Gelatin Based pH-Sensitive Hydrogels for Colon-Specific Oral Drug Delivery: Synthesis, Characterization, and *In Vitro* Release Study

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ABSTRACT: Based on gelatin (Gltn) and acrylic acid (AAc), biodegradable pH-sensitive hydrogel was prepared using gamma radiation as super clean source for polymerization and crosslinking. Incorporation of PAAc in the prepared hydrogel was confirmed by Fourier transform infrared spectroscopy (FTIR). The effect of PAAc content on the morphological structure of the prepared hydrogel swollen at pH 1, 5, and 7 was examined using scanning electron microscopy (SEM). The results showed the dependence of the porous structure of the prepared hydrogels on AAc content and the pH of the swelling medium. Swelling properties of gelatin/acrylic acid copolymer hydrogels with different AAc contents were investigated at different pH values. Swelling data showed that the prepared hydrogels possessed pronounced pH sensitivity. *In vitro* release studies were performed to evaluate the hydrogel potential as drug carrier using ketoprofen as a model drug. Experimental data showed that the release profile depends on both hydrogel composition and pH of the releasing medium. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 118: 2642–2649, 2010

Key words: γ-irradiation; gelatin; pH- sensitive; hydrogel; drug delivery; colon targeting

INTRODUCTION

Controlled drug delivery systems (DDS) are designed to deliver peptides, protein drug molecules, and drugs, which are poorly absorbed from the upper gastrointestinal tract (GIT), to the colon at predetermined rates for predefined periods of time.[1] Drug targeting not only reduces the dose to be administered, but also reduces the incidence of possible adverse effects associated with these chemotherapeutic agents.

Hydrogels are defined as two- or multi-component systems consisting of a three-dimensional network of polymer chains and water or biological fluids that fills the space between macromolecules.[2] The ability to swell and the extent of swelling of hydrogels are mainly governed by two factors, namely the hydrophilicity of polymer chains and the crosslink density. Typically in the swollen state, the mass fraction of water in a hydrogel is much higher than the mass fraction of the polymer.

Later, stimuli-responsive hydrogels have been studied since they exhibit reversible swelling behavior in response to external stimuli such as pH, temperature, or magnetic and electric field.[3–7] In particular, pH-sensitive hydrogels are widely used because of variations in pH that are known to occur at several body sites such as the gastrointestinal tract, vagina, and blood vessels.[8] All pH-sensitive polymers contain pendant acidic (e.g., carboxylic and sulfonic acids) or basic (e.g., ammonium salts) groups that either accept or release protons in response to changes in environmental pH.

Hydrogels from natural proteins such as gelatin, which is a high-molecular-weight polypeptide derived from collagen fibers by partial degradation and composed of amino acids, have received particular attention due to their natural origin, low cost, good biocompatibility, and biodegradability.[9] Furthermore, their resemblance to human tissues is of value for these polymers to be used to study or mimic solute transport through biological media. Such hydrogels have been widely used in DDS as well as in food industry as food additives.[10]

pH-sensitivity was obtained by the incorporation of anionic monomer such as AAc. Poly acrylic acid (PAAc) is a well-known bioadhesive polymer, which sticks to the mucosal surfaces.[11] Therefore, to prolong the residence time of a drug delivery vehicle in the target area, PAAc is often incorporated into a delivery formulation.[12] On the other hand, it was found that PAAc was able to protect some protein

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drugs from enzymatic degradation by inhibiting the hydrolytic activity of gastrointestinal enzymes.[13,14] Thus, PAAc-containing DDS have the ability to improve an *in situ* colonic absorption of various drugs.

Among various methods applied for the production of hydrogels, the radiation technique has many advantages, as a simple, efficient, clean, and environment-friendly process.[15] Application of radiation for the formation of hydrogels for biomedical use offers a unique possibility to combine the formation and sterilization of the product in a single technological step. This allows simplifying the technology and reducing production costs.

In the present work, attempts have been made to prepare pH-sensitive hydrogels using gelatin as a natural polymer and acrylic acid as a pH-sensitive monomer. To evaluate the prepared hydrogel as a carrier for DDS, Ketoprofen, which is an anti-inflammatory and analgesic agent, was used as a model drug. *In vitro* release studies in different pHs similar to the gastrointestinal fluids have been made to show the influence of the environmental pH and the preparation conditions on the release profiles.

EXPERIMENTAL

Materials

Acrylic acid (AAc) of purity 99.9% purchased from (Merck, Darmstadt, Germany) and gelatin purchased from (Sigma–Aldrich Company, Taufkirchen, Germany) were used as received without further purification. Ketoprofen, of pharmaceutical grade, is kindly provided by Alexandria pharmaceuticals Co. (Alexandria, Egypt). Citric acid, sodium citrate, sodium dihydrogen phosphate, and disodium hydrogen phosphate are analytical reagents and were purchased from El-Nasr Co. for Chemical Industries Cairo, Egypt and used without further purification.

