Synthesis of Enzyme-Digestible, Interpenetrating Hydrogel Networks by Gamma-Irradiation

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ABSTRACT: γ-Irradiation was used to prepare cylindrically shaped, enzyme-digestible hydrogels consisting of a moderately swelling albumin-crosslinked poly(vinyl pyrrolidone) (PVP) hydrogel core which formed a semi-interpenetrating network (SIPN) at its outer region with a polyelectrolyte homopolymer of acryloxyethyltrimethylammonium chloride (AETAC). In pepsin-free simulated gastric fluid (SGF), the presence of a SIPN resulted in only a marginal increase in swelling as compared to the pure PVP hydrogel. In distilled deionized water, however, the swelling of the 2-phase hydrogel system was dramatically increased.

The effects of γ-irradiation on the individual constituent polymers that comprised the 2-phase system were studied. Vinyl pyrrolidone (VP) formed PVP which subsequently crosslinked to form an insoluble three-dimensional network after 4 h of γ-irradiation. Polymers of AETAC (PAETAC) underwent chain scission following 30 min of γ-irradiation. FA became crosslinked as determined by sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE).

The swelling properties of albumin-crosslinked PVP and albumin-crosslinked PAETAC hydrogels were also studied as a function of γ-irradiation time and the concentration of FA in the monomer solution. The equilibrium swelling ratios of the prepared hydrogels in pepsin-free simulated gastric fluid (SGF) were dependent on the γ-irradiation time which affected the crosslinking or chain scission of the polymers. Both the PVP and PAETAC hydrogels underwent bulk degradation in pepsin-containing SGF.

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INTRODUCTION

Enzyme-digestible hydrogels have been prepared for long-term oral drug delivery in our previous studies [1-6]. Hydrogels were retained in the canine stomach for up to 60 h in the fasted and fed state [7]. The release of flavin mononucleotide (FMN) from the hydrogel and its subsequent absorption from the gastrointestinal tract was also examined [8]. FMN levels were detected in the blood for up to 54 h despite the fact that FMN absorption is restricted to the upper small intestine. Our results indicate that the size and integrity of the hydrogel are two important parameters that influence the retention of hydrogels in the fasted and fed stomach. Based on these findings, we postulated that long-term gastric retention of hydrogels can be achieved by utilizing a hydrogel system that possesses high mechanical integrity and high swelling ability. The high swelling capability of hydrogels allows us to make hydrogels which are small enough for easy swallowing in the dried state but swell in the stomach to a suitable size for gastric retention.

Fully interpenetrating networks (FIPNs) and semi-interpenetrating networks (SIPNs) are often used to improve the mechanical properties of highly swellable networks or the swelling characteristics of moderately swellable networks [9-12]. The IPN approach makes it possible to prepare a 2-phase hydrogel system or gradient-IPN [13,14] which is interpenetrated at the outer region by a highly swellable polyelectrolyte network (Figure 1). The 2-phase system could be prepared to have the swelling and mechanical properties necessary for gastric retention.

Hydrogel networks can be prepared by free radical polymerization using γ-irradiation. Networks form rapidly without the aid of a chemical initiator or in some cases a crosslinking agent [15-17]. Because of these advantages, γ-irradiation was used in the sequential preparation

Figure 1. Side (a) and top (b) view of 2-phase hydrogel system. The outer phase is a semi-interpenetrating network (SIPN) or fully interpenetrating network (FIPN) and the inner phase is a pure, moderately swelling network. The outer phase enhances swelling while the inner phase maintains mechanical integrity.
of a 2-phase hydrogel system. This article describes the effects of \( \gamma \)-irradiation on the individual constituents that comprise the 2-phase system and the preparation and characterization of the 2-phase, enzyme-digestible hydrogel system.

