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ORIGINAL PAPER

pH Sensitive hydrogels based on acryl amides and their swelling and diffusion characteristics with drug delivery behavior

K. S. V. Krishna Rao · Chang-Sik Ha

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Abstract pH Sensitive poly(acryl amide-co-2-acrylamido-2-methyl-1-propanesulfonic acid-co-acrylamidoglycolic acid) hydrogels were synthesized by free-radical copolymerization. These hydrogels were prepared with different ratios of monomers and a crossliker. These hydrogels were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, and X-ray diffraction. The diffusional exponent (n) values of synthesized hydrogels were found to be in the range between 0.49 and 0.59, indicating a quasi-Fickian diffusion mechanism with partly chain relaxation controlled diffusion. The hydrogels demonstrated a sharp change in its water absorbency and molecular weight between crosslinks of the network with a change in pH of the swelling media. 5-fluorouracil has been used as a model drug to study the drug release capability of these hydrogels.

Keywords Hydrogel · Acrylamide · pH sensitive · Crosslink · Swelling · Diffusion · Drug delivery

Introduction

Hydrogels are three-dimensional hydrophilic polymer networks that absorb large amount of water or other biological fluids within themselves, though they are not

K. S. V. Krishna Rao (✉) · C.-S. Ha (✉)
Department of Polymer Science and Engineering, Pusan National University,
Busan 609-735, South Korea
e-mail: drksvkrishna@yahoo.com

C.-S. Ha
e-mail: csha@pusan.ac.kr

Present Address:
K. S. V. Krishna Rao
Department of Chemistry, Yogi Vemana University, Vemana Puram, Kadapa 516 003, India

dissolved in water. Due to their high hydrophilicity, lack of toxicity, biocompatibility and similarity to natural tissues, hydrogels have shown many potential applications in the last decade [1, 2]. The water retention of these materials is due to the presence of hydrophilic functional groups, such as –OH, –COOH, $–CONH_2$, –CONH, or $–SO_3H$, along the polymer chains [2]. Stimuli sensitive or 'intelligent' gels have a great potential in pharmaceutical and biomedical applications because they show a sudden or gradual change of swelling properties in response to external stimuli, such as temperature, pH, ionic strength, light, electric and magnetic fields, etc. [3–8]. One of the most powerful applications of hydrogels is in controlled release system for targeting delivery to specific areas of a body. 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 the intimacy and extended duration of contact [9, 10].

A few polymers are already used as carriers or sustained release vehicles, while 'smart' hydrogels that react to disease-specific environmental triggers and/or chemical signals to affect drug release are emerging as components of a new generation of therapeutics [11]. One can improve and control the on-off swelling characteristics of hydrogels by incorporating anionic synthetic monomers or polymers (divinyl ether, maleic anhydride, 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS), poly(ethylene-*co*-maleic anhydride), poly(acrylic acid), poly(maleic anhydride), sulfonated poly(ethylene glycol), dextran sulfate, curdlan sulfate, and pentasan poly sulfate etc.) into the polymeric network [12–21]. In this way, the adsorption of proteins, platelet adhesion, antitumor, antiviral, antibacterial, interferon inducing, antifungal activities, and drug delivery will be enhanced. The anionic synthetic monomers or polymers provide strong electrolyte groups due to their complete dissociation of ionizable groups in an aqueous solution, and produce an electrostatic repulsion force among themselves, thus influencing the expansion of the network. In the present work, we have developed new pH sensitive poly(acryl amide-co-2-acrylamido-2-methyl-1-propanesulfonic acid-co-acrylamidoglycolic acid) hydrogels and studied their swelling and diffusion parameters. We also conducted experiments to reveal whether the resulting gels are capable of being triggered by an environmental stimulus such as pH. We also investigated the delivery behavior of 5-fluorouracil (5-FU), as a model drug, from the hydrogels.

Materials and methods

Analytical reagent grade samples of acrylamide (AAm), acrylamidoglycolic acid (AGA), 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS), N,N′-methylene-bis-acrylamide (MBA), potassium persulfate (KPS) N,N,N′,N′-tetramethylethylene diamine (TEMED), and 5-FU were purchased from Aldrich. All chemicals were used as received and experiments were carried out with double distilled water.

