Swelling and Drug Release Profile of Poly(2-ethyl-2-oxazoline)-Based Hydrogels Prepared by Gamma Radiation-Induced Copolymerization

A. El-Hag Ali,[1,2] A. S. AlArifi[1]

[1]*Chemistry Dept., Faculty of Science, King Saud University, Riyadh 11451, Kingdom of Saudi Arabia*
[2]*Polymer Chemistry Dept., National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt*

Received 10 April 2010; accepted 30 September 2010
DOI 10.1002/app.33480
Published online 12 January 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: Poly(2-ethyl-2-oxazoline) and acrylic acid were copolymerized in different compositions using γ-rays-induced polymerization and cross-linking to obtain a series of pH-sensitive hydrogels. The preparation parameters that may affect the copolymerization process such as the feed solution composition and irradiation dose were optimized. Swelling characteristics of the obtained polymeric hydrogels were evaluated. The results show the significant effects of the hydrogel composition, soaking time, and pH on the swelling equilibrium. The diffusion parameters obtained at pH 1 and 7 show the possibility of using the prepared hydrogels in the field of colon-specific drug delivery systems. Ibuprofen as a model drug was loaded into (poly(2-ethyl-2-oxazoline)/acrylic acid) copolymer hydrogel to investigate their drug release behavior at different pH values. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 120: 3071–3077, 2011

Key words: pH-sensitive; poly(2-ethyl-2-oxazoline); acrylic acid; hydrogel; γ-irradiation; swelling kinetics; drug release

INTRODUCTION

The increasing number of peptide and protein drugs being investigated demands the development of dosage forms that exhibit site-specific release. Delivery of drugs into systemic circulation through colonic absorption represents a novel mode of introducing peptide and protein drug molecules and drugs that are poorly absorbed from the upper gastrointestinal (GI) tract, destroyed or inactivated in acidic environment of the stomach or by pancreatic enzymes in the small intestine.[1–3] Oral colon-specific drug delivery systems offer obvious advantages over parenteral administration. Generally, each colon-specific drug delivery system has been designed based on one of the following mechanisms with varying degrees of success: (1) prodrugs, (2) pH-sensitive polymer coating, (3) time-controlled dissolution, and (4) microflora-activated drug release.[4,5]

Drug delivery technology can be brought to the next level by the fabrication of smart materials into a single assembled device that is responsive to the individual patient's therapeutic requirements and able to deliver a certain amount of drug in response to a biological state. The concept of using pH as a trigger to release a drug in the colon is based on the pH conditions that vary continuously down the GI tract.[6,7]

Hydrogels are water-swollen network of hydrophilic homopolymers or copolymers; it is interesting that they exhibit both liquid-like and solid-like properties. The liquid-like properties result from the fact that its major constituent is water. However, the polymer exhibits solid-like properties because of the network structure formed by cross-linking. Polymers containing ionizable functional groups that respond to change in pH are called pH-sensitive polymers. By generating the charge along the polymer backbone, the electrostatic repulsion results in an increase in the hydrodynamic volume of the polymer.

Poly(2-ethyl-2-oxazoline) (PEOz) is a tertiary amide polymer, which belongs to the group of polymers known as poly(oxazolines). PEOz has been shown to be a pH-sensitive, low cytotoxic polymer with favorable pKa value near neutral pH.[8,9] Poly(oxazolines) are useful in a variety of applications, including steric stabilizers and biocompatible materials for drug delivery.[10–12] On the other hand, acrylic acid (AAc) is a pH-sensitive monomer bearing carboxylic acid groups, which possess insensitive character to the acidic medium and allow swelling at pH values higher than their pKa value.

Correspondence to: A. El-Hag Ali (Elhagali_a@hotmail.com).

Contract grant sponsor: Sabic Research Grant; contract grant number: SCI-30-9.

The objective of this study was to develop an intelligent polymeric hydrogel for drug protection, self-regulated release, and targeted unidirectional release using PEOz and AAc. γ-rays-induced copolymerization and cross-linking was used to prepare PEOz/AAc copolymer hydrogels of different compositions. The parameters affecting the copolymerization process such as feed solution composition and concentration and irradiation dose were optimized. The prepared hydrogels were characterized by investigating their swelling characteristics. The ability of the prepared hydrogels to perform as a pH-sensitive drug carrier for colon-specific drug delivery system was evaluated using ibuprofen as a model drug.