Preparation of Gltn/AAc gels

Gltn/AAc hydrogels were obtained by γ-irradiation-induced copolymerization of 20 wt % aqueous solutions of Gltn and AAc mixtures of different compositions, in wt %, in small glass vials using ^{60}Co gamma rays, 20 and 30 kGy, at a dose rate 10.28 kGy/h. After copolymerization, the vials were broken, the formed polymeric cylinders were removed and cut into disks of 2 mm thickness and 5 mm diameter. All samples were washed with excess water to remove the unreacted component, then air dried at room temperature up to constant weight.

Gel fraction

The gel fraction Gel (%) is defined as the ratio of the dry gel weight (W_d) to the initial weight of the gel (W_o). To extract the soluble parts of the hydrogels (i.e., the ungelled part), the prepared hydrogels were soaked in water for 48 h at 80°C. Then, they were taken out and washed with hot water to remove the soluble part, dried, and weighed to find the weight of the insoluble part (W_d). The gel percent in the hydrogel was determined from eq. (1):

$$\text{Gel\%} = \frac{W_d}{W_o} \times 100 \quad (1)$$

Where W_d and W_o are dry hydrogel weights after and before extraction, respectively.

Preparation of buffer solutions of different pH's

0.2 *M* citric acid/trisodium citrate and 0.2 *M* sodium dihydrogen phosphate/disodium hydrogen phosphate were used to prepare buffer solutions ranged from 3–5 and 6–8, respectively.[16] HCl was used to prepare aqueous solutions of pH 1.

Swelling studies

The dried hydrogels were weighed and placed into 50 mL of different buffer solutions at 37°C. The pH range studied varied from 1 to 8. At certain time intervals, hydrogel samples were taken out of the buffer solution, and the excess of buffer was removed by blotting with filter paper. The weight of the wet hydrogel was then measured. The swelling ratio (S) was determined from the eq. (2):

$$S = \frac{W_s - W_o}{W_o} \times 100 \quad (2)$$

Where W_s and W_o are the weights of the swollen and the dried hydrogel, respectively. The experiments were repeated three times, and the results were reported as average values.

Scanning electron microscopy

The morphology of the hydrogel surfaces were observed by scanning electron microscopy (SEM) (Jeol, JSM) at a voltage of 30 kV. The hydrogel samples were allowed to swell till equilibrium, freeze dried, and then the surfaces were pre-coated with a thin gold layer to reduce charging.

Ultraviolet (UV) measurements

Determination of the released amount of the drugs under investigation was carried out at 260 nm using JASCO V560 spectrophotometer.

Fourier-transform infrared (FTIR) measurements

Mattson 1000, Unicam, England in the range from 4000 to 400 cm^{-1} was used to determine the FTIR spectra of dry copolymer.[17]

Preparation of drug-loaded gel

15 mg of the drug were dissolved in 20 mL phosphate buffer of pH 7. The dry Gltn/AAc copolymer hydrogels were soaked into the drug solution at room temperature until equilibrium. The drug loaded gels were dried at room temperature for 48 h.

Loaded drug release

Dug release experiment was carried out at HCl aqueous solution of pH 1, which is almost similar to that of stomach medium for 3.5 h and at buffer solution of pH 7, which is similar to that of the intestine medium for 21.5 h. Three preweighed samples were allowed to swell each in 25 mL aqueous HCl solution of pH 1 and then transferred to 100 mL 0.2 *M* phosphate buffer (pH 7) at the physiological temperature 37°C. At different time intervals, 1 mL of each sample solution was withdrawn, and the amount of drug released was determined according to the results of UV measurements at 260 nm.[18] After each measurement, the sample used was returned to the original medium solution to maintain a constant volume of surrounding release medium. The amount of drug released was computed by comparing the absorbance with the standard curve prepared for the pure drug in the appropriate concentration regions.

RESULTS AND DISCUSSION

Ionizing radiations such as γ-rays and electron beams are able to generate radicals on the monomer and polymer in addition to the production of OH° and H° radicals as the primary products of water radiolysis. On exposure to γ-ray, as ionizing radiation, monomers radicals combine and propagate to form linear or branched but soluble polymers. In the same time, Gltn and the formed PAAc are also radiolyzed that the H° and OH° radicals are very efficient for abstracting hydrogen from polymer molecule. These macro radicals contribute to chain initiation and crosslinking formation. Such crosslinking process is a chemical bonding between the polymeric chains which makes such hydrogels insoluble even at elevated temperatures.[19]