**MATERIALS AND METHODS**

**Functionalization of Albumin**

Functionalized albumin (FA) was used as an enzyme-digestible cross-linking agent. FA was prepared from human serum albumin (Sigma, Fraction V) and glycidyl acrylate (Aldrich) as described previously [1,2]. Briefly, 200 \( \mu \)L of glycidyl acrylate was added to 5 mL of 5% human albumin in phosphate buffered saline solution (PBS) while stirring at room temperature. After 5 h, 1 mL of 20% glycine solution was added to stop the reaction. The solution was then dialyzed against PBS extensively. The extent of alkylation (degree of modification) by glycidyl acrylate was measured using a method described by Snyder and Sobocinski [18]. The alkylation reaction was carried out for 5 h, 12 h, 19 h, and 49 h which produced a degree of modification of 15%, 27%, 50%, and 90%, respectively.

**Effect of \( \gamma \)-Irradiation Dose on Monomers**

Vinyl-2-pyrrolidinone (VP, Aldrich), acryloxyethyltrimethylammonium chloride (AETAC, Polysciences), and FA were separately irradiated to study changes in the bulk properties of each constituent as a function of \( \gamma \)-irradiation dose. Hydroquinone and methyl ether hydroquinone were removed from samples of AETAC by ion exchange chromatography using DE-HIBIT 100 ion exchange resins (Polysciences). The concentration of VP, AETAC, and FA was 36% (w/v), 36% (w/v), and 3% (w/w) of the monomer, respectively. A solution of VP, AETAC, or FA was transferred into a 1 mL disposable syringe, degassed, and then purged with nitrogen prior to \( \gamma \)-irradiation. Radioactive Co-60 was used as a source of \( \gamma \)-irradiation at dose rate of 0.094 Mrad/h. Monomer solutions were exposed to \( \gamma \)-irradiation for periods ranging from 5 min to 4 h. The effect of \( \gamma \)-irradiation dose on the bulk properties of all samples was evaluated by viscometry. Viscometric analysis was carried out using either a Brookfield model LVT viscometer or a Cannon-Fenske viscometer depending on the viscosity to be measured. The relative viscos-
ity between non-irradiated and irradiated samples was calculated and compared as a function of $\gamma$-irradiation dose. Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was also run on irradiated samples of FA to assess the effect of $\gamma$-irradiation on molecular weight changes of FA.

**Preparation of Individual Hydrogel Networks**

Albumin-crosslinked PVP and albumin-crosslinked PAETAC hydrogels were synthesized separately. As mentioned above, hydroquinone and methyl ether hydroquinone were removed from AETAC samples by ion exchange chromatography using DE-HIBIT 100 ion exchange resins. The concentration of VP and AETAC was 36% (w/v), while the concentration of FA ranged from 0.5% (w/w) to 8% (w/w) of the monomer. The degree of FA modification was also varied from 15% to 90%. The monomer solution was transferred into a 1 mL disposable syringe, degassed, and then purged with nitrogen prior to $\gamma$-irradiation. Monomer solutions were exposed to $\gamma$-irradiation for periods of 5 min to 4 h. Following $\gamma$-irradiation, the gels were removed, cut into discs (5 mm diameter by 3 mm length), washed over a 3-day period in distilled deionized water, and then air dried at room temperature.

**Swelling Studies**

The swelling properties of albumin-crosslinked PAETAC and albumin-crosslinked PVP hydrogels were studied as a function of the $\gamma$-irradiation dose, the concentration of FA, and the degree of albumin modification. Dried hydrogels were weighed and then placed in pepsin-free simulated gastric fluid (SGF) at 37°C [19]. At specific timed intervals, the swelling gels were removed, weighed, and then returned to their original solution. The swelling ratio ($Q$) was determined from the following relationship:

$$Q = \frac{W^*}{W}$$

where $W^*$ and $W$ are the weights of the swollen and dried gels, respectively. Dynamic swelling studies were carried out until equilibrium was reached. The most suitable $\gamma$-irradiation dose for the preparation of the 2-phase system was determined based on its effect on the individual polymer constituents and the swelling properties of PAETAC and PVP hydrogels.
Enzyme-Catalyzed Degradation Studies

