Drug Release Properties of Poly(vinyl pyrrolidone)/Acrylic Acid Copolymer Hydrogels

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ABSTRACT: pH-sensitive hydrogels composed of poly(vinyl pyrrolidone)/acrylic acid (PVP/AAc) were prepared by means of γ-radiation induced graft copolymerization and crosslinking. The effects of pH and ionic strength on the equilibrium of swelling for the prepared hydrogels were investigated. Studying the diffusion's parameters and coefficient as a function of the pH values for the surrounding solution showed drastic changes in the swelling parameters as a result of changing the surrounding solution pH values. To estimate the ability of the prepared copolymer to be used as a colon-specific drug carrier, the release of indomethacin was monitored as a function of time at pH 1 and 7. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 120: 3484–3489, 2011

Key words: pH sensitive; hydrogel; swelling kinetics; drug release

INTRODUCTION

In recent years, pharmaceutical technologies have involved seriously in the development of new drug administration methods as well as the design and application of controlled dosage systems.[1,2] Interest in developing drug delivery systems targeting a specific site required research attention to modulate drug release system for a specific target in human body with time, thus modifying therapeutic requirements began since 1980s.[3,4]

Stimuli responsive hydrogels have received a considerable interest for a variety of biomedical and biotechnological applications because of their general good tissue compatibility and possibility for fabrication. Therefore, pH-responsive hydrogels have been frequently considered as a potential drug delivery system.[5–8]

Poly(vinyl pyrrolidone), PVP, is a well-known hydrophilic water-soluble polymer widely used in biomedical applications because of its low toxicity and high biocompatibility. Therefore it has been selected for designing a regulating drug delivery system suitable for colon treatments, where it releases a proper amount of drug at a suitable timing period in response to the pH-stimuli. However pure PVP is not suitable for such purpose because of its high solubility in water and low response towards pH stimuli. To improve the water resistivity and the responsivity of PVP towards pH stimuli, it has to be treated with the most effective pH responsive monomers, namely acrylic acid (AAc), using γ-irradiation to obtain homogeneous crosslinked copolymer gels suitable for pH sensitive drug delivery system.

Radiation processing has become one of the effective methods for the preparation of functional polymeric materials. The principal advantages of this method are; freedom from toxic impurities such as initiators and crosslinking agents and also involving simultaneous radiation induced sterilization of the produced materials. On exposing to gamma radiations, radicals are generated both on the monomer and polymer in addition to the primary products of water radiolysis; $OH^{\bullet}$ and $H^{\bullet}$ radicals. These macro radicals contribute to chain initiation and crosslinking formation. Such crosslinking process forms chemical bonding between the polymeric chains, which makes such hydrogels insoluble even at elevated temperatures.[9]

EXPERIMENTAL

Materials

The PVP of molecular weight, 14,000, was obtained from Laboratory Rasayan S. D. Fine-Chem. and Acrylic acid, (AAc), from (Aldrich), Indomethacin, kindly provided by Tabuk Pharmaceutical Mfg.,

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Tabuk, KSA. Citric acid, Sodium citrate, Sodium dihydrogen phosphate, and Disodium hydrogen phosphate, analytical reagents, were analytical grade, purchased from Winlab, UK.

Preparation of PVP/AAc copolymer hydrogels

PVP/AAc copolymer hydrogels were obtained by γ-radiation-induced copolymerization, thus PVP/AAc aqueous mixtures of different AAc content; ranged from 20 to 80 wt % and total concentration of 20 wt %, were placed in small glass vials and subjected to ^{60}Co gamma rays at a dose rate 2.03 kGy/h to complete 40 kGy at room temperature. The irradiation facility was constructed by the Faculty of Science, King Saud University, KSA. After irradiation, the obtained samples were cut into disks, washed extensively with water for the removal of soluble monomer and polymer and finally dried in air at room temperature up to constant weight. Insoluble fraction was defined as the gel involving crosslink network structure. Gel fraction was calculated using the following equation:

$$\text{Gel fraction } (\%) = \frac{W_g}{W_f} \times 100$$

where W_g and W_f are the weights of crosslink gels and PVP/AAc in the feed solution, respectively.