Structure and morphology characterization

FTIR analysis

To confirm the presence of AAc in the prepared hydrogel, spectra of the native Gltn and Gltn/AAc copolymer hydrogel sample are compared in Figure 1. In the case of native Gltn [Fig. 1(a)], the wide absorption band around 3389 cm^{-1} was due to the stretching vibration of O—H and N—H groups. The band appearing at 1648 cm^{-1} indicates amide I band (C—O) was attributable to both a random coil and a-helix conformation of Gltn. The N—H bending

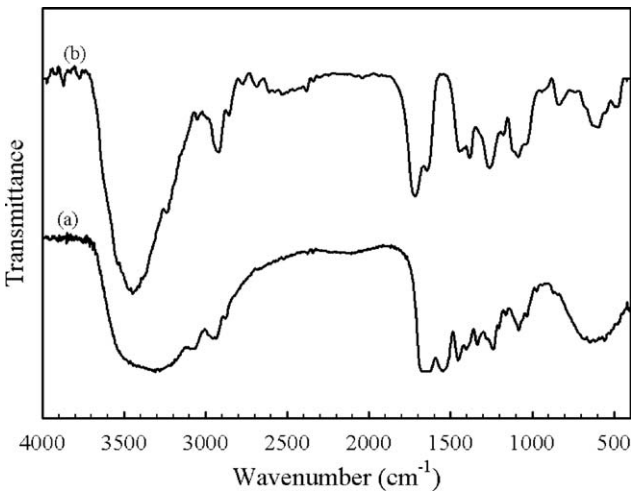

Figure 1 FTIR spectra of (a) pure gelatin and (b) gelatin/AAc copolymer hydrogel. AAc content 75 wt %.

vibration is indicated by a band observed at 1540 cm^{-1} (amide II), while bands at 1239 cm^{-1} indicate the C—N bond stretching vibration.[20–22]

Also, it can be seen from Figure 1(b) that the band appears at 1720 cm^{-1} was assigned to the absorption of carbonyl group of poly(acrylic acid) moieties. The band at 1263 cm^{-1} was characteristic absorption of C—O stretching vibration. The peaks at 1453 and 1165 cm^{-1} were absorption bands of poly(acrylic acid).

Gel fraction

Gelation degree of the prepared hydrogel was tested to follow the extent of crosslinking process. There are many factors affecting the gel content such as, composition and irradiation dose. The effect of various Gltn/AAc compositions on the gelation process at different irradiation doses was investigated and shown in Figure 2. It is clear that the gel content of Gltn/AAc hydrogel increase with increasing of AAc content in the feed solution as well as irradiation dose to reach a maximum value ranged from 96% to 99%. The maximum gelation degree could be attributed to the high tendency of AAc, as a vinyl monomer, for polymerization and crosslinking and the stability of the gelatin at the doses under investigation. Consequently, the high gelation degree of the prepared hydrogels make them considerably safe to be used as drug carrier for drug delivery system.

Swelling behavior of Gltn/AAc hydrogels

Effect of irradiation dose on the equilibrium swelling of Gltn/AAc hydrogels

The swelling behavior of the Gltn/AAc hydrogels of different AAc contents that were prepared at different irradiation doses was investigated at pH 1 and

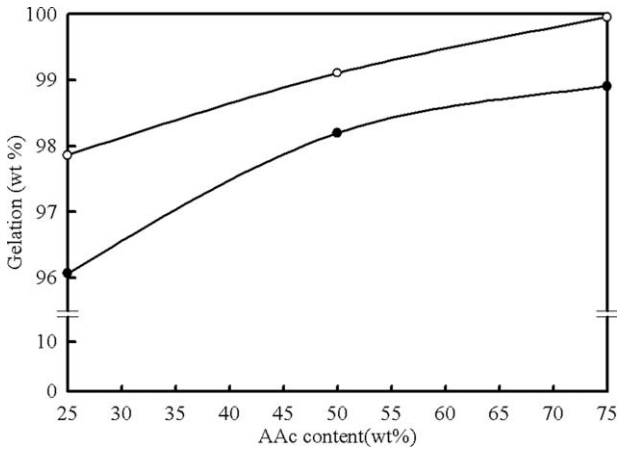

Figure 2 Effect of AAc content on the gelation percent of Gltn/AAc hydrogel at different irradiation doses (kGy); (●) 20 and (○) 30.

pH 7 and shown in Figure 3. At pH 1 [Fig. 3(a)], the increase of acrylic acid content leads to a slight decrease in the equilibrium swelling of the prepared hydrogel. Such decrement would attributed to the increment in the number of associated carboxylic groups which are able to form inter-molecular hydrogen bonding. Consequently, reduction in the equilibrium swelling takes place. Further decrement in the equilibrium swelling was observed for the samples prepared at higher irradiation dose (30 kGy). Such decrement is attributed to the increase in the crosslinking density. On the other hand, swelling experiments at pH 7 [Fig. 3(b)], showed an opposite swelling behavior. It is clear that the increase of the acrylic acid content remarkably increases the swelling equilibrium of the prepared hydrogels. Such increment in the equilibrium swelling is also attributed to the increase in the number of carboxylate ions which are responsible hydration as a result of their intermolecular electrostatic repulsion. In similar manner, the increase in the exposure dose used for preparation leads to the reduction in the swelling equilibrium as a result of the increase in crosslinking density.

