Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

Synthesis of Carboxymethyl Cellulose Based Drug Carrier Hydrogel Using Ionizing Radiation for Possible Use as Site Specific Delivery System

Amr El-Hag Ali[a]; Hassan A. Abd El-Rehim[a]; H. Kamal[a]; Dalia El-Sayed A. Hegazy[a]
[a] National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt

To cite this Article El-Hag Ali, Amr , Abd El-Rehim, Hassan A. , Kamal, H. and Hegazy, Dalia El-Sayed A.(2008) 'Synthesis of Carboxymethyl Cellulose Based Drug Carrier Hydrogel Using Ionizing Radiation for Possible Use as Site Specific Delivery System', Journal of Macromolecular Science, Part A, 45: 8, 628 — 634
To link to this Article: DOI: 10.1080/10601320802168751
URL: http://dx.doi.org/10.1080/10601320802168751

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2008) **45**, 628–634

ISSN: 1060-1325 print/1520-5738 online
DOI: 10.1080/10601320802168751

Synthesis of Carboxymethyl Cellulose Based Drug Carrier Hydrogel Using Ionizing Radiation for Possible Use as Site Specific Delivery System

AMR EL-HAG ALI, HASSAN A. ABD EL-REHIM, H. KAMAL, and DALIA EL-SAYED A. HEGAZY
National Center for Radiation Research and Technology, Nasr City, Cairo, Egypt

Received January, 2008, Accepted February, 2008

A unique natural polymer based colon specific drug carrier was prepared from carboxymethyl cellulose (CMC) and acrylic acid (AAc) in aqueous solution employing γ-radiation induced copolymerization and crosslinking. The effect of preparation conditions such as the natural polymer content and irradiation dose on gelation process was investigated. The swelling behavior of the prepared hydrogels was characterized by investigating the time and pH dependent swelling of the (CMC/AAc) hydrogels of different CMC content. The effects of the hydrogel composition and pH of the swelling medium on the swelling indices were estimated. The results show that the increment in the CMC content in the feed solution enhances the gelation process. The results also show the dependence of the swelling indices on both hydrogel composition and pH value of the swelling medium. To evaluate the ability of the prepared hydrogel to be used as a colon-specific drug carrier, the release profile of theophylline was studied as a function of time at pH 1 and pH 7.

Keywords: pH-sensitive; carboxymethyl cellulose; hydrogel; γ-irradiation; swelling kinetics; drug release

1 Introduction

Cellulose is a naturally occurring polysaccharide and it is the most abundant renewable resource available to mankind. Glucose constitutes a major energy source in human and animal diets. In addition, cellulose products, such as carboxymethyl cellulose (CMC) are widely used as raw materials in numerous industrial applications, e.g. in the paper, paint, textile, food and pharmaceutical industries. CMC as a natural polymer has great potential for providing a broad range of important functional properties and possesses several advantages that make them excellent materials for industrial and biomedical use; they are non-toxic, renewable, biodegradable and modifiable (1–3). As environmental requirements have become of great importance in today's society, there is increasing interest in the industrial and biomedical use of renewable resources, and considerable efforts are now being made in the research and development of cellulose as the basic material in new applications.

During the last decades, the field of drug delivery and controlled release has seen a dramatic development. Ideal drug delivery system (DDS) should deliver a drug to a specific site, in a specific time and release pattern. In the early times, the basic arrangement was to get a constant (zero order kinetic) or sustained drug release in order to avoid the problems associated with a multiple conventional administration in chronic treatments. Today, the challenges are much more ambitious. The current trends of new controlled release devices include the optimization on the targeting to specific sites and the fitting of the drug release to the circadian rhythm. Furthermore, drug delivery technology covers other specific needs such as: (1) to get a slow release of water soluble drugs; (2) to improve the bioavailability of low water soluble drugs; (3) to deliver two or more agents in the same formulation; (4) to develop carriers readily clearable; (5) to improve the biodistribution of drugs with a high rate of metabolism or rapid clearance; (6) to control the release of highly toxic drugs and; (7) to improve the targeting to the target tissues or cells.