Preparation of hydrogels

AAm, AMPS, and AGA random copolymeric hydrogels were prepared by radical copolymerization. Monomers dissolved in 3.0 mL of distilled water were added to

Table 1 Preparation of poly(AAm-co-AMPS-co-AGA) hydrogels, % equilibrium swelling (ES), encapsulation efficiency (EE) and diffusion parameters (D) in water

Sample code	AAm (g)	AMPS (g)	AGA (wt%)[a]	MBA (mol %)[a] $\times 10^{-4}$	% ES	5-FU % EE	n	k ($\times 10^2$)	D (x 10^5 cm^2 s^{-1})
F1	2.0	0.0	–	6.48	818	33.5	0.525	3.41	10.4
F2	1.8	0.2	–	6.48	1018	35.0	0.517	3.87	12.0
F3	1.8	0.2	5	6.48	1503	35.5	0.515	4.58	14.1
F4	1.8	0.2	10	6.48	1849	38.3	0.510	4.58	15.6
F5	1.8	0.2	10	3.24	2803	44.4	0.592	2.55	17.8
F6	1.8	0.2	10	12.96	1450	36.7	0.497	4.75	14.7

For detailed explanation of parameters, see Eqs. (2)–(7)

[a] Based on unit amounts of AAm

the mixture of 1.0 mL of crosslinking agent (MBA, 1 wt% aqueous solution), 1.0 mL of potassium persulfate (5 wt% aqueous solution) and 1.0 mL of the accelerator (TEMED, 1 wt% aqueous solution). Polymerization was carried out in petri dishes maintained at 45 °C until polymerization was complete. After the reaction, hydrogels obtained were cut into disks of 1.5 mm diameter, washed with water to remove any unreacted reagents and vacuum dried until attainment of constant weight. The complete conversion of monomers was confirmed gravimetrically. Table 1 summarizes poly(AAm-co-AMPS-co-AGA) hydrogels prepared for this work.

Swelling experiments

The % swelling ratio (% SR) and the % equilibrium swelling (% ES) were calculated as:

$$\% \text{ SR} = \left(\frac{m_t - m_d}{m_d}\right) \times 100 \tag{1}$$

$$\%\text{ES} = \left(\frac{m_\infty - m_d}{m_d}\right) \times 100 \tag{2}$$

where m_t and m_d are weights of swollen hydrogels for a given time and dried hydrogels, respectively. Here, m_∞ is the weight of equilibrium swollen hydrogels. Dynamic and equilibrium swelling experiments on hydrogels of this study have been performed in distilled water and different pH solutions (1.0, 4.0, 7.2, and 10.0) at 30 °C (±0.5 °C) using an electronically controlled oven (WTB Binder, Model BD-53, Tuttilgen, Germany). Circularly cut (diameter = 0.3 cm) disk-shaped hydrogel samples were stored in a desiccator over anhydrous calcium chloride maintained at 30 °C for about 24 h before use. Initial weight of the hydrogel was taken over a single-pan digital microbalance (Mettler, Model AE240, Greifensee, Switzerland) sensitive to ±0.01 mg. Hydrogels were placed in air-tight test bottles containing 50 mL of distilled water. Test bottles were then placed in an oven maintained at the desired constant temperature. Weight of the samples was determined at the pre-selected time intervals by removing the samples from the test bottles, gently wiping

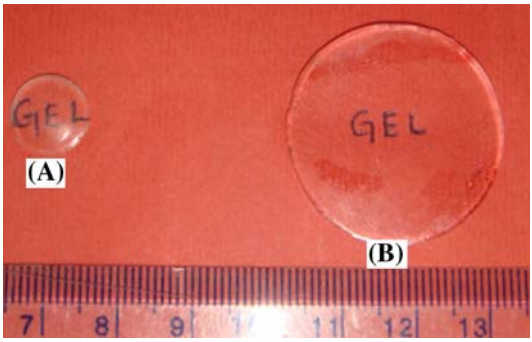

Fig. 1 Photographs of poly(AAm-co-AMPS-co-AGA) hydrogels in dried (**a**) and swollen (**b**) state

the liquid droplets adhered to the surface by pressing them in between tissue paper wraps, and again placing them into the oven. In order to minimize solvent evaporation losses, this step was completed in a short time period, say, within 15–20 s. The photographs of the dried and swollen hydrogels are displayed in Fig. 1.

Diffusion coefficient (D) was computed from swelling results using the Eq. (3).

$$D = \pi\left(\frac{h\theta}{4Q_\infty}\right)^2 \tag{3}$$

where θ is the slope of the linear portion of the swelling curve before attainment of 60% equilibrium and h is the initial disk thickness [22].