Effect of pH on the swelling behavior of the Gltn/AAc hydrogels

The pH of the immersion medium has direct control over the degree of swelling of network of the pH-responsive hydrogels. Therefore, the effect of using different pHs on the swelling behavior of the Gltn/AAc hydrogel containing different amounts of AAc was investigated and shown in Figure 4. All the investigated hydrogels show pH-dependent swelling behavior for all copolymer compositions; at low pHs, up to 4, there is no significant swelling i.e., the swelling degree is very limited. As the pH value increases, more than pH 4, the swelling degree of the gel increases. Moreover, the magnitude of the swelling increases by increasing AAc content in the hydrogel. These results can be attributed to the pKa value of AAc, which is around pH 4. At lower pH values, such phase transition can be attributed to the dissociation state of the ionizable carboxylic groups of acrylic acid. Below pH 4 that is below pKa of carboxylic acid, the carboxylic groups are completely associated forming inter- and/or intramolecular hydrogen bonding resulted in the collapse of the hydrogel. However, at pH values higher than pH 4, the carboxylic groups start to dissociate forming carboxylate ions. The electrostatic repulsion between the carboxylate ions resulted in an increase in the free spaces available for swelling. In addition, the high hydrophilicity of such carboxylate ions would lead to that remarkable increase in the swelling degree along the phase transition.

Effect of ionic strength on the swelling behavior of the Gltn/AAc hydrogels

It is well known that the presence of ions in the swelling medium has a profound effect on the

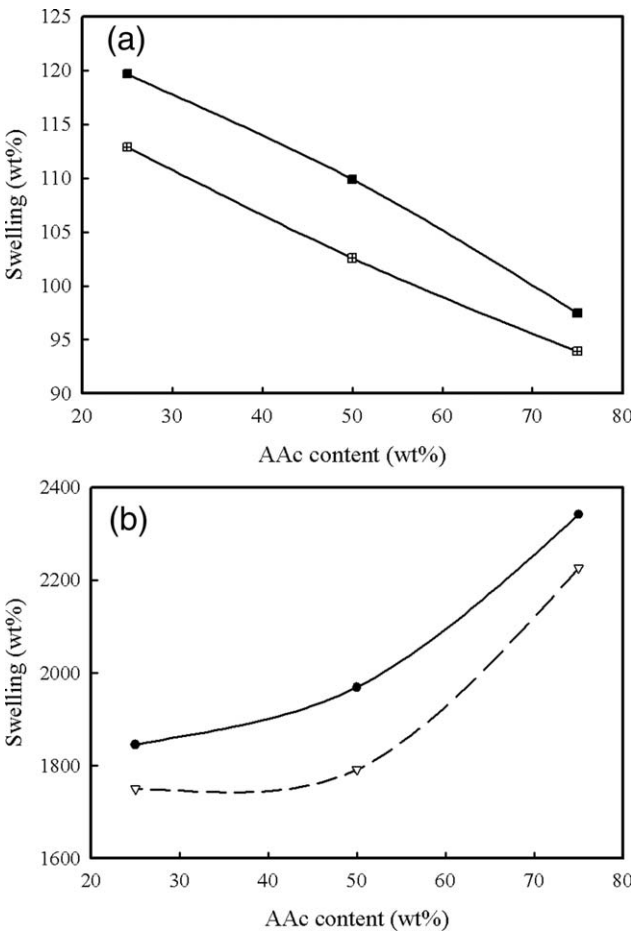

Figure 3 Effect of AAc content on the equilibrium swelling of Gltn/AAc copolymer hydrogel at (a) pH 1 prepared at different irradiation doses (●) 20 and (▽) 30 kGy and at (b) pH 7 prepared at different irradiation doses (■) 20 and (□) 30 kGy.

