous PAA solution.

First, a hydrogen of PAA polymer, designated as PAAH, and the solvent, HOH, absorb the γ-rays and go to the transient activated state of PAAH* and HOH*, respectively. In the activated state, the covalent bonds of the PAAH* and HOH* molecules dissociate, causing the formation of free radicals. If C–H bond of the polymer breaks, then a polymer radical, PAA•, and a hydrogen radical, H•, is formed.

Dissociation of the activated water molecule causes the formation of a hydroxyl radical, HO•, and hydrogen radical, H•. Two hydrogen radicals can recombine causing the evolution of hydrogen gas. If the diffusion of polymer radical is slow, such as γ-irradiation of polymers in the solid state, then polymer radical PAA• recombines with hydrogen radical, H•, to form the original polymer molecule, PAAH. The recombination reaction lowers the efficiency of cross-linking with γ-irradiation.

The rate of recombination reaction is minimum in dilute polymer solution due to high diffusivity of polymer radicals. Energy transfer reactions between inactivated molecules, PAAH or HOH, and activated molecules, PAAH* or HOH*, can occur in irradiation of polymer solutions. Also, radical transfer reactions, between PAA and water molecules with radicals, PAA•, H• or HO•, can occur in solution. In aqueous polymer solutions, due to high absorption of γ-irradiation by water molecules, radical transfer reactions between polymer and hydroxy or hydrogen radicals dominate to form polymer radicals which increase the rate of cross-linking reaction. Therefore, the most important reactions in γ-radiation cross-linking of PAA in aqueous solution are as follows:

\[
PAA_m + HOH \rightarrow PAA_m + (H\bullet \text{ or } HO\bullet) \quad (1)
\]

\[
PAAH + (H\bullet \text{ or } HO\bullet) \rightarrow PAA\bullet + (HOH) \quad (2)
\]

\[
PAA_m + PAA_n \rightarrow PAA_m + PAA_n \quad (3)
\]

\[
PAA_{m+n} \rightarrow PAA_m + PAA_n \quad (4)
\]

The first reaction involves the transfer of radicals from polymer to water molecules, which reduces the efficiency and extent of cross-linking. Reaction 2 involves the transfer of radical from water to polymer which increases the concentration of PAA radicals and increases the rate of cross-linking and gelation. In the third reaction, two polymer radicals, PAA•, with m and n repeat units combine to form a cross-linked point. In the forth reaction, a polymer radical, PAA•, with m+n repeat units degrades to form a polymer with m repeat units, PAA_m, and a polymer radical with n repeat units, PAA_n. The last reaction decreases the efficiency of gelation. As the concentration of polymer in aqueous solution increases, the rate of degradation reaction increases. Therefore, the concentration of polymer significantly affects the minimum dose required for gelation.

Figures 1 and 2 depict the weight/swelling ratio
Synthesis of Acrylic Acid Hydrogel by γ-Irradiation Cross-linking of Polyacrylic Acid

Figure 1. Weight swelling ratio as a function of time for 2.5% w/w PAA in aqueous solution during γ-irradiation cross-linked with radiation doses of 5 (a), 10 (b), 15 (c), and 25 kGy (d) in which the swelling measurements were performed in pH 4 medium.

as a function of time for 2.5% w/w PAA in aqueous solution cross-linked with radiation doses ranging from 5 to 25 kGy in which the swelling measurements were performed in buffered pH 4 and 7, respectively.

Figure 2. Weight swelling ratio as a function of time for 2.5% w/w PAA in aqueous solution during γ-irradiation cross-linked with radiation doses of 5 (a), 10 (b), 15 (c), and 25 kGy (d) in which the swelling measurements were performed in pH 7 medium.

Figure 3. Weight swelling ratio as a function of time for 10.0% w/w PAA in aqueous solution during γ-irradiation cross-linked with radiation doses of 5 (a), 10 (b), 15 (c), 20 (d), and 25 kGy (e) in which the swelling measurements were performed in pH 4 medium.

Figure 4. Weight swelling ratio as a function of time for 10.0% w/w PAA in aqueous solution during γ-irradiation cross-linked with radiation doses of 5 (a), 10 (b), 15 (c), 20 (d), and 25 kGy (e) in which the swelling measurements were performed in pH 7 medium.
Figures 3 and 4 show the same results for 10% w/w PAA in aqueous solution cross-linked with radiation doses ranging from 5–25 kGy. As the pH was increased from 4 to 7, the rate of swelling increased for all radiation doses and for 2.5% and 10% w/w PAA solutions. As the radiation dose was increased from 5 to 25 kGy, the rate of swelling decreased drastically. As the concentration of PAA increased from 2.5% to 10% w/w, the rate of swelling decreased.

Therefore, according to Figures 1–4, swelling behaviour of γ-radiation cross-linked samples depended on concentration of polymer and dose of irradiation.