Weight gain, Q_∞ of the soaked hydrogel at equilibrium is expressed in mole percent units (i.e., number of moles of solvent sorbed by 100 g of the polymer), which is calculated as (4);

$$Q_\infty = \left(\frac{m_\infty - m_i}{m_i}\right)\frac{100}{M_s} \tag{4}$$

where $m_\infty$and m_i are, respectively, weight gains at equilibrium time and initial weight; M_s is the molecular weight of the sorbed liquid [23].

Loading of 5-fluorouracil in the copolymeric networks and encapsulation efficiency

5-Fluorouracil was loaded into networks by a swelling equilibrium method. The hydrogels were allowed to swell in the drug solution of known concentration for 24 h at 37 °C. The solubility of 5-FU in water is very low (13 mg/mL). However, the solubility of its sodium salt increases to 65 mg/mL [24]. In order to load the maximum drug into the polymeric network, gel disks were immersed in a 5-FU aqueous solution, which was neutralized with NaOH. During this process, drug in the solvent was adsorbed onto the hydrogels.

The loading efficiency of 5-FU in the hydrogels was determined spectrophotometrically. The drug-loaded hydrogel disk was placed in 20 mL of buffer solution and stirred vigorously for 48 h to extract drug from the hydrogels. The solution was filtered and assayed by UV spectrophotometer (model Anthelie, Secomam, Dumont,

France) at fixed λ_{max} value of 270 nm. The results of % drug loading and encapsulation efficiency (EE) were calculated using Eqs. (5) and (6), respectively. These data are compiled in Table 1.

$$\%\ \text{Drug loading} = \left(\frac{\text{Weight of drug in hydrogel}}{\text{Weight of hydrogel}}\right) \times 100 \tag{5}$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) \times 100 \tag{6}$$

In vitro release study

Dissolution was carried out using the fully automated dissolution system (Logan System 888J, NJ, USA) equipped with six baskets. Dissolution rates were measured at 37 °C under 100 rpm speed. Drug release from the hydrogels was studied in pH 7.4 and 1.0. Aliquot samples were withdrawn at regular time intervals and analyzed by UV spectrophotometer at fixed λ_{max} value of 270 nm.

Characterization

Fourier transform infrared spectroscopy (Nicolet, Impact 410) analysis was performed to identify the chemical structure of the hydrogels. Furthermore, to investigate the drug nature in the hydrogel matrix, DSC (Model-DSC SP, UK) analysis was preformed for 5-FU, 5-FU loaded hydrogel, and pristine hydrogel. The measurement conditions were with a scanning rate of 10 °C/min and nitrogen gas flow rate of 50 mL/min. To support this DSC study, XRD analysis was performed with General Area Detector Diffraction System (Philips, X'pert-PW3040) using Cu Kα radiation.

Results and discussion

FTIR analysis

Representative FTIR spectrum of a hydrogel is presented in Fig. 2. Two peaks around 1,663 and 1,608 cm^{-1} are due to amide-I and amide-II of acrylamide units. C–N and C–H stretching bands appear at 1,440 and 2,922 cm^{-1}, respectively, further confirming the presence of amide groups. A broad band observed between 3,600 and 3,000 cm^{-1} is due to the overlapping of the O–H stretching bands of carboxylic acid and O–H group of alcohol of AGA and N–H of the amide groups. Moreover, a band is observed at 1,694 cm^{-1} as well as at 1,641 cm^{-1} due to the presence of COO^- of AGA in the spectrum of poly(Am-co-AMPS-co-AGA) hydrogel.

AMPS characteristic peaks are observed at 1,420 cm^{-1} (w) and 1,285 cm^{-1} (m) for anti-symmetric and symmetric S–O group, respectively. Additional characteristic absorption bands of monomers appear at 1,449 and 1,301 cm^{-1} due to C–C multiple bond stretching and C–H bending vibrations, respectively. Thus the FTIR spectrum confirms the presence of three repeating units, that is, AAm, AGA, and AMPS in the copolymer structure.

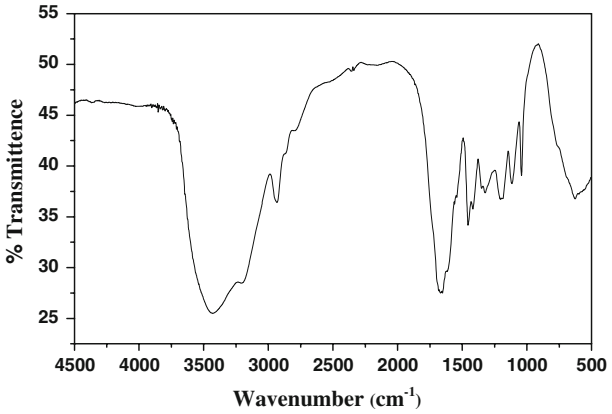

Fig. 2 FTIR spectrum of poly(AAm-co-AMPS-co-AGA) hydrogel

Differential scanning calorimetry

DSC thermograms of pristine hydrogel, 5-FU-loaded hydrogels, and pure 5-FU are displayed in Fig. 3. 5-FU shows a sharp peak at 285.16 °C due to polymorphism and melting, but in case of 5-FU-loaded hydrogels, no characteristic peak was observed at 285.16 °C, suggesting that 5-FU is molecularly dispersed in the hydrogel network.