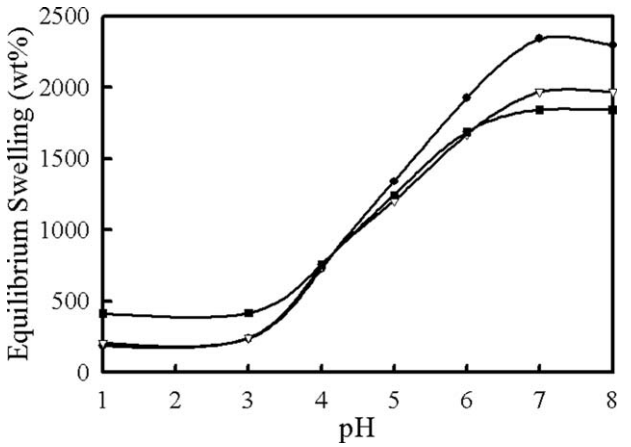

Figure 4 pH dependent swelling of Gltn/AAc copolymer hydrogel of different AAc content (wt %); (■) 25, (▽) 50, and (●) 75.

swelling behavior of the hydrogel. The principal behind this ionic dependence of swelling is that it is the balance between the osmotic pressure of the swelling system and elastic response of the polymeric material that controls the extent of swelling. The osmotic pressure results from the difference between the mobile ion concentrations between the interior of the hydrogel network and the external immersion medium. According to Donnan equilibrium theory, the increase in the ionic concentration reduces the mobile ion concentration difference between the polymer gel and external medium (osmotic swelling pressure) which, in turn, reduces the gel volume, i.e., the gel shrinks.[23]

The effect of salt concentration on the equilibrium swelling of the prepared Gltn/AAc copolymer hydrogels of different AAc contents has been investigated by increasing the ionic strength of the external solution by adding sodium chloride to the external solution in the concentration range 0.01–0.10 *M*.

It is clear from Figure 5 that the equilibrium swelling decreases by increasing the ionic strength of the solution. Also it can be seen that the copolymer of higher AAc content is more affected by such increase. The decrease in the swelling equilibrium accompanied the increase in ionic strength due to the electrostatic shielding effect of the counter ion on the dissociated carboxylate ions which reduces the electrostatic repulsion between such group and consequently decreases the free spaces available for swelling.

Swelling kinetics

Hydrogels, which are hydrophilic network polymers and glassy in the dehydrated form, have the ability to release the entrapped drug in aqueous medium and regulating such release by controlling water diffusion. The release of water-soluble drug from such dehydrated hydrogel takes place by simultaneous absorption of water and desorption of drug via a swelling controlled diffusion mechanism. Studying of the swelling kinetics would give good prediction of the diffusion behavior and the ability of the hydrogel to be used as drug delivery system. Diffusion of water to the glassy polymeric matrix generally exhibits a behavior ranging from Fickian to Case II extremes depending on the experimental conditions and thermodynamic compatibility between water and copolymer hydrogel.[24] Diffusion type can be distinguished by fitting the fractional swelling of water (F) to the empirical relation (3):

$$M_t/M_\infty = Kt^n \tag{3}$$

Where M_t is the amount of drug released or water absorbed, M_∞ is the same variable at equilibrium, k is the release or adsorption constant and n is the swelling or release index, which characterizes the mode of drug transport. The values of k and n are found by fitting the data to the above expression. For non-swollable polymeric systems, n was found to be around 0.5 implying that the diffusion is the controlling mechanism for water absorption and drug release which is simply called Fickian type of diffusion. However, for $0.5 < n < 1.0$ an anomalous diffusion behavior is followed that it is time dependent mechanism and it is called non-Fickian type of diffusion and finally for $n = 1$ drug release or water adsorption shows a zero order profile.

Figures 6 and 7 show the effect of pH value of the surrounding medium on swelling kinetics, and the type of water diffusion to the glassy copolymer and Table I summarizes diffusion data of (Gltn/AAc) copolymers of different compositions concluded from similar figures.

Meanwhile, it would be useful to study the effect of pH on the diffusion coefficient for the transport

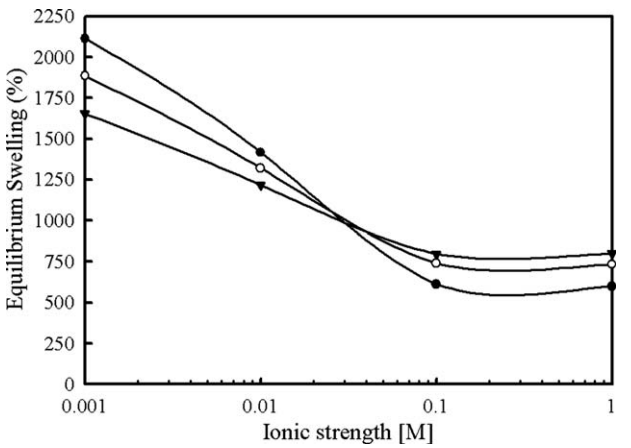

Figure 5 Effect of ionic strength on the equilibrium swelling of Gltn/AAc copolymer hydrogels of different AAc content (wt %); (▼) 25, (○) 50, and (●) 75.