EXPERIMENTAL

Materials

AAc of 99.9% purity and PEOz, purchased from Aldrich (Germany), were used as received. Ibuprofen, pharmaceutical grade, was kindly provided by Tabuk Pharmaceutical Mfg. Co., Tabuk, KSA. Citric acid, sodium citrate, sodium dihydrogen phosphate, disodium hydrogen phosphate, and analytical reagents of analytical grade were purchased from Winlab, UK.

Preparation of PEOz/AAc hydrogels

PEOz/AAc hydrogels were obtained by γ-radiation-induced homo/copolymerization of mixtures of different compositions in glass vials. The ^{60}Co gamma radiation source used was Nordion 2.2, at a dose rate of 10 kGy/h. The irradiation facilities are established by King Abdualziz City for Science and Technology. All samples were cut into disks, washed in excess water to remove the unreacted component, and 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_0). 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 hydrogels was determined from the following equation:

$$\text{Gel\%} = \frac{W_d}{W_o} \times 100$$

where W_d and W_0 are dry hydrogel weights after and before extraction, respectively.

Preparation of buffer solutions of different pH's

Citric acid/trisodium citrate and sodium dihydrogen phosphate/disodium hydrogen phosphate were used to prepare buffer solutions of pH ranging from 3 to 5 and 6–7, respectively.[13] HCl was used to prepare solutions of pH 1.

Swelling study

Dynamic swelling experiments were performed in buffer solutions of different pH at 37°C ± 0.2°C. Swollen gels removed from the swelling medium at regular intervals were dried superficially with filter paper, weighed, and placed in the same bath. The measurements were continued until a constant weight was reached for each sample. The amount of solution absorbed was monitored gravimetrically. The degree of swelling (S%) was calculated using the following equation:

$$\text{S\%} = \frac{(W_s - W_0)}{W_0} \times 100$$

where W_0 and W_s are the weights of the dried gel at time 0 and of the hydrogel swollen at different buffer solutions, respectively.

Preparation of drug-loaded hydrogel

For the investigation of drug-release behavior of PEOz/AAc hydrogels prepared in this study, ibuprofen was used as the model drug. Ibuprofen is an effective nonsteroidal anti-inflammatory drug. It is a core medicine in the World Health Organization's Essential Drugs List, which is a list of minimum medical needs for a basic health care system.[14] PEOz/AAc dry gels of different compositions were immersed in saturated aqueous solution of ibuprofen at room temperature until equilibrium, and the drug-loaded gels were dried at room temperature.

Drug release experiments

The drug release experiments were performed by placing the drug-loaded hydrogel in 25 mL of a pH 1 solution for 3.5 h and then in 250 mL of a pH 7 buffer solution. The buffer solution was stirred constantly. To follow the release of the drug, aliquots were drawn from the solution at various times, and the absorption at 272 nm was measured using a UV spectrophotometer (Perkin–Elmer Lmbda1 UV–vis spectrophotometer; Waltham, MA). The concentration of the drug in the external solution at any selected time (M_t) was calculated from the corresponding calibration curve of the absorption against drug concentration. From this value, the amount of

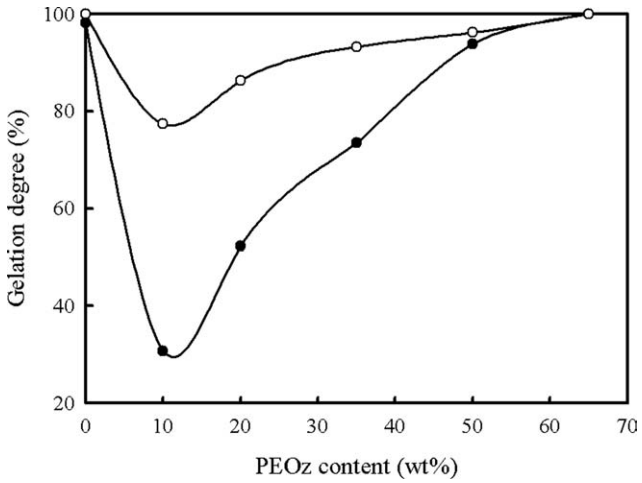

Figure 1 Effect of PEOz content in the feed solution on the gelation degree of PEOz/AAc copolymer at different irradiation doses. (●), 20; and (○), 40 kGy.

drug released at the selected time was estimated. All release experiments were performed in triplicate.