The pepsin-catalyzed degradation of PVP and PAETAC hydrogels was studied to determine whether \( \gamma \)-irradiation prevented degradation due to the possibility of main chain crosslinking during network formation. Dried hydrogels were weighed and then placed in pepsin-containing SGF at 37°C. The concentration of pepsin was 250 units/mL (from porcine stomach mucosa, 2500 units/mg, Sigma). At specific timed intervals, the swelling gels were removed, weighed, and then returned to their original solution. The swelling ratio (\( Q \)) of degrading samples was compared to that of nondegradable control samples.

Preparation of 2-Phase Hydrogel System

The 2-phase hydrogel was prepared sequentially by starting with a dried, albumin-crosslinked PVP hydrogel. The PVP gel was prepared in a 5 mL disposable syringe. The concentration of FA, the degree of FA modification, and the \( \gamma \)-irradiation time were 8% (w/w) of the monomer, 90%, and 4 h, respectively. Once polymerization was complete, the gels were removed, cut into cylinders (12 mm diameter by 25 mm length), washed over a 3-day period in distilled deionized water, and air dried at room temperature. The PVP gel (9 mm diameter by 20 mm length) was then immersed in a polyethylene scintillation vial (12 mm diameter) that contained both AETAC and FA monomer (Figure 2). The concentration of FA in the monomer solution was varied from 0.5% to 3% (w/w) of the monomer while the penetration time into the PVP gel ranged from 30 min to 3 h prior to \( \gamma \)-irradiation. Samples were degassed and purged with nitrogen. The samples were then irradiated for 30 min under nitrogen to form a 2-phase hydrogel system. Following \( \gamma \)-irradiation, samples were washed in distilled deionized water for 5 days to remove pure PAETAC hydrogel from the surface of the 2-phase gel (Figure 2). After washing, the samples were air dried at room temperature. Appropriate control samples were prepared by immersing the PVP hydrogel in solutions of either the FA (FA-control) or the AETAC (AETAC-control) for periods of 30 min to 3 h prior to \( \gamma \)-irradiation for 30 min under nitrogen.

Characterization of the 2-Phase Hydrogel System

The penetration of the AETAC into albumin-crosslinked PVP hydrogels was monitored over time to estimate the size of the glassy phase...
Figure 2. Sequential preparation of 2-phase hydrogel system. The dried PVP gel was immersed in a polyethylene scintillation vial that contained both AETAC and FA monomer. The penetration time was varied from 30 min to 3 h prior to γ-irradiation. Samples were then irradiated for 30 min in the 2-phase hydrogel system. The 2-phase gels were washed in distilled deionized water to remove pure PAETAC hydrogel from the surface. Dynamic swelling studies were carried out to determine whether the formation of a FIPN in the outer region of the PVP gel improved its swelling properties. Dried hydrogels were placed in pepsin-free SGF at 37 °C. Over specific time intervals the samples were removed, weighed,
and then returned to their original solution. The swelling ratio ($Q$) was calculated as described previously. The swelling properties of the 2-phase gel were compared with the FA-control, AETAC-control, and pure PVP hydrogels.