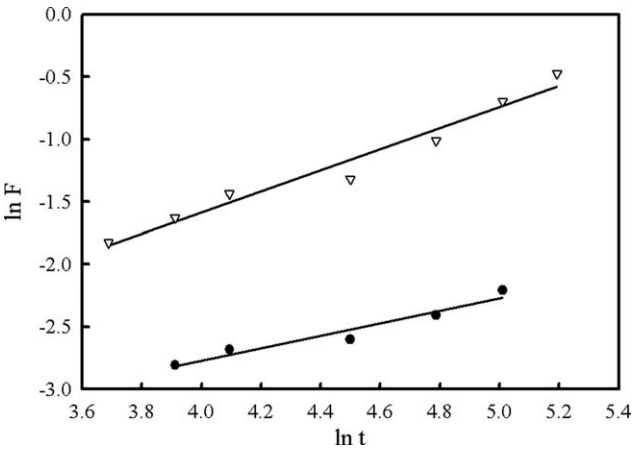

Figure 6 Representation of the fractional swelling (F) of Gltn/AAc copolymer hydrogels of composition (25/75 wt %) in buffer solutions of different pH against time (ln t). (●) pH 1 and (▽) pH 7.

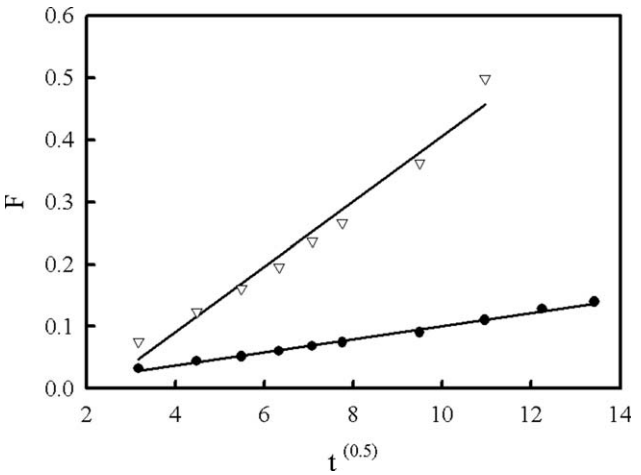

Figure 7 Representation of the fractional swelling (F) of (Gltn/AAc copolymer hydrogels of composition (25/75 wt %) in buffer solutions of different pH against time ($t^{0.5}$). (●) pH 1 and (▽) pH 7.

of water towards the interior of the hydrogels. For controlled diffusion process, the fraction of swelling due to the water uptake (F) can be also expressed by eq. (4)[25]:

$$F = 4(Dt/\pi h^2)^{1/2} \quad (4)$$

where D is the diffusion coefficient for the transport of water towards the interior of the hydrogel, h is the hydrogel thickness, and t is the time. Equation (4) is a solution of Fick's second low under simple boundary conditions such as swelling in water and biological fluids or simple geometric forms such as disks, cylinders, and spheres. Diffusion coefficient as determined from the slopes of the initial linear part of the plot of water uptake (F) against the square root of time ($t^{1/2}$), Figure 6, were summarized in Table II.

The data in the Table II show the effect of copolymer composition on the apparent diffusion coefficient (D) at pH 1 and 7. Data show that, for all compositions, the diffusion coefficient within the hydrogel in buffer solution of pH 7 is higher than that in pH 1. In the same time, at pH 1, diffusion coefficient decreases by increasing AAc, whereas it increases by increasing AAc at pH 7. Such behavior is directly related to the pH dependent association/dissociation behavior of AAc as mentioned in the pH-dependent swelling of the prepared hydrogel.

Structure topography of Gltn/AAc copolymer hydrogels

SEM was utilized to investigate the surface topography of Gltn/AAc copolymer hydrogels of different AAc content that allowed swelling at pH 1, 5, and 7. Figure 8(a) shows the morphological structure of Gltn-AAc hydrogel of composition 50/50 wt % at pH 1, it can be seen that the sample has a tightly closed surface structure. However, clear porous structure is observed for the samples swollen at pH 5 and 7 were shown in Figure 8(b,c), respectively. Meanwhile, it is clear that the increase in the pH value enlarge the pore size structure of the prepared hydrogel. These results confirm the aforementioned results; as the pH increases the degree of swelling increases resulting in highly porous gel structure. Figure 8(d) shows the surface structure of the gel containing higher PAAc content; 25/75 wt % Gltn-AAc. It is clear that as the content of PAAc content increases in the hydrogel, its pore size formed at pH 7 increases. The increment of the pore size may be due to the ionic repulsion caused by the formation of carboxylate ions at pH 7.