Swelling study

The air dried polymer gel samples were swollen in different pH's buffer solutions ranged from 1 to 7 at 37°C. Swelling ratio (S) at different time interval up to equilibrium swelling after 24 h was determined using the following equation:

$$S = \frac{W_s - W_o}{W_o} \times 100$$

where W_s and W_o are the weight of swollen and dry gel respectively.

Preparation of pH buffer solutions

A volume of 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.[10] A volume of 0.2*M* HCl was used to prepare solutions of pH 1.

Microscopic observations

The microstructure of pH-responsive gel was observed with JEOL JXA-733 scanning electron microscope (SEM). Gels were coated with gold before microscopic observation.

Preparation of indomethacin-loaded gel

Gels were immersed in a saturated aqueous solution of indomethacin at room temperature to reach equilibrium, after which the drug loaded gels were dried at room temperature.

Indomethacin release

Gels loaded with indomethacin were subjected to swelling in buffer solutions of pH 1 and 7. First, the drug loaded gels were immersed in a 25 mL of aqueous HCl solution of pH 1 for 3.5 h, and then transferred to a 100 mL of phosphate buffer (pH 7). One milliliter of sample solution was withdrawn at time intervals to follow the release process.

UV-vis spectrophotometer measurements

The released amount of the model drug was measured using Perkin Elemer, Lambda1 UV–vis spectrophotometer in the range from 190–900 nm.

RESULTS AND DISCUSSION

The effect of preparation conditions such as composition and concentration of the feed solutions on the copolymerization of PVP/AAc has been studied by means of the swelling behavior for all prepared copolymer hydrogels possessing almost 100% gelation.

Swelling behavior study

Effect of solution pH

The tailoring of good drug targeting carriers is largely dependent on the response dynamics of the carrier to the change in solution pH. The performance of hydrogels as carriers for drug delivery can be evaluated by studying their swelling behavior at a range of pH values. In this work, the equilibrium swelling behavior of PVP/AAc copolymer hydrogel was investigated as a function of pH. Figure 1 indicates that the prepared copolymer hydrogels possessed a typical pH-sensitive behavior. The pH sensitivity of the studied hydrogels was fully dependent on their composition. It was clear that all the investigated copolymer hydrogels possessed an abrupt change in the swelling degree at pH value around 4, which is the pKa value of AAc.[11] At pH values lower than the pKa value of AAc, the carboxylic groups were completely warped as they were fully associated in forming intermolecular/intramolecular hydrogen bonding, thus a very low degree of swelling was occurring. At pH values

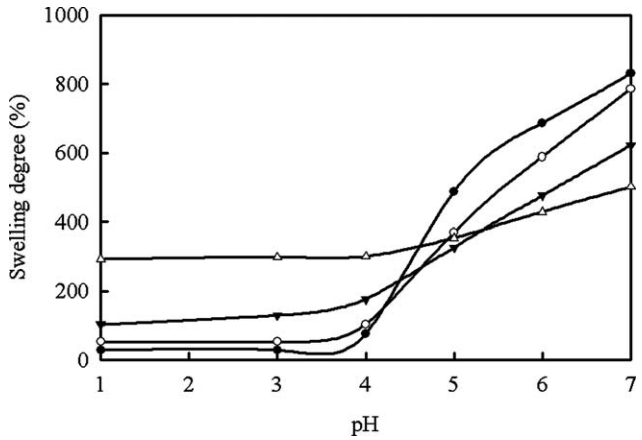

Figure 1 pH dependent swelling of PVP/AAc copolymer hydrogels of different AAc content; (△) 20, (▼) 40, (○) 60, and (●) 80 wt %.

higher than the pKa value of AAc, the swelling degree increases due to the dissociation of the carboxylic groups breaking intermolecular/intramolecular hydrogen bonding. Increasing AAc content in the hydrogel meant more of carboxylate groups and consequently increasing the electrostatic repulsion, which resulted in the expansion of the network structure.