RESULTS AND DISCUSSION

Effect of the preparation condition on gelation process

Figure 1 shows the dependence of the gelation degree of the prepared copolymer on the feed solution composition at different irradiation doses. From the figure, it is clear that pure AAc undergoes almost 100% gelation, that it is a radiation cross-linkable monomer, and that the produced homopolymer is stable against ionizing radiation. The inclusion of PEOz within the feed solution leads to drastic decrease in the gelation process. Such decrement is receded by the further increase in PEOz content in the feed solution. Maximum gelation, about 100%, was reached at 65 wt % of PEOz. Any further increase in the PEOz content leads to the prevention of the gelation process, and no gel is formed at all. The figure also shows that all of the compositions under investigation possess higher gelation degrees at the higher irradiation dose. The increase in the irradiation dose increases the gelation degrees.

The abovementioned results can be explained by assuming a polyelectrolyte complex between PEOz and AAc because of the complexing ability of the PEOz.[15] Such complex formation process would lead to the grafting of AAc to the PEOz chains. Such complexation will separate the grafted AAc, which will minimize the possibility of the homopolymerization and self–bridging, i.e., the recombination of macro polyacrylic acid radicals. By increasing the PEOz content in the feed solution, the mixture viscosity increases, and, as a result, the possibility of homopolymerization and self-bridging increases, which consequently leads to the increment in the grafted chain length. The increase in the degree of branching in addition to the ability for complex formation would lead to the formation of highly entangled structure, which is not easy to be dissolved even at boiling water. The data also propose that PEOz has a very low sensitivity to ionizing radiation that at higher PEOz contents as well as pure PEOz solution no gel was achieved.

In the same manner, the higher the irradiation dose, the longer the propagation reaction. In other words, at higher dose, the formed free radicals are active for longer time, which increases their chance to homopolymerize and form such entangled structure. The figure also shows that even at high dose pure PEOz and PEOz-rich mixture were not able to form gel, which assists our assumption that PEOz is not a radiation-cross-linkable polymer.

When a dry glassy gel is brought into contact with water, water diffuses into the network, resulting in the expansion of the hydrogel. Diffusion involves the migration of water molecules into pre-existing or dynamically formed spaces between the hydrogel chains. Swelling of the hydrogel involves large segmental motion, resulting in the increased separation of the hydrogel chains. The swelling equilibrium occurs when the values of the osmotic force driving water molecule into the network and of the elastic force of the stretched subchains become equal. The equilibrium water content of a pH-sensitive hydrogel is a function of the cross-linking degree and the network structure, i.e., its hydrophilicity, which, in turn, depends on the degree of ionization of the functional groups. Therefore, an investigation of the equilibrium water content can elucidate the network structure and the degree of ionization of the functional groups.

Swelling studies

Studying the effect of the feed solution composition and irradiation dose on the equilibrium swelling of the prepared PEOz/AAc copolymer in double distilled water, Figure 2, shows interesting and unexpected results. Even though it is well known that PEOz possesses high hydrophilic character, the inclusion of the PEOz markedly decreases the swelling ability of the prepared PEOz/AAc copolymer, and any further increase in PEOz content in the feed solution leads to further decrease in the equilibrium swelling to reach about 1% of the pure AAc at 65 wt % PEOz. The apparent relative hydrophobicity of the prepared copolymer may be attributed to strong complex formed between the hydrophilic moieties of PEOz and PAAc chains, which may reduce the high hydrophilic character of both of the copolymer constituents by consuming their hydrophilic function groups. The figure also confirms the role of radiation