Figure 8 The morphological structure of Gltn/AAc hydrogel of composition (50/50 wt %) swollen; (a) at pH 1, (b) at pH 5, and (c) at pH 7, and (d) of higher PAAc content; (25/75 wt %).

TABLE I
Effect of pH on the Diffusion Parameters of Gltn/AAc Hydrogels of Different AAc Content (wt %) Prepared at 30 kGy

	AAc content (wt %)								
	75			50			25		
pH	n	k	r^2	n	k	r^2	n	k	r^2
1	0.50	−4.8	0.94	0.517	−4.99	0.934	0.538	−4.30	0.964
7	0.89	−5.18	0.98	0.82	−4.8	0.979	0.83	−4.5	0.98

TABLE II
Effect of pH on the Apparent Diffusion Coefficient of Gelatin/AAc Hydrogels of AAc Content (wt %) Prepared at 30 kGy

	AAc content (wt %)					
	75		50		25	
pH	D^ae-3	r^2	D^ae-3	r^2	D^ae-3	r^2
pH 1	10.62	0.99	9.24	0.99	20.73	0.99
pH 7	52.64	0.97	51.15	0.97	75.86	0.97

[a] Diffusion coefficient data are the mean of triplicates.

Colon-specific drug delivery of Gltn/AAc hydrogel

Recently colon has been accepted as an increasingly important site for drug delivery. Targeted drug delivery to colon would therefore ensure direct treatment at the disease site, lower dosing, and a reduction in systemic side effects. Drugs that are degraded and/or poorly absorbed in the upper gut may be preferentially absorbed from the colon. To accept the copolymer as carrier for Colon-specific drug delivery system, it should not release the drug and protect it at stomach, pH 1, and start to release the drug at colon and small intestine, pH 7. Ketoprofen is an anti-inflammatory, analgesic agent, and of extensive use in the treatment of rheumatic pains. Ketoprofen is chosen as a model drug for this investigation. As the proposed hydrogel system shows a fair pH-dependent swelling, it may bear potential to be used for colon-targeted drug delivery as it is expected to demonstrate minimum release in the acidic pH and maximum in the medium of pH 7. To confirm this, the release behavior of the Ketoprofen molecules from the prepared hydrogel which depend on many factors, such as, hydrogel composition, preparation dose, release condition (e.g., pH) have been examined.

Effect of matrix composition and preparation dose on the drug release

Figure 9 shows the drug release behavior of Gltn/AAc copolymer hydrogel of different compositions as a function of time at pH 1 and 7. The figure shows that there is no significant drug release at pH 1, whereas the drug release occurs as soon as the copolymer transferred to buffer solution of pH 7. The results show that the drug release is not only pH dependent but it also shows the influence of the copolymer composition on the release rate and total released drug. As the AAc content increase in the copolymer, the release rate as well as the total released drug increases. This results can be explained on the basis of higher rate of swelling due to deprotonation of carboxylic group (—COOH) of polymer chain to carboxylate ion ($—COO^-$) in a medium of pH value higher than its pKa, which leads to polymer chain