Effect of solution ionic strength

Solution ionic strength is an important factor that may affect the swelling behavior of the hydrogel used as site specific drug carrier and consequently influencing its performance. Figure 2 showed the effect of ionic strength on the swelling equilibrium of the prepared PVP/AAc copolymers of different compositions. It was clear that the swelling equilibrium of the prepared hydrogels was dramatically affected by the change in the solution ionic strength. This work result showed that the swelling equilibrium decreased by increasing the solution ionic strength. Whereas, the copolymer of higher AAc content showed more response towards the ionic strength of the solution. The decrease in the swelling equilibrium, which accompanied the increase in solution ionic strength was due to the electrostatic shielding effect of the counter ion produced from the dissociated carboxylate ions, thus reducing the electrostatic repulsion between these counter ions and consequently decreased the free spaces needed for swelling.[12]

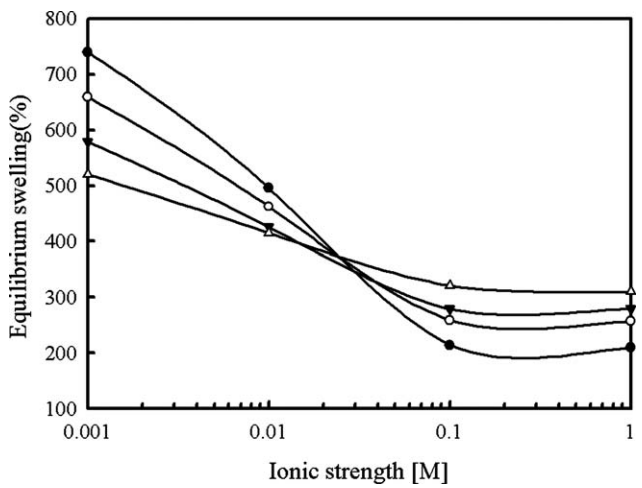

Figure 2 Effect of ionic strength on the equilibrium swelling in water for the prepared PVP/AAc copolymers of different AAc content; (△) 20, (▼) 40, (○) 60, and (●) 80 wt %.

Swelling kinetics

Swelling kinetics of the prepared PVP/AAc copolymer hydrogels were studied as a function of solution pH values. For the determination of the swelling mechanism, both diffusion exponent "*n*" and coefficient "*D*" were obtained from samples swelling in buffer solutions of pH 1 and 7. Typical dynamic swelling curves of PVP/AAc copolymer hydrogel containing 80% AAc at pH 1 and 7 are demonstrated in Figures 3–5. Figure 3 shows the time dependent swelling of PVP/AAc copolymer hydrogel containing 80% AAc at pH 1 and 7. PVP /AAc hydrogel showed a gradual and a very low swelling degree at pH 1, while the opposite occurred at pH 7. After 300 min, the water uptake at buffer solution of pH 7 was about 400 wt %, which was about 16 times higher than those obtained at pH 1 buffer solution. Such behavior could be attributed to the presence of AAc, which acted as a swelling controlling agent. At pH values lower than the pKa of AAc the swelling processes were more restrict due to the formation of

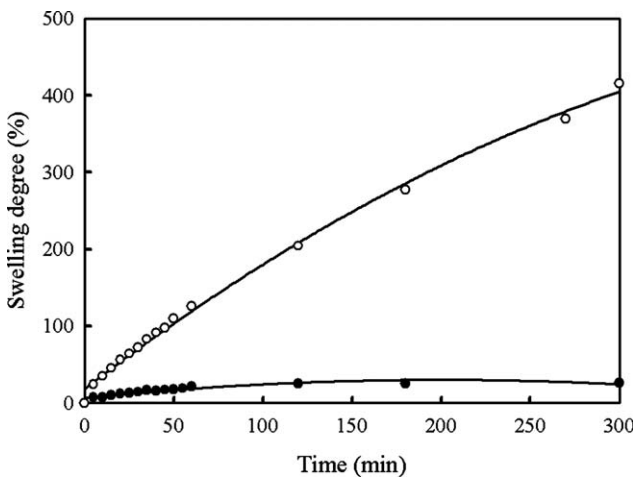

Figure 3 Time dependent swelling of PVP/AAc copolymer hydrogel containing 80% AAc in buffer solutions of (●) pH 1 and (○) pH 7.