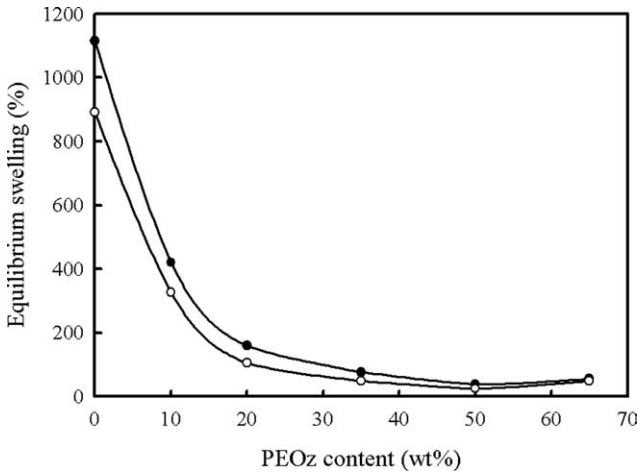

Figure 2 Effect of PEOz content in the feed solution on the equilibrium swelling of PEOz/AAc copolymer in water. Preparation irradiation doses: (●), 20; and (○), 40 kGy.

dose in the increase of system entanglement by increasing the degree of branching, which results in a decrease in the equilibrium swelling.

Figure 3 shows the effect of feed solution composition on the swelling equilibrium of the prepared PEOz/AAc copolymer at pH 1 and buffer solution of pH 7. The data clearly show that, at pH 1, an obvious effect arises from changing the feed solution composition. It is clear that the incorporation of PEOz within PAAc reduces its swelling equilibrium to a value which is less than one half of the pure PAAc at 20 wt % of PEOz to reach about 5% of that of pure PAAc at 50 wt % of PEOz. On the other hand, at pH 7, changing the PEOz content in the feed solution results in a remarkable increment in the swelling equilibrium of the PAAc to be more than 150% of the pure PAAc at 20 wt % of PEOz. At

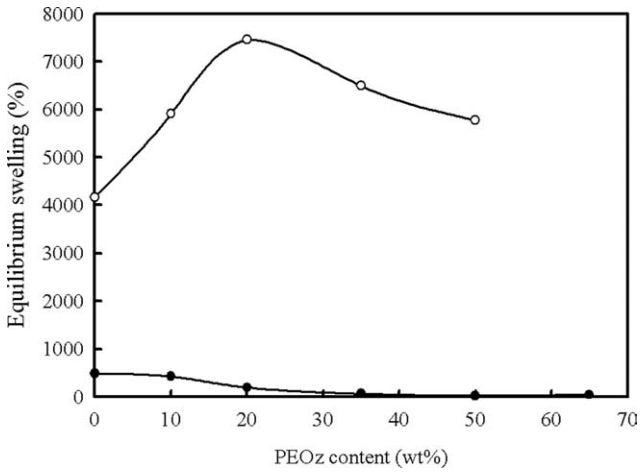

Figure 3 Effect of PEOz content in the feed solution on the equilibrium swelling of PEOz/AAc copolymer at (●) pH 1 and (○) buffer solution of pH 7. Preparation irradiation dose, 40 kGy.

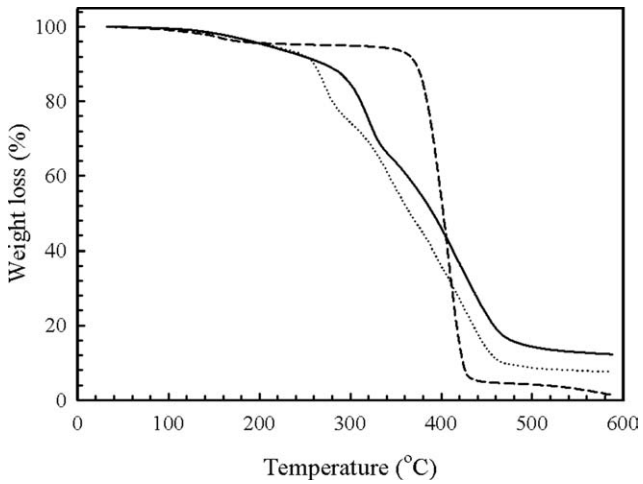

Figure 4 TGA traces of (. . .), PAAc; (- - -), PEOz; and (—), PEOz/AAc of 50 wt % PEOz

higher content of PEOz, more than 50 wt %, the prepared PEOz/AAc undergoes a slow dissolution.