RESULTS

Effect of $\gamma$-Irradiation Dose on Monomers

The change in the relative viscosity of the VP, AETAC, and FA solutions by $\gamma$-irradiation is shown in Figure 3. The formation of PVP molecules by $\gamma$-irradiation led to a rise in the relative viscosity of the VP solution. After 4 h of $\gamma$-irradiation of the VP solution, an insoluble network or hydrogel was formed. The polymerization of AETAC was marked by an initial rise in relative viscosity by $\gamma$-irradiation up to 30 min. The relative viscosity, however, decreased as the $\gamma$-irradiation time exceeded 30 min (Figure 3). The relative viscosity increased from 1 to 33.8 over the first 30 min and then decreased to 4.8 after 4 h of $\gamma$-irradiation. The transient increase in the relative viscosity indicates scission in the polymer chains formed in the early stages of $\gamma$-ir-
radiation. The relative viscosity of FA was not significantly changed over the first 2 h of γ-irradiation. However, the relative viscosity increased over forty-fold after 4 h of γ-irradiation. The increase in relative viscosity was believed to be due to crosslinking of FA by the vinylic pendant groups on FA. SDS-PAGE on irradiated samples of FA confirmed that crosslinking took place (Figure 4). As the irradiation time increased from 15 min to 1 h (lanes 2, 3, and 4 in Figure 4), the intensity of the high molecular weight bands at the top of the gel increased while that of the low molecular weight bands decreased. This indicates that the macromolecular size of FA had increased due to crosslinking. Crosslinking had become so extensive after 2 h (lane 5 in Figure 4) that only a negligible fraction of individual FA remained.

Characterization of PVP and PAETAC Hydrogels

Albumin-crosslinked PVP and PAETAC hydrogels were studied to determine how the swelling properties of each hydrogel could be controlled by varying the γ-irradiation time, FA concentration in the monomer solution, and the degree of albumin modification. PVP and PAETAC hydrogels were formed after as little as 5 min of γ-irradiation. Shown in Figure 5a is the effect of γ-irradiation time on the swelling properties of PVP hydrogels prepared with 90%-modified FA at a concentration of 4% (w/w) of the monomer. As the irradiation time in-
Figure 5a. Dynamic swelling of albumin-crosslinked PVP hydrogels in pepsin-free simulated gastric fluid. The concentration of FA in the monomer solution was 4% (w/w) of the monomer and the degree of albumin modification was 90%. Hydrogels were prepared by 0.25 h (Δ), 0.5 h (▲), 1 h (■), 2 h (●), and 4 h (□) of γ-irradiation (n = 4).

Figure 5b. Equilibrium swelling of albumin-crosslinked PVP hydrogels in pepsin-free simulated gastric fluid (□) and the change in relative viscosity of VP (▲) as a function of γ-irradiation time (n = 4).
creased from 15 min to 2 h, the equilibrium swelling increased from 23 to 45. The increase in swelling was due to an increased degree of polymerization. Shown in Figure 5b are that both the relative viscosity of the VP solution (without FA) and the equilibrium swelling ratio of the PVP gel increased after 2 h of \( \gamma \)-irradiation. The swelling ratio decreased to 38 after 4 h of \( \gamma \)-irradiation (Figure 5b). The decrease in swelling was due to increased crosslinking density resulting from increased crosslinking of either PVP or FA as observed in Figure 3. Shown in Figure 6a are the effects of \( \gamma \)-irradiation time on swelling properties of PAETAC hydrogels prepared with 90%-modified FA at a concentration of 4\% (w/w) of the monomer. As the \( \gamma \)-irradiation time increased from 15 min to 4 h, the equilibrium swelling ratio increased from 44 to 57. Shown in Figure 6b is that the increase in gel swelling at irradiation times exceeding 30 min correspond to a decrease in the relative viscosity of the homopolymer. Thus, it is likely that main chain scission in the network resulted in increased swelling of the PAETAC hydrogel.

Based on the viscosity and swelling data, we concluded that a 4 h \( \gamma \)-irradiation time was sufficient to prepare PVP hydrogels with the mechanical integrity needed for the 2-phase hydrogel system. Although the kinetics of polymerization may be altered during the formation of the IPN, 30 min appears to be the optimum irradiation time for preparing the PAETAC network since main chain scission may be minimized.