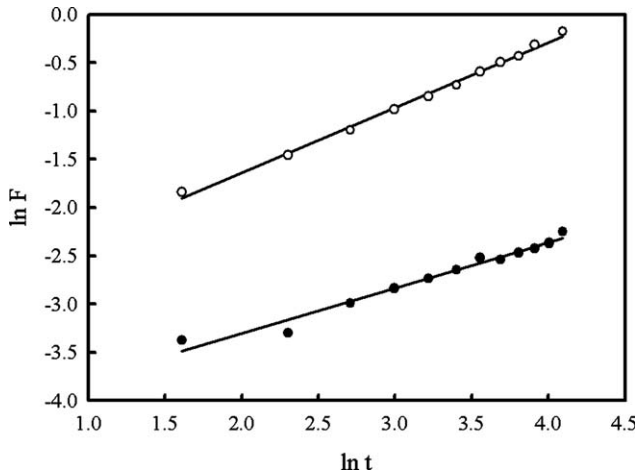

Figure 4 Linear dependence of ln F on ln t of PVP/AAc of AAc content; 80 wt % at (●) pH 1 and (○) pH 7.

hydrogen bonding, which enhanced the crosslinking density of the hydrogel, thus AAc serves as pseudo crosslinker. However, at pH 7 the formed hydrogen bonds were disconnected and the repulsion between the dissociated carboxylate groups increased the water uptake rate.

For most polymeric hydrogels, swelling and drug release could be explained in terms of the simple diffusion for water uptake by the hydrogel, which leads to the dissolution and release of the drug from the polymeric matrix. Fick's law of diffusion and useful approximation are applied to estimate the diffusion type through the polymeric matrix.[13] The following is Fick's law of diffusion.

$$F = M_t/M_\infty = Kt^n$$

where M_t and M_∞ are the amount of drug released or water absorbed at time and equilibrium respectively, K is the release or adsorption constant and n is the swelling or release index.

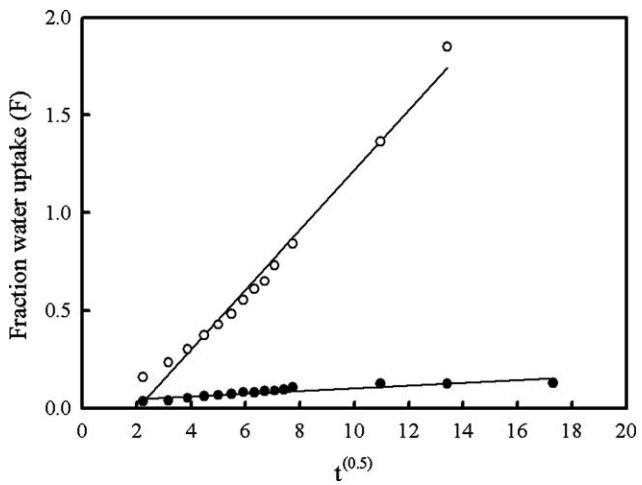

Figure 5 Linear dependence of fraction water uptake (F) against the square root of time ($t^{0.5}$) of PVP/AAc of AAc content; 80 wt % at at (●) pH 1 and (○).