X-ray diffraction studies

XRD studies help to find the crystallinity of drug in the hydrogels. The most intensive peaks of 5-FU are observed at 2θ of 29° and 32°, suggesting its crystalline nature. But, these peaks are found in 5-FU loaded hydrogel with very less intense,

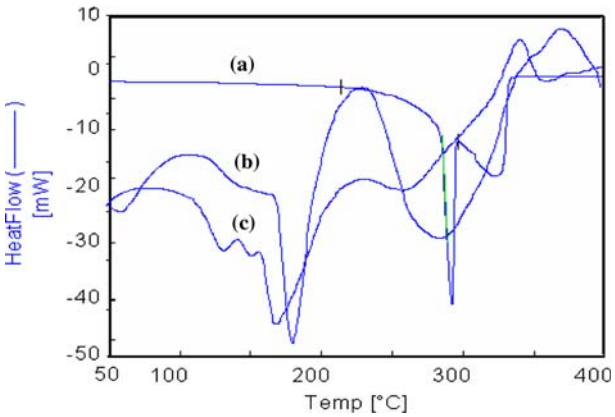

Fig. 3 DSC thermograms of pure 5-FU (**a**), 5-FU loaded poly(AAm-co-AMPS-co-AGA) hydrogels (**b**), and placebo poly(AAm-co-AMPS-co-AGA) hydrogels (**c**)

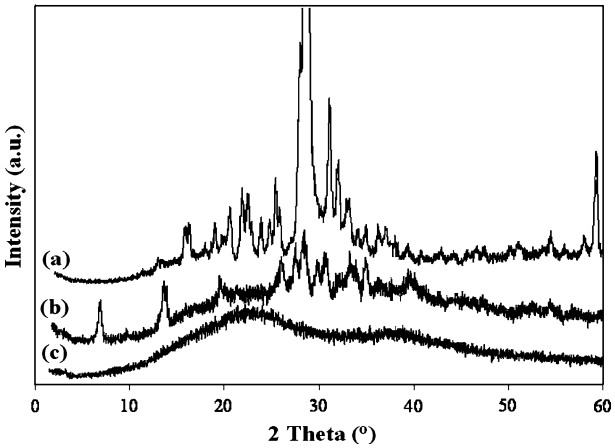

Fig. 4 XRD patterns of pure 5-FU (**a**), 5-FU loaded poly(AAm-co-AMPS-co-AGA) hydrogels (**b**), and placebo poly(AAm-co-AMPS-co-AGA) hydrogels (**c**)

indicating that the drug is dispersed at the molecular level in the polymer matrix. These XRD curves are displayed in Fig. 4.

Swelling kinetics

The swelling kinetic curves of the hydrogels with different AMPS, AGA, and MBA content are shown in Fig. 5. The data shows that the swelling rate increased with increasing amount of anionic moiety in the hydrogel network and decreased with increasing MBA content from 3.24×10^{-4} to 12.96×10^{-4} mol %. The hydrogel with 3.24×10^{-4} mol % of MBA has the swelling ratio about 674% within 1 h and 2,344% within 5 h, whereas the hydrogel with 12.96×10^{-4} mol % of MBA has about 349 and 1,247%, respectively, within the same time frames. Before the swelling in the dry hydrogel, there are strong intermolecular interactions, such as hydrogen bondings and hydrophobic interactions, which remain in a glassy state [25]. This suggests that a glassy inner core might exist in the dry hydrogel having a higher crosslinking level because the high crosslinking may lead to such strong interactions.