The swelling properties of the PVP and PAETAC hydrogels were altered by varying the concentration of FA in the monomer solution. As the concentration of FA in the PVP hydrogel increased from 5\% to 8\% (w/w) of the monomer, the equilibrium swelling ratio decreased from 29 to 19, respectively (Figure 7a). As the concentration of FA in the PAETAC hydrogel decreased from 3\% to 0.5\% (w/w) of the monomer, gel swelling increased from 45 to 123, respectively (Figure 7b). PAETAC hydrogels were also prepared with 50\%- , 27\%- , and 15\%-modified FA; however, the resulting hydrogels could not be handled without breaking due to their low crosslinking density.

**Enzyme-Catalyzed Degradation Studies**

Pepsin-catalyzed degradation was observed with both PVP and PAETAC hydrogels. The concentrations of FA in PVP and PAETAC hydrogels were 8\% (w/w) and 0.5\% (w/w) of the monomer, respectively. Both PVP (Figure 8a) and the PAETAC (Figure 8b) hydrogels underwent bulk degradation which was characterized by a higher degree of
Figure 6a. Dynamic swelling of albumin-crosslinked PAETAC hydrogels in pepsin-free simulated gastric fluid. The concentration of FA in the monomer solution was 4\% (w/w) of the monomer and the degree of albumin modification was 90\%. Hydrogels were prepared by 0.25 h (Δ), 0.5 h (○), 1 h (●), 2 h (■), and 4 h (□) of γ-irradiation (n = 4).

Figure 6b. Equilibrium swelling of albumin-crosslinked PAETAC hydrogels in pepsin-free simulated gastric fluid (□) and the change in relative viscosity of AETAC (▲) as a function of the γ-irradiation time (n = 4).
Figure 7a. Dynamic swelling of albumin-crosslinked PVP hydrogels in pepsin-free simulated gastric fluid. Hydrogels were prepared by 4 h of $\gamma$-irradiation. The concentration of 90%-modified FA was 5% (○), 6% (●), 7% (■), and 8% (△) (w/w) of the monomer ($n = 4$).

Figure 7b. Dynamic swelling of albumin-crosslinked PAETAC hydrogels in pepsin-free simulated gastric fluid. Hydrogels were prepared by 0.5 h of $\gamma$-irradiation. The concentration of 90%-modified FA was 0.5% (△), 1% (■), 2% (●), and 3% (□) (w/w) of the monomer ($n = 4$).
Figure 8a. Dynamic swelling of albumin-crosslinked PVP hydrogels in the presence (■) and in the absence (□) of pepsin. The activity of pepsin in simulated gastric fluid was 250 units/mL. Hydrogels were prepared by 4 h of γ-irradiation and 90%-modified FA at a concentration of 8% (w/w) of the monomer (n = 4).

Figure 8b. Dynamic swelling of albumin-crosslinked PAETAC hydrogels in the presence (■) and in the absence (□) of pepsin. The activity of pepsin in simulated gastric fluid was 250 units/mL. Hydrogels were prepared by 0.5 h of γ-irradiation and 90%-modified FA at a concentration of 0.5% (w/w) of the monomer (n = 4).
swelling as compared to non-degrading control samples and a gradual decline in mechanical integrity. After 96 h of incubation, the swelling ratio of the PVP hydrogel was 27 in the presence of pepsin and 19 in the absence of pepsin. Even after 96 h, PVP gels still maintained their mechanical integrity, although it was considerably less than that at earlier time points. The swelling ratio of the PAETAC hydrogel was 160 in the presence of pepsin and 123 in the absence of pepsin. The PAETAC hydrogel underwent gel disruption in the presence of pepsin at times exceeding 96 h. After the gel disruption point, the hydrogel could no longer be handled due to a significant loss in mechanical integrity [1]. The slower degradation rate of PVP hydrogels as compared to that of the PAETAC hydrogels was attributed to the higher crosslinking density and also to the possible presence of main chain crosslinking in the PVP network.