Figure 5 shows equilibrium weight swelling of 2.5% and 10% w/w PAA solutions as a function of irradiation dose measured in buffered pH 4. In pH 4, the equilibrium swelling was less dependent on irradiation dose for 2.5% w/w PAA in solution and the values ranged from 110 to 70 corresponding to radiation doses of 10 and 15 kGy, respectively. However in the same pH, for 10% w/w PAA solution, the equilibrium swelling decreased significantly when the irradiation dose was increased from 5 to 25 kGy and the swelling values ranged from 140 to 40, corresponding to radiation doses of 5 and 20 kGy, respectively.

Figure 6 shows the equilibrium swelling of the same samples in pH 7. In pH 7, the final swelling decreased significantly as the irradiation dose increased for 2.5% and 10% w/w PAA solutions. For 2.5% w/w solution in pH 7, the maximum and minimum swelling was 500 and 300 corresponding to radiation doses of 5 and 25 kGy, respectively. For 10% w/w solution in pH 7, the maximum and minimum swelling was 550 and 100 corresponding to radiation doses of 5 and 25 kGy, respectively.

For all the radiation cross-linked PAA samples, the final swelling leveled off for radiation doses greater than 15 which indicated that the degradation of polymer during γ-irradiation became more significant as the irradiation dose increased.

The molecular weight between cross-links, \( M_c \), was determined from the swelling data using the following equation proposed by Peppas [16] for equilibrium swelling of anionic polyelectrolyte gels:
\[
\frac{V_w}{4!} \left( \frac{\phi_{p,sw}}{u_{mp,d}} \right)^2 \frac{K_a}{(10^{-pH} + K_a)^2} = \\
\ln(1 - \phi_{p,sw}) + \phi_{p,sw} + \chi_{pw} \phi_{p,sw}^2 \\
\left( \frac{V_w}{u_{p,d} \overline{M}_c} \right) \left( 1 - \frac{2 \overline{M}_c}{\overline{M}_n} \right) \phi_{p,sw} \left[ \left( \frac{\phi_{p,sw}}{\phi_{p,sw}} \right)^{-1} - \frac{1}{2} \left( \frac{\phi_{p,sw}}{\phi_{p,sw}} \right) \right]
\]

(5)

In the above equation, \(V_w\) is the molar volume of the swelling agent, water, \(I\) is the ionic strength of the aqueous solution, \(f\) is the ionizable fraction of the monomers in the hydrogel, \(\phi_{p,sw}\) is the volume fraction of polymer in the swollen state, \(u_{mp,d}\) is the molar volume of the polymerized monomer in dry state, \(K_a\) is the dissociation constant of the ionic COOH group of PAA, \(\chi_{pw}\) is the PAA-water interaction parameter, \(u_{p,d}\) is the specific volume of polymer in dry state, \(\overline{M}_c\) is the average molecular weight between cross-links, \(\overline{M}_n\) is the average molecular weight of polymer before \(\gamma\)-irradiation, and \(-P\) is the volume fraction of polymer in the relaxed state after cross-linking but before swelling. The volume fraction of polymer in the swollen state, \(\phi_{p,sw}\), was calculated from the weight swelling ratio, \(Q_w\), by the following equation:

\[
\phi_{p,sw} = \frac{1}{1 + Q_w \left( \frac{\rho_p}{\rho_w} \right)}
\]

(6)

In the above equation, \(\rho_p\) and \(\rho_w\) are the densities of polymer and water, respectively.

The value of 0.45 for compatibility parameter between PAA and water, \(\chi_{pw}\), from reference 40 was used. The value of 4.5 was used for the \(pK_a\) of the acid group of PAA from reference 41 and it was assumed that \(pK_a\) was independent of \(pH\). The experimental temperature was 25 °C and the value of 1.2 g/cm\(^3\) was used for the density of PAA at this temperature [43].

The number average molecular weight of PAA sample before cross-linking, \(\overline{M}_n\), was approximated by \(M_0\) of the sample that was equal to \(1.6 \times 10^4\) g/mol. \(\overline{M}_c\) of cross-linked samples as a function of irradiation dose is given in Figure 7 for aqueous solutions containing 2.5% and 10% w/w PAA. For 2.5% w/w PAA solution, the \(\overline{M}_c\) values for irradiation doses of 5, 10, 15, and 25 kGy were 12600, 12300, 6000, and 8100 g/mol, respectively.

For 10% w/w PAA solution, the \(\overline{M}_c\) values for irradiation doses of 5, 10, 15, 20, 25 kGy were 34600, 10300, 9600, 5200, and 5700 g/mol, respectively. These results indicated that the extent of cross-linking was almost independent of irradiation dose for 2.5% w/w PAA solution. At low concentration of PAA, the distance between chains was longer and the rate of radical transfer from polymer to water (reaction 1) was higher compared to the rate of cross-linking reaction (reaction 3). Therefore, no significant change in \(\overline{M}_c\) was observed when irradiation dose was increased. On the other hand, at high concentrations of PAA, the distance between chains was shorter and the rate of radical transfer from polymer to water was lower compared to the rate of cross-linking reaction.