To understand the water retention of the poly(AAm-co-AMPS-co-AGA) hydrogels synthesized by the redox free-radical polymerization with MBA crosslinker, the water-retention properties of the copolymers were carried out by deswelling experiments at room temperature. The deswelling curves of the poly(AAm-co-AMPS-co-AGA) copolymers are illustrated in Fig. 6. Equal weights of swollen copolymer gels were taken in a watch glass, and the weight loss of water of the swollen gels was estimated by gravimetric analysis at different time intervals. The deswelling studies indicated that the less crosslinked hydrogels had higher losses of water content at the initial stage of the deswelling experiment. This kind of gel deswelling or collapse has been ascribed to the formation of an ion-cluster, and the dependence on the solvent polarity and the polymer charge density has been

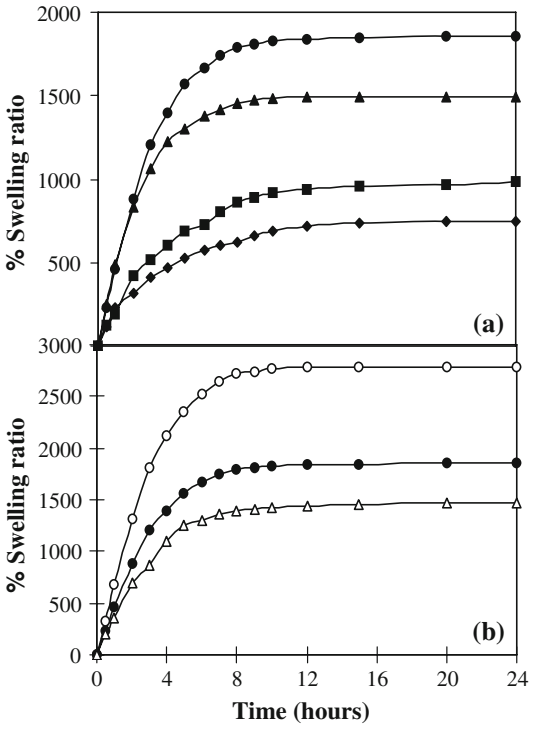

Fig. 5 % Swelling ratio of different hydrogels in water with various amounts of monomers (AMPS and AGA) (**a**) (*filled diamond*) F1, (*filled square*) F2, (*filled triangle*) F3, (*filled circle*) F4; and various amounts of MBA (**b**) (*filled circle*)F4, (*open circle*) F5, (*open triangle*) F6

theoretically predicted [26]. From these results, we concluded that the deswelling rates were slower and water retention capacity was higher for the hydrogel crosslinked by higher contents of MBA.

To determine the nature of water diffusion into hydrogels, initial swelling data were fitted to the following exponential equation [27]:

$$\frac{m_t}{m_\infty} = kt^n \tag{7}$$

where m_t and m_∞ represent the amount of water absorbed by the hydrogel at time t and at equilibrium, k is a characteristic constant of the hydrogel, and n is a characteristic exponent of the mode of transport of the penetrate. These results are shown in Table 1. For the first case, $n = 0.5$, corresponding to a Fickian diffusion, the rate of diffusion is much slower than the rate of relaxation. For the second case, $n = 1$, the diffusion is very fast, contrary to the rate of relaxation, and the third case corresponds to an anomalous diffusion (or non-Fickian diffusion) with n values lying between 0.5 and 1. A slight variation of the diffusion exponent with MBA content is observed, but mostly n is close to 0.5 though they are not exactly equal to 0.5. It can be said that the overall process is quasi-Fickian diffusion with partly anomalous behavior, that is, chain relaxation controlled process. The trace of the anomalous behavior may be due to the regularity of the chain and strong interchain interactions via the formation of hydrogen bonding, leading to a compact structure

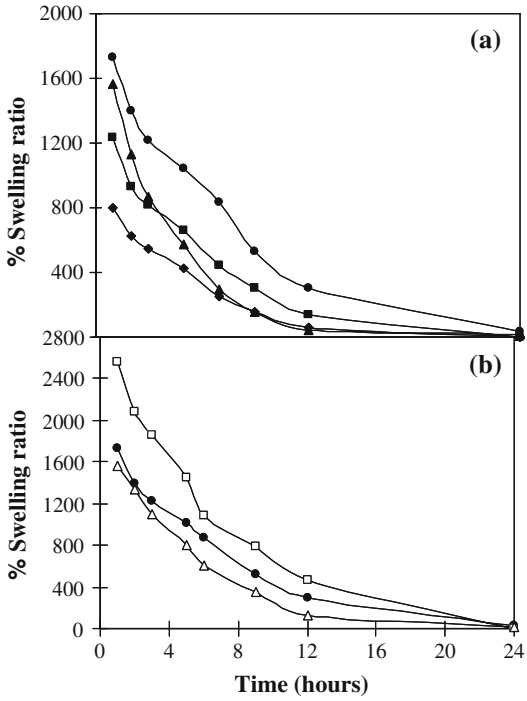

Fig. 6 % Deswelling ratio of different hydrogels in water with various amounts of monomers (AMPS and AGA) (**a**) (*filled diamond*) F1, (*filled square*) F2, (*filled triangle*) F3, (*filled circle*) F4; and various amounts of MBA (**b**): (*filled circle*) F4, (*open circle*) F5, (*open triangle*) F6

that would accentuate the anomalous aspects of diffusion even for a molecule as small as water.