Characterization of 2-Phase Hydrogel System

Initial washing of the 2-phase hydrogel in distilled deionized water led to the detachment of pure PAETAC hydrogel from the surface of the 2-phase hydrogel (Figure 2). In the swollen and dried states, the 2-phase hydrogel system was clear and transparent indicating a high degree of chain entanglement within the IPN phase [9]. After prolonged swelling in distilled deionized water, the 2-phase hydrogel system exhibited swelling characteristics that were similar to the pure PAETAC hydrogel while maintaining mechanical integrity that resembled the pure PVP gel. In pepsin-free SGF, however, the degree of swelling was considerably lower than that in distilled deionized water. Shown in Figure 9 is that the swelling size of the 2-phase hydrogel (C) was approximately 1.5 times larger than the pure PVP gel (B) after equilibration in SGF. In distilled deionized water, a two-fold increase in the swelling size of the 2-phase gel was observed (D in Figure 9).

The dynamic swelling ratios of the 2-phase hydrogel system with the PAETAC-control, FA-control, and the pure PVP hydrogels are compared in Figure 10a. The swelling behavior of 2-phase hydrogels was not significantly different from that of PAETAC-control gels. The swelling behavior of FA-control gels was similar to that of pure PVP hydrogels. The data indicate that the presence of FA in the solution did not significantly alter the swelling properties of the 2-phase hydrogel. Thus, it appears that FA did not diffuse into the PVP gel and as a result a SIPN was formed in the outer phase of the 2-phase hydrogel [21]. The extent of swelling was only slightly higher when the monomer solution was allowed to penetrate into the PVP gel for 3 h prior to $\gamma$-irradiation.
Figure 9. Swelling size of the albumin-crosslinked PVP hydrogel in simulated gastric fluid (B), the 2-phase hydrogel system in pepsin-free simulated gastric fluid (C), and the 2-phase hydrogel system in distilled deionized water (D). A dried PVP hydrogel (A) was used for comparison.

Figure 10a. Dynamic swelling of 2-phase hydrogels in pepsin-free simulated gastric fluid. The 2-phase hydrogels were prepared by immersing the PVP gel in a solution containing FA and AETAC (■). Pure PVP hydrogels (▲) and PVP hydrogels immersed for 3 h in solutions of either AETAC (■) or FA (△) were used as controls (n = 4).
Figure 10b. Dynamic swelling of 2-phase hydrogels in pepsin-free simulated gastric fluid. 2-Phase hydrogels were prepared by immersing the PVP gel in a solution of AETAC for 1.5 h (■) and 3 h (●). PVP hydrogels (○) were used as a control (n = 4).

(Figure 10b). The small differences in swelling were attributed to the limited extent of AETAC penetration into the PVP gel prior to irradiation (Figure 11). Illustrated in Figure 11 is the size of the glassy phase of the gel decreased only from 20 mm x 9 mm to 17.5 mm x 7.8 mm after 3 h of penetration. It should be noted, however, that the effect of penetration time on gel swelling was more pronounced in distilled deionized water than in pepsin-free SGF.

DISCUSSION

The objective of this work was to utilize γ-irradiation in the preparation of a 2-phase hydrogel system. For this reason, our initial experiments were focused on how γ-irradiation influenced the properties of the individual constituents that would comprise the 2-phase system. It was observed that γ-irradiation of VP for 4 h resulted in crosslinking the PVP chains. The formation of a three-dimensional network following γ-irradiation is consistent with previous literature on PVP [15,22]. Solutions of AETAC, however, formed PAETAC molecules that underwent scission in the main chain during γ-irradiation. Main chain scission was probably due to the cationic charge on the side chain of the
monomer which may have hindered the formation of crosslinks or end-links by charge repulsion. The influence of charge on main chain scission on crosslinking has also been observed with poly(acrylic acid) [22]. It has been shown that partially neutralized poly(acrylic acid) undergoes main chain scission following γ-irradiation whereas fully protonated polyacrylic acid becomes crosslinked during γ-irradiation.