The reduction in the equilibrium swelling of PAAc at pH 1 on the introduction of PEOz might be referred to the formation of a strong polyelectrolyte complex between the entangled PAAc and PEOz in addition to the hydrogen bonding formed between the associated carboxylic groups of PAAc. Such complex consumed the functional groups responsible for the hydrophilicity of both polymers. On contrary, at pH 7, the dissociation of the hydrogen bonding and the polyelectrolyte takes place as a result of the dissociation of the carboxylic groups into carboxylate groups. The dissociation of such complex frees up the hydrophilic groups of both polymers. In addition, the repulsion forces between the dissociated carboxylate groups increase the free spaces between the polymer chains, which leads to higher swelling equilibrium.

Effect of the copolymer composition on its thermal behavior

Figure 4 shows the TGA trace of pure PEOz, pure PAAc, and their copolymer of PEOz 50 wt %. The pure PEOz shows two thermal degradation steps: the first at about 100°C, at which the polymer lost the water associated the hydrophilic functional groups and then the second, at which the polymer undergo a mean degradation step at about 400°C.[16,17] On the other hand PAAc possesses its characteristic four thermal degradation steps: the loss of the water associated with the copolymer, an intermolecular dehydration and anhydride formation, decarboxylation, and, finally, back bone degradation at 155, 245, 260, and 410°C, respectively.[18] PEOz/AAc copolymer shows a TGA trace, which is different from those of its constituents; it shows higher thermal stability than that of PEOz and lower stability than that

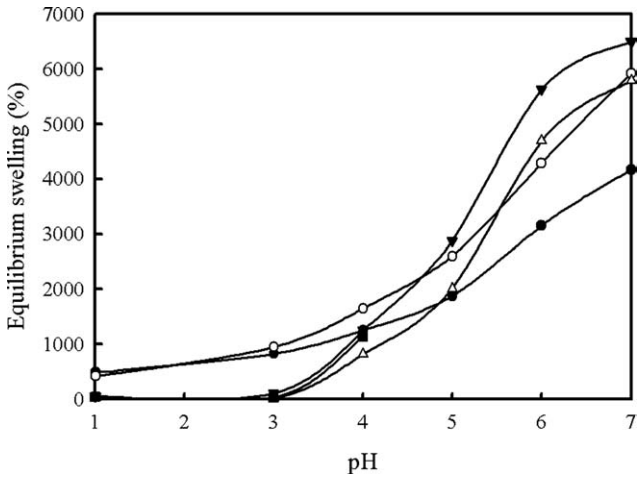

Figure 5 pH-dependent swelling profile of PEOz/AAc copolymer of different PEOz contents. (●), 0; (○), 10; (▼), 35; (△), 50; and (■), 65 wt %.

of PAAc. In addition to the absence of the first degradation step of PEOz, the copolymer does not show the characteristic degradation steps of PAAc.

TGA, which is the most widely method used for comparing the stabilities of polymeric materials, was used to characterize the effect of the copolymerization of PEOz and PAAc on their thermal properties. The TGA results show another evidence for the formation of a strong polyelectrolyte complex composed of PAAc and PEOz. The formed complex was responsible for the increment in the thermal stability of PEOz at the range 100–120°C, indicated by the absence of the degradation step in that temperature range, which might be referred to the consumption of the hydrophilic groups in the formation of proposed polyelectrolyte complex. In addition, the absence of the dehydration degradation step might be attributed to the change in the molecular structure of the carboxylic groups. Such a structural change resulted in the inhibition of the cyclization reaction between the carboxylic groups in AAc chains.[18] The absence of the PAAc degradation steps is also a clear indication for the complex formation.

pH-dependent swelling of PEOz/AAc copolymer

Figure 5 shows the pH-dependent swelling profile of PEOz/AAc copolymer of different compositions. The data show that the prepared copolymers of different PEOz content possess pH-sensitive behavior. All of the prepared copolymers show very low swelling equilibrium at pH values lower than 4, whereas they possess marked increase in the swelling degree at pH values higher than 4. The data also show that the presence of PEOz within the copolymer increases the magnitude of the pH threshold by lowering the equilibrium swelling at pH values less than 4 and increase it at higher values.