Effect of pH and ionic strength

Hydrogels, due to pH sensitivity, play a significant role in controlled oral drug delivery systems. These hydrogels can be prepared by the incorporation of weakly acidic monomers that have the functionalities such as sulfonic and carboxylic acids. While those kinds of delivery systems show low swelling degree in acidic medium of the stomach, their swelling degree increases as they passes down the gastrointestinal tract due to an increase in the pH. Thus, a pH-sensitive drug delivery system protects the drug from the acidity of the stomach and releases the drug in the small intestine or colon depending upon the composition of the hydrogel. In this study, the effect of pH on the swelling behavior of the poly(AAm-co-AMPS-co-AGA) hydrogel was investigated by varying the pH of the swelling medium in the range of 1.0–10.0. Dynamic swelling results were depicted in Fig. 7, which reveals that the swelling percent increases as a function of pH for F4. As can be seen from Fig. 7a, there was a considerable change in the dynamic swelling curves between pH 1 and 10. In particular, there existed a noticeable increase in the equilibrium swelling value of F4 when the pH of the swelling medium was increased from 4.0 to 7.2. This is because the ionization of the polymeric networks containing carboxylic acid groups takes place as the pH of the external medium increases [28]. In addition, sodium carboxylate in the polymeric backbone dissociates at this pH value and electrostatic

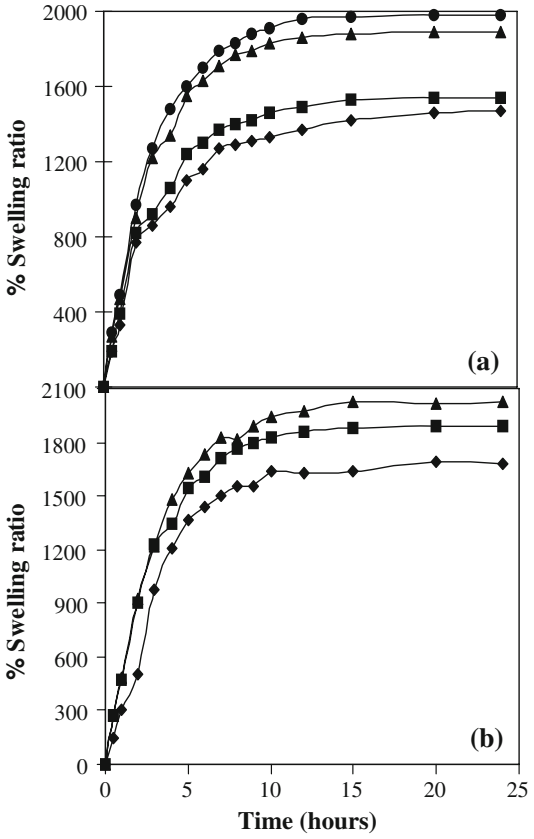

Fig. 7 % Swelling ratio of F4 in **a** different pHs: (*filled diamond*) 1.0, (*filled square*) 4.0, (*filled triangle*) 7.2, (*filled circle*) 10.0 at $I = 0.10$ M and **b** different ionic strength in (*filled triangle*) $I = 0.05$ M, (*filled square*) $I = 0.10$ M, (*filled diamond*) $I = 0.15$ M in pH = 7.4

repulsion among the similarly charged $-COO^-$ groups and osmotic pressure inside the hydrogel increase, resulting in the sharp increase in the swelling degree of the hydrogel. The rapid increase in the equilibrium swelling continued until the pH of the swelling medium reached to 7.2. However, beyond this pH value, this effect was not significant since it reached an equilibrium state. These results proved the pH-sensitivity of the prepared hydrogel (F4).

Swelling properties of F4 was investigated as a function of time in three different pH 7.4 solutions with ionic strengths of 0.05–0.15 M. Figure 7b demonstrates that as the ionic strength increased from 0.05 to 0.15 M, the swelling percent of the hydrogels decreased because the difference in the concentration of mobile ions between the hydrogel and the solution was reduced. As a result of this, osmotic swelling pressure was reduced, resulting in lower swelling percent values. According to the Donnan osmotic pressure equilibrium, an increase in the concentration of the movable counter ions of a solution leads to a decrease in the osmotic pressure within the hydrogel, causing the hydrogel to shrink [28, 29]. As far as swelling results are concerned, it can be concluded that the swelling behaviors of the prepared hydrogels are mainly dependent upon the ionic strength of the swelling medium.