TABLE I
Calculated Values for Swelling Indices of PVP/AAc Hydrogel of Different Compositions in Buffer Solutions of pH 1 and 7

	Diffusion parameters			
	pH 1		pH 7	
AAc content (wt %)	n	r^2	n	r^2
20	0.49	98	0.58	99
40	0.478	98	0.62	99
60	0.448	99	0.67	99
80	0.425	99	0.69	99

The values of K and n are found by fitting the data to the above expression. For nonswollable 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, which is a time dependent mechanism called non-Fickian type of diffusion. Finally for $n = 1$ drug release or water adsorption shows a zero order profile.[14,15]

Swelling indices were calculated to investigate the effect of both copolymer composition and solution pH values on the diffusion type. Figure 4 shows the linear dependence between ln F and ln t for PVP/AAc hydrogel containing 80 wt % AAc. Table I shows that all the PVP/AAc hydrogel samples possessed Fickian type of diffusion at pH 1 whereas they undergo non-Fickian type at pH 7. It also shows that the prepared PVP/AAc hydrogel is a good candidate as a carrier for the drug delivery system.

For controlled diffusion process, the fraction of swelling due to the water uptake (F) can be also expressed by the following equation.[16]

$$F = 4\left(\frac{Dt}{\pi h^2}\right)^{0.5}$$

where D is the diffusion coefficient for the transport of water towards the interior of the hydrogel, h is the dried gel thickness, and t is the time.

This equation is a solution of Fick's second law under simple boundary conditions such as swelling in water and biological fluids or simple geometric forms such as discs, cylinders, and spheres. Diffusion coefficient was determined from the slopes of the initial linear part of the plot of water uptake (F) against the square root of time ($t^{0.5}$) as shown in Figure 5. Table II showed the effect of copolymer composition on the apparent diffusion coefficient (D) at pH 1 and 7. Data showed that, for all

TABLE II
The Apparent Diffusion Coefficient (*D*) of PVP/AAc Copolymer of Different Compositions at pH 1 and 7

AAc content (wt %)	Apparent diffusion coefficient			
	pH 1		pH 7	
	$D \times 10^{-3}$ m^2 min^{-1}	r^2	$D \times 10^{-3}$ m^2 min^{-1}	r^2
20	7.79	95	84.2	98
40	4.85	97	108.8	97
60	4.45	99	148.6	96
80	3.89	99	164.5	96

compositions, the diffusion coefficients for the hydrogels in buffer solution of pH 7 were about 15–50 times higher than that in pH 1. However, at pH 1, diffusion coefficients decreased by increasing AAc, whereas the opposite occurred at pH 7. Such behavior was directly related to the pH dependent association/dissociation behavior of AAc as mentioned in the pH dependent swelling of the prepared hydrogel.

Topography structure of PVP/AAc copolymer hydrogels

SEM images were used to investigate the topography structure of PVP/AAc copolymer hydrogels at pH 1 and 7. Figure 6(a) shows the surface structure of PVP/AAc copolymer hydrogel swollen at pH 1. It can be observed that the sample has a tightly closed surface structure. Whereas, a large pore structure is observed in the same sample after swollen at pH 7, as shown in Figure 6(b). These results confirmed the aforementioned results; as the pH increased the degree of swelling increased resulting in a highly porous gel structure.

Drug release

Indomethacin is a nonsteroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. Indomethacin as model drug, was loaded to the prepared PVP/AAc hydrogels in order to evaluate the possible use of the prepared hydrogels as colon drug delivery system, the drug loaded hydrogels were immersed in a buffer solution of pH 1 for 210 min (mean gastric residence time) after which they were immersed in a buffer solution of pH 7 for 16 h (far in excess for small intestine time) and the amount of drug released was determined.[17] Figure 7 showed the pH sensitive release profiles of indomethacin from PVP/AAc hydrogels of different AAc contents by immersing them for sufficient time in a buffer solution of pH 1 and then in a buffer solution of pH 7. The results showed that there was