Therefore, \(\overline{M}_c\) decreased significantly as the irradiation dose was increased. For 10% w/w solution, \(\overline{M}_c\) leveled off for irradiation doses of 20 and 25 kGy.
due to the increased rate of degradation of polymer by reaction 4.

The swelling mechanism of the γ-cross-linked samples was determined using the following equation:

\[ \frac{(M_t - M_0)}{M_0} = Kt^n \]  

(7)

In the above equation, \( M_t \) and \( M_0 \) are the weight of the swollen and dry sample at time \( t \), respectively, \( K \) is the swelling constant, and \( n \) is the swelling exponent. For disk-shaped samples, \( n \) is 0.5 if swelling is by Fickian diffusion of water, \( n \) is between 0.5 and 1.0 for non-Fickian or anomalous diffusion, \( n \) is 1.0 for case-II diffusion, and \( n \) is greater than 1 for supercase-II diffusion. The swelling data versus time was fitted to the above equation using the linear least squares method and the swelling power, \( n \), was determined. The values of \( n \) are shown in Table 1 as a function of concentration of PAA in solution, irradiation dose, and the pH of the swelling medium.

For 10% w/w PAA solutions swollen in pH 4, the mechanism of swelling was Fickian as the average swelling power was 0.54 for radiation doses between 5 to 25 kGy which indicated that chain relaxation had little effect on the rate of swelling. For 2.5% w/w PAA solutions swollen in pH 4, the mechanism of swelling was a combination of Fickian and anomalous diffusion as the average \( n \) value was 0.61 indicating that chain relaxation contributed to the rate of swelling.

<table>
<thead>
<tr>
<th>PAA (%)</th>
<th>Irradiation dose (kGy)</th>
<th>Swelling power (n) pH=4</th>
<th>Swelling power (n) pH=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>5</td>
<td>0.63</td>
<td>1.00</td>
</tr>
<tr>
<td>2.5</td>
<td>10</td>
<td>0.63</td>
<td>0.94</td>
</tr>
<tr>
<td>2.5</td>
<td>15</td>
<td>0.59</td>
<td>0.75</td>
</tr>
<tr>
<td>2.5</td>
<td>25</td>
<td>0.57</td>
<td>0.77</td>
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<tr>
<td>10</td>
<td>5</td>
<td>0.43</td>
<td>0.76</td>
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<tr>
<td>10</td>
<td>10</td>
<td>0.59</td>
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<tr>
<td>10</td>
<td>20</td>
<td>0.53</td>
<td>0.64</td>
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<tr>
<td>10</td>
<td>25</td>
<td>0.59</td>
<td>0.70</td>
</tr>
</tbody>
</table>

For 10% w/w PAA solutions in pH 7, the mechanism of swelling was anomalous diffusion as the average \( n \) value was 0.73 and chain relaxation had a major contribution on the rate of swelling. For 2.5% w/w PAA solutions swollen in pH 7, the swelling mechanism was between anomalous and case-II as the average \( n \) value was 0.87 indicating that chain relaxation was the rate limiting step. Supercase-II diffusion was not observed in the swelling of γ-irradiation cross-linked PAA solutions. The range of \( n \) values observed can have great implications for applications in drug delivery systems. As the \( n \) value approaches one, the rate of swelling and the rate of release of bioactive agent from the hydrogel becomes constant. Therefore, it is possible to synthesize hydrogels with zero order release rate by cross-linking polyacrylic acid in solution with γ-irradiation.

**CONCLUSION**

Polyacrylic acid, synthesized by precipitation polymerization of acrylic acid in benzene, was successfully cross-linked in solution with γ-irradiation with doses ranging from 5 to 25 kGy. Kinetics of swelling and equilibrium swelling of these gels were measured in buffered pH 4 and 7. The highest and lowest swelling ratio obtained at equilibrium was 140 and 40 in pH 4 and 540 and 100 in pH 7, respectively.

From the equilibrium swelling data, the average molecular weight between cross-links was determined using the swelling equation for anionic polyelectrolyte gels in buffered solution. The average molecular weight between cross-links ranged from 12600 to 6000 g/mol depending on irradiation dose for solutions containing 2.5% w/w PAA and 34600 to 5200 g/mol for solutions containing 10% w/w PAA, respectively.

Mechanism of swelling depended on pH of the swelling medium and percent of PAA in solution during γ-irradiation. Swelling mechanism followed case-II diffusion and the rate of swelling was constant for samples containing 2.5% w/w PAA in solution.
during irradiation swollen in pH 7 swelling medium.

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