Network parameters

The molecular mass between crosslinks (M_c) is one of the basic structural parameters of crosslinked polymeric networks that controls the volume phase transition temperature and mechanical properties of the hydrogels. It is well known that with increasing level of crosslinking, the M_c of the hydrogel would be decreased, and the pore density in the network would be increased. In this study, the experimental M_c values were calculated from equilibrium swelling ratios of the hydrogels by using the following equation based on the phantom network model [30, 31]:

$$\overline{M_c}(Exp) = -\frac{\left(1-\frac{2}{\phi}\right)V_1\rho_2(v_{2r})^{\frac{2}{3}}(v_{2m})^{\frac{1}{3}}}{\mathrm{In}(1-v_{2m})+v_{2m}+\chi v_{2m}^2} \tag{8}$$

where Φ is the functionality of the crosslinks ($\Phi = 4$), V_1 is the molar volume of the solvent (18 mL/mol), v_{2r} is the volume fraction of the polymer network after preparation, v_{2m} is the volume fraction of the polymer network in the swollen gel at the equilibrium state, and χ is the polymer-solvent interaction parameter. The v_{2r} and v_{2m} values were calculated from the following expression, which is valid at swelling equilibrium.

$$v_{2r} = \left[1+\frac{\left(\frac{m_r}{m_d}-1\right)\rho_2}{\rho_1}\right]^{-1} \tag{9}$$

$$v_{2m} = \left[1+\frac{\left(\frac{m_s}{m_d}-1\right)\rho_2}{\rho_1}\right]^{-1} \tag{10}$$

where m_r is the weight of the hydrogel after preparation, m_s is the weight of the hydrogel at equilibrium, and m_d is the weight of the hydrogel after drying, ρ_1 and ρ_2 are densities of the polymer network and solvent, respectively.

The χ parameters of the hydrogels can be obtained experimentally via the following expression [32]:

$$\chi = \frac{1}{2}+\frac{v_{2m}}{3} \tag{11}$$

The M_c values of hydrogels collected in Table 2 indicated that the values of M_c increased with decreasing volume fraction of the swollen hydrogel. This is due to the presence of the ionizable groups (i.e., –COOH and $–SO_3H$) in the hydrogel matrix at constant crosslinking ratio. Similar nature was also observed in case of increased crosslinker ratio.

Drug delivery

To investigate the release behavior of a model drug from poly(AAm-co-AMPS-co-AGA) hydrogels, 5-FU was incorporated into the hydrogels by soaking the dried

Table 2 The characteristic data of hydrogels related to the crosslinking density using Eqs. (8)-(11)

Sample codes	V_{2m} ($\times 10^2$)	χ	Mc (g mol^{-1})
F1	9.64	0.529	355
F2	9.34	0.528	211
F3	6.12	0.519	1,215
F4	4.19	0.514	1,981
F5	3.05	0.510	4,076
F6	4.78	0.515	1,426

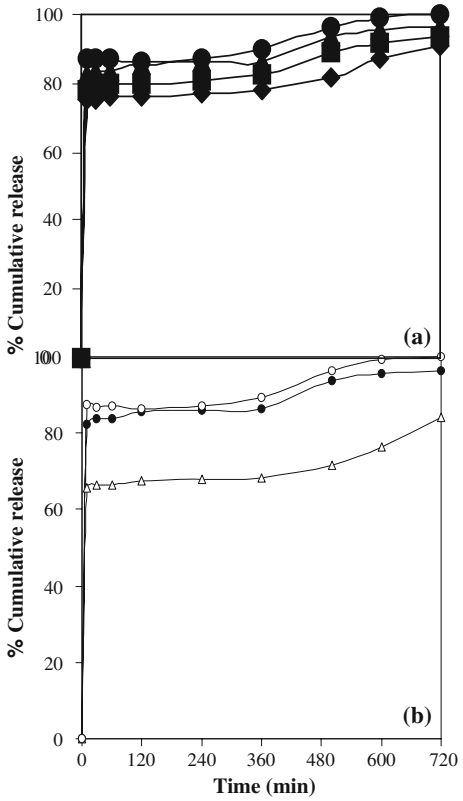

Fig. 8 % Cumulative release of 5-FU from hydrogels with various amounts of monomers (AMPS and AGA) (**a**) (*filled diamond*) F1, (*filled square*) F2, (*filled triangle*) F3, (*filled circle*) F4; and various amounts of MBA (**b**): (*filled circle*) F4, (*filled circle*) F5, (*open triangle*) F6