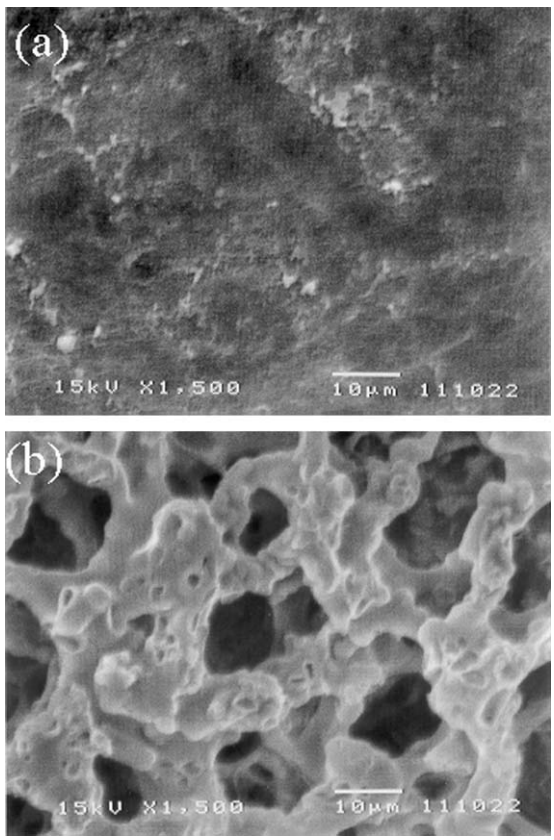

Figure 6 SEM images of surface structure for the PVP/AAc copolymer hydrogel containing 80 wt % AAc swollen at (a) pH 1 and (b) pH 7.

almost no drug release at pH 1, that is, in the stomach simulated media. As the pH values changed from 1 to 7, a drastic increase in drug release was observed. Strong release of Indomethacin was noticed during the first 2 h of immersion time and

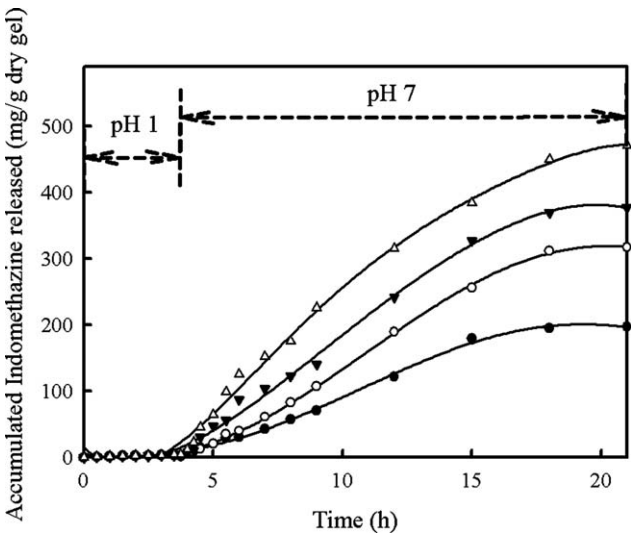

Figure 7 Drug release profile of indomethacin as model drug from PVP/AAc copolymer hydrogel of different AAc content; (△) 20, (▼) 40, (○) 60, and (●) 80 wt %.

the maximum release was achieved after 3 h thereafter tended to level off. Also, it was observed that the amount of drug released from AAc rich hydrogels was higher than those hydrogels containing less amount of AAc. The rate of drug release increased as the swelling increased.

CONCLUSION

pH-sensitive hydrogels composed of PVP and AAc were synthesized using a clean initiator and cross-linker, which is γ-radiation. Swelling kinetics showed that the hydrogel followed Fickian diffusion type in the stomach like medium, that is, pH 1, where as it followed non-Fickian diffusion type in the intestine like medium, that is, pH 7. Furthermore, diffusion coefficient for PVP/AAc hydrogels showed high sensitivity to solution pH values. SEM images showed clearly the effect of pH on the topographical structure of PVP/AAc hydrogels. The aforementioned characteristics recommend the prepared hydrogel to be used as site specific drug carrier for colon.

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