γ-Irradiation times influenced the swelling properties of the PVP and PAETAC hydrogels. Although the kinetics of homopolymerization is different from that in the presence of a crosslinking agent [23], the change in swelling as a function of irradiation time correlated well with the change in viscosity of the respective homopolymers. As a result, the decrease in the swelling ratio of PVP hydrogels prepared with 4 h of γ-irradiation was consistent with the main chain crosslinking observed with PVP homopolymers. Even though main chain crosslinking was likely, it did not prevent pepsin-catalyzed degradation of the hydrogel. Conversely, the increase in swelling associated with the PAETAC hydrogels was consistent with main chain scission of the PAETAC homopolymer after only 30 min of γ-irradiation. Based on the

![Figure 11. Penetration of AETAC into PVP hydrogels. PVP hydrogels were immersed in Biuret's reagent containing 36% (w/v) AETAC for up to 3 h. The length (ℓ) and diameter (∅) of the glassy phase, and the thickness of the rubbery phase (Δ) were measured at 0.5 h, 1.5 h, and 3 h (n = 3).](image-url)
data, we concluded that in order to effectively prepare the 2-phase hydrogel system, 4 h and 30 min would be necessary to form the PVP hydrogel and the IPN, respectively. Furthermore, the swelling properties of PVP and PAETAC hydrogels were readily controlled by varying the concentration of FA in the monomer solution. In short, γ-irradiation was very effective in the preparation of albumin-crosslinked PVP and PAETAC hydrogels.

Although our initial objective was to synthesize a FIPN as the outer phase of the 2-phase gel system, it was likely that a SIPN was formed. The lack of FA penetration into the PVP hydrogel may be attributed to the size of the FA (~66,500 Daltons) and the mesh-size restrictions imposed by the highly crosslinked PVP network. Over the 3 h penetration period, only the AETAC was capable of moving inside the PVP gel. The result was a 2-phase hydrogel consisting of a pure PVP hydrogel as the inner phase and a SIPN as the outer phase. It may be possible, however, to prepare a FIPN as the outer phase if the penetration time was prolonged to allow enough time for the slow diffusion of FA into the PVP gel.

In pepsin-free SGF, the 2-phase hydrogel system exhibited slightly greater swelling as compared to the pure PVP gel. Enhanced swelling associated with the formation of a 2-phase system was best illustrated in Figure 9 where a dramatic increase in swelling upon exposure to distilled deionized water is shown. The marginal increase in swelling in SGF as compared to the pure PVP gel was attributed to the limited degree of AETAC penetration prior to SIPN formation (Figure 11), and the hydrophilicity and cationic nature of the resulting PAETAC chains. The swelling pressure (\(\pi\)) is described as the osmotic-pressure difference between a hydrogel and its external solution. For permanently charged networks, \(\pi\) is dependent on the polymer/solvent interaction (\(\pi_{\text{mix}}\)), the elastic properties of the network (\(\pi_{\text{elas}}\)), and the difference in ion concentrations between the hydrogel and its surrounding solution (\(\pi_{\text{ion}}\)) [24–26]. Since these contributions are additive, increasing the difference in ion concentration between a polyelectrolyte gel and its surrounding solution will increase gel swelling while decreasing the difference will lower swelling. Thus, it was not surprising that the 2-phase hydrogel achieved a significantly greater degree of swelling in distilled deionized water than in pepsin-free SGF. In future experiments, the swelling properties of the 2-phase hydrogel will be improved by either increasing the monomer solution penetration time to increase the ionic character of the SIPN or by using a more hydrophilic polyelectrolyte to enhance polymer/solvent interaction.

In summary, γ-irradiation was successfully used to prepare a 2-phase,
enzyme-degradable hydrogel system that may, with additional modifications, be used as a gastric retention device for long-term oral drug delivery.

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REFERENCES