hydrogels in a 5-FU saturated solution. As the dried hydrogels absorbed water, the 5-FU was transported with water due to the concentration gradient of 5-FU between the outside and the inside of the hydrogel. The encapsulation efficiencies of 5-FU in poly(AAm-co-AMPS-co-AGA) hydrogels are in the range between 33.5 and 44.4%. The in vitro drug-release studies were performed in pH 7.4 buffer media up to 12 h and, hence, the present hydrogel developed is appropriate for the controlled release of 5-FU over an extended period of time up to 12 h. Figure 8 displays the release profiles of hydrogels cross-linked with different amounts of MBA containing 5-FU in pH 7.4 media prepared with AAm/AMPS/AGA copolymer. The % cumulative

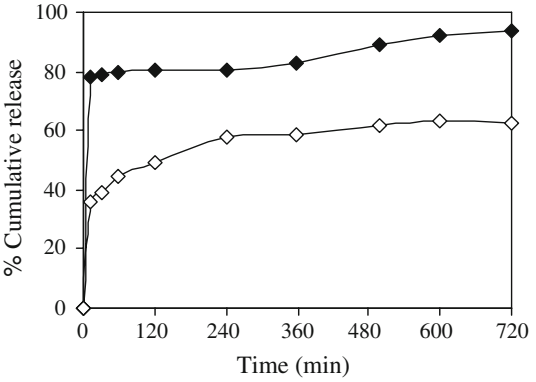

Fig. 9 % Cumulative release of 5-FU from F4 at two different pH: (*open diamond*) 1. 0 and (*filled diamond*) 7.4

release for the hydrogels cross-linked with 12.96×10^{-4} mol % of MBA is lower, while intermediate values were observed for 6.48×10^{-4} mol % containing MBA microgels due to a decrease in matrix swelling as a result of increased MBA content of hydrogels. However, drug release from hydrogels is attributed to three types of mechanisms: (1) release from the surface of hydrogel particles, (2) diffusion through the swollen rubbery matrix and (3) release due to hydrogel erosion in the external environment. Initially, higher release rates were observed due to the dissolution of the surface-adhered 5-FU. At longer times, the drug release is controlled by diffusion rather than erosion of the matrix, so it becomes much slower when compared to the initial release rates. Of all the formulations developed, formulation F4 and F5 exhibited 100% release of 5-FU within 12 h compared to other formulations. In Fig. 9, the poly(AAm-co-AMPS-co-AGA) hydrogels showed a pH-sensitive release behavior. At low pH (1.0) small amounts of 5-FU were released from the hydrogels while at high pH (7.4) relatively large amounts of 5-FU were released from the hydrogels. This pH-sensitive behavior of hydrogels indicates that the hydrogels can be used as a biological on–off switch for an intelligent drug delivery system triggered by the external pH change in a body. In addition, the poly(AAm-co-AMPS-co-AGA) hydrogels released most of the 5-FU within about 30 min, which means the hydrogels can release solute such as drugs and biologically active materials inside the hydrogels for a short period and fastly release the solute from the hydrogels in response to an increase in the external pH above the pKa of the hydrogel.

Conclusion

pH-Sensitive poly(AAm-co-AMPS-co-AGA) hydrogels having various compositions of AMPS, AGA and crosslinker, MBA, were prepared by free-radical polymerization. The produced hydrogels were characterized in terms of equilibrium swelling, average molecular weights between crosslinks, and diffusion/swelling characteristics. It is seen that the swelling of the hydrogels increased with increasing AMPS and AGA concentrations, but decreased with the crosslinker concentration.

The diffusion type of hydrogel systems was of a quasi-Fickian diffusion character with partly chain relaxation controlled process. As the hydrogels contained ionizable functional groups, their swelling behavior was essentially dependent on pH, leading to a typical pH-sensitive swelling behavior of anionic hydrogels, i.e., low swelling ratios at low pH and high swelling ratios at high pH. These results indicate that the poly(Am-co-AMPS-co-AGA) hydrogels can be used as a biological on–off switch with which the release of materials from the hydrogel can be controlled by the external pH change and pKa of the hydrogels. In addition, the pKa determining the on–off switch can be tailored by changing the type or composition of monomers and crosslinkers used to prepare the hydrogels.

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