Such phase transition can be attributed to the dissociation state of the PAAc, which is the equilibrium between the ionizable carboxylic groups (COOH) and the ionized carboxylate groups (COO^-) of AAc.[19] Below pH 4, i.e., below pKa of carboxylic acid, the carboxylic groups are completely associated, forming inter- and/or intramolecular hydrogen bonding, which 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, which resulted in an increase in the free spaces available for swelling, in addition to the hydrophilicity of such carboxylate ions would make that remarkable observed increase in the swelling degree along the phase transition.

Swelling kinetics of PEOz/AAc copolymer at different pH

Hydrogels represent an important group of biomaterials for the controlled release of bioactive agents. Therefore, a thorough understanding of fluid–polymer interactions of such systems is critical for the development of these materials for biomedical applications. In most of polymeric hydrogels, swelling and drug release could be explained in terms of simple diffusion of water. The release of a drug incorporated in a polymeric system takes place by migration of the solute to the medium that surrounds the system by molecular diffusion through the support or by diffusion through micropores of the polymeric matrix. Analyzing the fluid transport in swellable polymers is important to understand the diffusion mechanism 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 is described to estimate the diffusion mode through the polymeric matrix.[20,21]

$$\frac{M_t}{M_\infty} = Kt^n$$

where k is the constant related to the structure of the network and the penetrant, n is the diffusion exponent, t is time, and M_t and M_∞ are the amounts of fluid absorbed at any time t and at equilibrium, respectively. A plot of $\ln M_t/M_\infty$ vs. $\ln t$ was used to calculate n and k from the slope and intercept, respectively. This equation is applicable to the initial stages of swelling, where a linear fit of the data was observed.

There are three models that describe the diverse range of responses of hydrophilic polymer networks to the presence of water. These models are based on

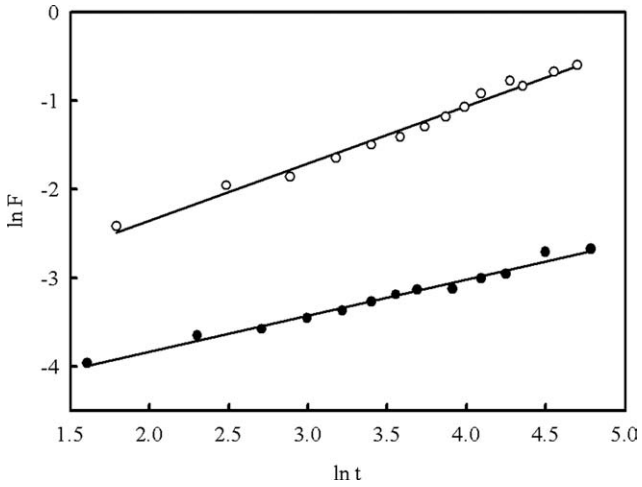

Figure 6 Representation of the fractional swelling (ln F) of (PEOz/AAc) (50/50 wt %) copolymer in buffer solutions of different pH against time (ln t). (○), pH 1; and (●), pH 7.

the relative rates of penetrant diffusion and polymer chain relaxation; Fickian diffusion at which $n \leq 0.5$, also known as Case I diffusion, occurs when the rate of diffusion is significantly slower than the rate of relaxation of the polymer chains. Case II transport at which $n = 1$ arises when the rate of diffusion is greater than the rate of the relaxation of the polymer chains. The main feature of this second limiting model is the establishment of a sharp boundary between the glassy core and the swollen shell, which advances at a constant velocity. Finally, non-Fickian or anomalous diffusion ($0.5 < n < 1$) occurs when the rates of diffusion and polymer relaxation are comparable and is connected with the transition region between the two limiting cases of Case I and Case II.

To investigate the effect of copolymer composition and pH of the swelling medium on the diffusion mode, swelling indices were calculated. Figure 6 shows the linear dependence of $\ln(M_t/M_\infty)$ on $\ln(t)$ of PEOz/AAc hydrogel of copolymer composition (PEOz/AAc) 50/50 (wt %), and Table I provides calculated values for swelling indices of PEOz/AAc of different compositions at buffer solutions of pH 1 and 7 from similar curves. The table shows that all the samples possessed Fickian type of diffusion at pH 1, whereas they underwent non-Fickian type of diffusion at pH 7. The abovementioned data show that the prepared PEOz/AAc hydrogel is a good candidate as a carrier for drug delivery system.