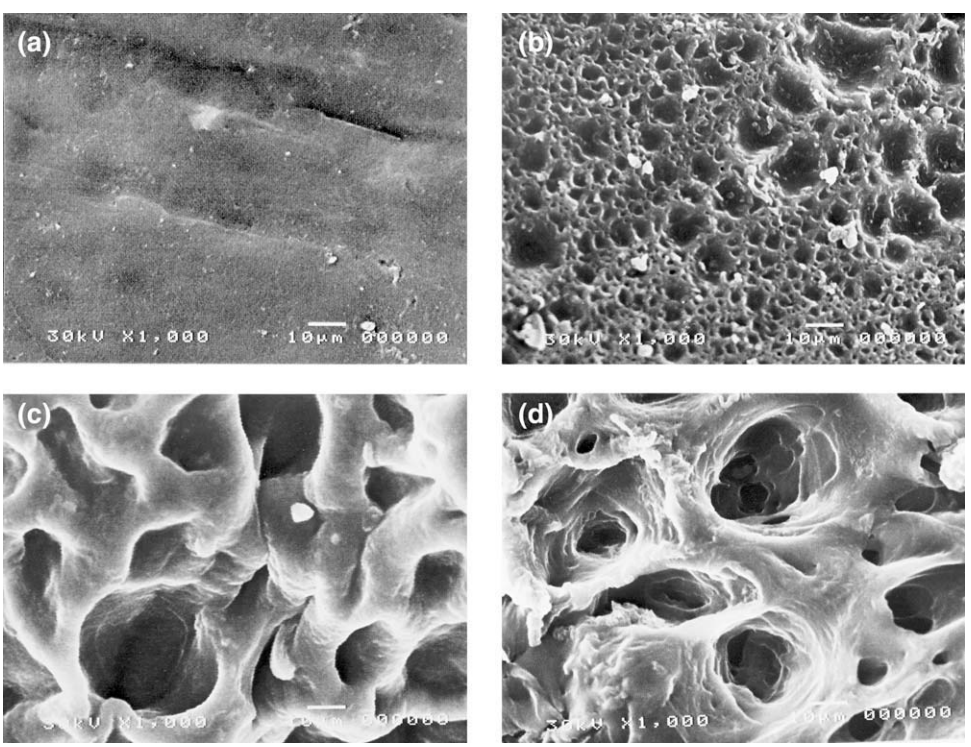

Figure 8 The morphological structure of Gltn/AAc hydrogel of composition (50/50 wt %) swollen; (a) at pH 1, (b) at pH 5, and (c) at pH 7, and (d) of higher PAAc content; (25/75 wt %).

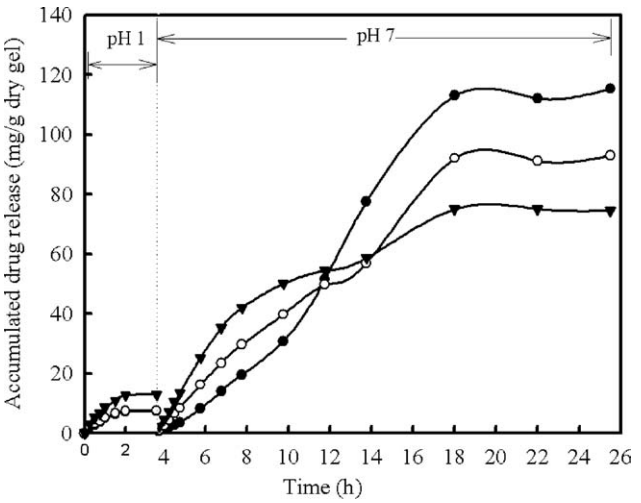

Figure 9 Drug release behavior of Gltn/AAc copolymer hydrogel of different AAc content (wt %) as a function of time at pH 1 and 7. (▼) 25, (○) 50, and (●) 75.

repulsion, followed by higher relaxation of the polymer chains and as a result, higher release of ketoprofen in phosphate buffer (pH 7). However, in the medium pH 1, the H-bonded compacts the gel structure and restricts the movement of polymeric segments within the gel, thus resulting in minimum release.

Effect of preparation dose on the drug release

Figure 10 shows the effect of preparation dose on the Ketoprofen release from Gltn/AAc copolymer hydrogel of composition (25/75) at pH 1 and 7. It can be seen that, as the irradiation dose increase the amount of the released drug decreased and this is may be due to the increase in the crosslinking density between the hydrogel chains which retard the swelling process consequently, the amount of drug released decrease.

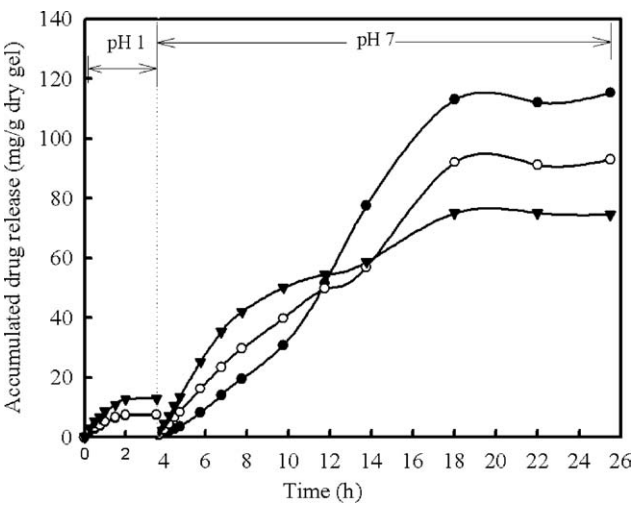

Figure 10 Release profile of ketoprofen as model drug from Gltn/AAc hydrogel of composition (25/75 wt %) prepared at different irradiation dose; (○) 20 and (●) 30 kGy.

CONCLUSIONS

pH-sensitive hydrogels composed of Gltn and AAc were synthesized using γ-radiation as a clean initiator and crosslinker. Swelling kinetics studies show that the hydrogel possess Fickian diffusion in the stomach like medium, i.e., pH 1, where as it possess non-Fickian diffusion in the intestine like medium, i.e., pH 7. Furthermore, diffusion coefficient within Gltn/AAc hydrogels shows high sensitivity to pH as well as the ionic strength of the swelling medium. SEM studies also showed clearly the effect of pH on the topographical structure of Gltn/AAc hydrogels. The aforementioned characteristics recommended the hydrogel to serve as site specific drug carrier.

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