Hydrogels are one of the upcoming classes of polymer-based controlled release drug delivery systems. Besides exhibiting swelling-controlled drug release, hydrogels also show stimuli-responsive changes in their structural network and hence, the drug release. Because of large variations in physiological pH at various body sites in normal, as well as pathological conditions, pH sensitive hydrogels have been extensively investigated.

PAAc and its lightly crosslinked commercial forms like Carbopol and Polycarbophil, usually exhibit strong pH-responsive property, and also appear to be biocompatible (4). However, PAAc highly swells in water and dissolves at

Address correspondence to: Amr El-Hag Ali, National Center for Radiation Research and Technology, Ahmed El-Zomor, P. O. Box 29, Nasr City, Cairo, Egypt. E-mail: elhagali_a@hotmail.com

high pH solutions. High water swelling property critically limits its use as a drug carrier, since the drug is quickly delivered across the hydrogel.

In this work, a series of CMC/AAc copolymer hydrogels will be synthesized, as part of a continuing effort to prepare a drug carrier based on PAAc by simultaneously occurring reactions of radiation induced copolymerization and crosslinking in aqueous solution (4, 5). Swelling characteristics of the prepared hydrogels will be studied. The ability of the CMC/AAc hydrogel to be used as a carrier for drug delivery system will be estimated.

2 Experimental

2.1 Materials

Acrylic acid (AAc) of purity 99.9% (Merck, Germany) and carboxymethyl cellulose (CMC) (El-Nasr Co. for Chemical Industries, Egypt) were used as received. Theophylline, of pharmaceutical grade, was kindly provided by Alexandria Pharmaceuticals Co., Alexandria, Egypt. Citric acid, Sodium citrate, Sodium dihydrogen phosphate, and Disodium hydrogen phosphate, analytical reagents, were purchased from El-Nasr Co. for Chemical Industries, Egypt and used without further purification.

2.2 Preparation of CMC/AAc Gels

CMC/AAc gels were obtained by γ-irradiation-induced copolymerization of 20 wt% aqueous solutions of AAc and CMC mixtures with different compositions in small glass vials using ^{60}Co gamma rays at a dose rate 10.28 kGy/h. After copolymerization, the vials were broken, the formed polymeric cylinder were removed and cut into discs of 2 mm thickness and 5 mm diameter. All samples were washed in excess water to remove the unreacted component, then air dried at room temperature. All of the samples used in the drug release evaluation study possess almost 100% conversion.

2.3 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. 0.2 M HCl was used to prepare solutions of pH 1. Sodium chloride was used to change the ionic strength of the buffer solution at pH 7.

2.4 Swelling Study

The prepared crosslinked gels were soaked in a buffer solution of different pH's ranging from 1 to 7 at 37°C. The swelling ratio (S) was determined from the following equation:

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

where W_s and W_o are the weights of the swollen and dry hydrogel, respectively.

2.5 Ultraviolet (UV) Measurements

Determination of the released amount of the drugs under investigation was carried out at 270 nm using JASCO V560 spectrophotometer in the range from 200–900 nm.

2.6 Preparation of Drug-loaded Gel

Fifteen mg of the drugs was dissolved in a 20 ml phosphate buffer of pH 7. The dry CMC/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.

2.7 Loaded Drug Release

CMC/AAc gels loaded with Theophylline were allowed to swell in buffer solutions of pH 1 and 7. At first, the loaded gel were put in 25 ml of 0.2 M HCl (pH 1) for 3.5 h, then transferred to 150 ml 0.2 M phosphate buffer (pH 7) for 21.5 h. A 1 ml sample was withdrawn at time intervals to follow the release process.

3 Results and Discussion

Hydrogels can be fabricated in several ways which involves crosslinking of either linear polymers or simultaneous polymerization of monofunctional monomers and crosslinking with polyfunctional monomers (7–10). Polymers from natural, synthetic or semi-synthetic sources can be used for synthesizing hydrogels. Usually, polymers containing hydroxyl, amine, amide, ether, carboxylate and sulfonate as functional groups in their side chains are used.