TABLE I
Effect of Copolymer Composition on the Diffusion Parameters at pH 1 and 7

PEOz content (wt %)	Diffusion parameters					
	pH 1			pH 7		
	n	k	r^2	n	k	r^2
0	0.48	−3.00	0.99	0.654	3.37	0.99
10	0.49	−3.69	0.98	0.683	3.46	0.97
20	0.48	−4.23	0.98	0.779	3.46	0.989
35	0.48	−5.03	0.99	0.934	4.76	0.992
50	0.40	−4.57	0.99	0.648	3.84	0.988
65	0.27	−4.72	0.962	Soluble sample		

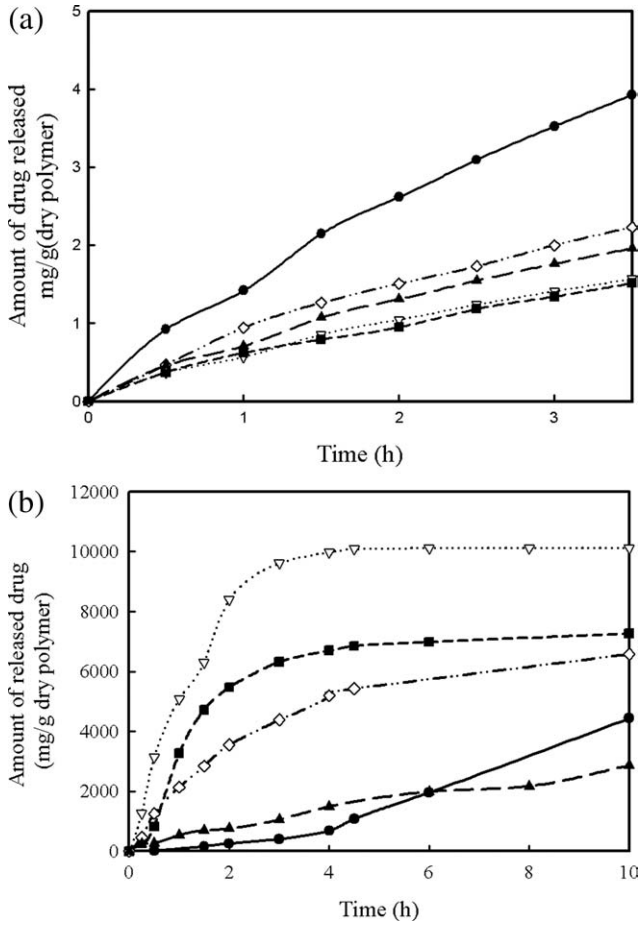

Figure 7 (a) Release profile of ibuprofen at solution of pH 1 from (PEOz/AAc) copolymer of different PEOz content. (●), 0; (■), 10; (□), 20; (◇), 35; and (▲); 50 wt %. (b) Release profile of ibuprofen buffer solutions of pH 7 from (PEOz/AAc) copolymer of different PEOz content. (●), 0; (□) 10; (■), 20; (▲), 35; and (◇), 50 wt %.

In vitro drug release study

Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. Drugs that are destroyed by the stomach acid and/or metabolized by pancreatic enzymes are of slight effect in the colon, and sustained colonic release of drugs can be useful in the treatment of colonic diseases and more effective with direct delivery of drugs to the affected area. Oral administration of the drug-loaded gel reach the stomach (pH 1–2.5) through gullet,

then pass into the terminal ileum (pH 7.5 ± 0.4) from the proximal small intestine (pH 6 ± 0.5) and the colon (pH 6.5), where the release of drugs usually involves the simultaneous absorption of GI juice and desorption of the drug via swelling-control diffusion mechanism.[22]

In this respect, evaluation of the prepared PEOz/AAc copolymer for the possible use in colon drug delivery system was carried out using ibuprofen as a model drug. The drug-loaded gel was immersed at buffer solution of pH 1 for 210 min (mean gastric residence time) followed by immersing in buffer solution of pH 7 for 16 h (far in excess for small intestine time), and the amount of drug released was determined. Figure 7 shows the pH-sensitive release profiles of ibuprofen from PEOz/AAc copolymer of different PEOz contents by immersing them in buffer solution of pH 1 and then in buffer solution of pH 7. The data show that there is no drug release in the stomach media, i.e., at pH 1. By changing pH from 1 to 7, drastic increase in drug release was observed. Continuous release of ibuprofen was noticed during the immersion time, which reached its maximum after 18 h; thereafter, it tends to level off. Also, it was observed that the amount of drug released from P(AAc)-rich gel is higher than that of gel containing less amount of P(AAc). The rate of release increases as the swelling increase.

CONCLUSIONS

A new pH-sensitive hydrogel composed of PEOz and AAc was synthesized by γ-radiation-induced copolymerization and cross-linking. The prepared copolymer showed a unique pH sensitivity of different magnitude depending on the copolymer composition. Investigating the ability of the prepared copolymer to be used as a carrier for colon-specific drug delivery system not only shows promising results in the field of drug targeting, but it also shows the possibility of controlling the released amount and release rate by controlling the copolymer composition.

References

1. Yang, L.; James, S. C.; Joseph, A. Int J Pharm 2002, 235, 1.
2. He, C. X.; Tabata, Y.; Gao, J. Q. Int J Pharm 2010, 386, 232.
3. El-Hag Ali, A.; Al Arifi, A. Carbohydr Polym 2009, 78, 725.
4. Rubinste, A. Crit Rev Ther Drug Carrier Syst 1995, 12, 101.
5. Kinget, R.; Kalala, W.; Vervoort, L.; Van Den Mooter, G. J Drug Target 1998, 6, 129.
6. Tan, M. L.; Choong, P. F. M.; Dass, C. R. Peptides 2010, 31, 184.
7. He, C.; Cui, F.; Yin, L.; Qian, F.; Tang, C.; Yin, C. Eur Polym J 2009, 45, 368.
8. Wang, C. H.; Hsiue, G. H. J Polym Sci: Polym Chem 2002, 40, 1112.
9. Wang, C. H.; Hsiue, G. H. Biomacromolecules 2003, 4, 1487.
10. Gaertner, F. C.; Luxenhofer, R.; Blechert, B.; Jordan, R.; Essler, M. J Control Rel 2007, 119, 291.
11. Mero, A.; Pasut, G.; Via, L. D.; Fijten, M. W. M.; Schubert, U. S.; Hoogenboom, R.; Veronese, F. M. J Control Rel 2008, 125, 87.
12. Lee, S. C.; Kim, C.; Kwon, I. C.; Chung, H.; Jeong, S. Y. J Control Rel 2003, 89, 437.
13. Cruickshank, R.; Duguid, J. P.; Marmion, B. P.; Swain, R. H. A. Medical Microbiology, Vol. II: The Practice of Medical Microbiology; Churchill Livingstone: New York, 1975.
14. WHO Model List of Essential Medicines; World Health Organization: Geneva, Switzerland, March 2005. Retrieved March 12, 2006.
15. Ogoshi, T.; Chujo, Y. Polymer 2006, 47, 4036.
16. Rivas, B. L.; del Pizarro, G.; Catalan, R. E.; Tagle, L. H. Thermochim Acta 1990, 160, 307.
17. Ong, C. H.; Goh, S. H.; Chan, H. S. O. Polymer 1997, 38, 1065.
18. Cerri, P.; Guerra, G. D.; Maltinti, S.; Tricoli, M. Macromol Rapid Commun 1994, 15, 983.
19. Kostum, G.; Vogel, V.; Anderussov, K., Eds. Dissociation of Constants of Organic Acids in Aqueous Solutions; Butterworths: London, 1961.
20. Fujita, H. Fortschr Hochpolym-Forsch 1961, 3, 1.
21. Peppas, N. A. Pharma Acta Helv 1985, 60, 110.
22. Evans, D. F.; Pye, G.; Bramley, R.; Clark, A. G.; Dyson, T. J.; Hardcastle, J. D. Gut 1988, 29, 1035.