Irradiation of polysaccharide materials evokes some effects depending on the kind of the natural polymer, irradiation parameters, the phase of natural polymer under processing and others. The two main reactions, which influence the final properties of polymers include: (1) scission of main chain, leading to diminishing of the molecular weight of macromolecules and (2) crosslinking, the opposite process to degradation, which leads to the formation of macroscopic, insoluble material. The yield of scission and crosslinking, or more precisely the mutual ratio of these two parameters, determines the nature of the outcome materials.

3.1 Effect of Irradiation Dose and CMC Content on Gelation of CMC/AAc Copolymer

Figures 1 and 2 show the effect of irradiation dose on the conversion and gelation degrees of CMC/AAc copolymer hydrogels at different CMC content. The figures show that both conversion and gelation degrees slightly decreased by

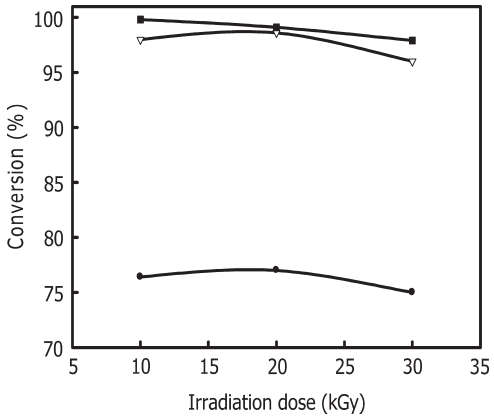

Fig. 1. Effect of irradiation dose on the conversion degree of (CMC/AAc) copolymer hydrogels at different CMC content; (●) 15, (▽) 25 and (■) 50 wt%. Total concentration: 20 wt% in H_2O.

increasing the irradiation dose from 10 or 30 kGy. Meanwhile, the figures also show that the increase in the CMC content from 15 to 50 wt% dramatically increases the conversion to be more than 95% compared to 75% and increases the gelation percent from 65% to be about 95%. The results can be explained in the light of chain scission/crosslinking balance. At low CMC concentration, even though AAc has a high ability for copolymerization and crosslinking, the main chain scission is the predominant reaction due to low viscosity of the medium which lowers the probability of the recombination of the degraded CMC chains and/or the grafted PAAc onto CMC segments. Consequently, a loose network of low crosslinking density is obtained. Meanwhile, the increase in the CMC content within the reaction medium increases the viscosity of the reaction medium, which consequently reduces the mobility of CMC segments and as a result increases the probability of the recombination of the degraded CMC chains, as well as crosslinking and self bridging of the PAAc. Consequently, a perfect network of higher crosslinking density is obtained. It was reported that radiation crosslinking of nonionic cellulose derivatives, except CMC, is possible in aqueous solution due to inherent repulsive forces between CMC chains of high polar character (11). On the other hand, radiation crosslinking of CMC could be achieved by the use of a crosslinking agent and/or increasing its concentration in the aqueous solution (12–14).

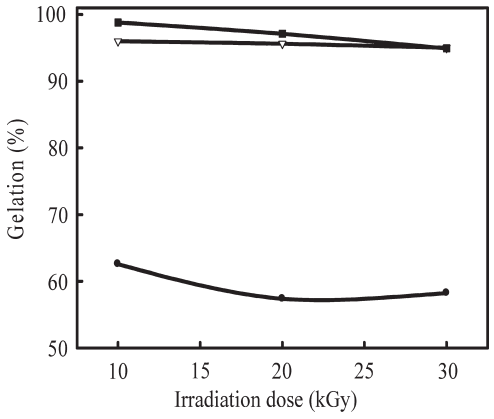

Fig. 2. Effect of irradiation dose on the gelation degree of (CMC/AAc) copolymer hydrogels at different CMC content; (●) 15, (▽) 25 and (■) 50 wt%. Total concentration: 20 wt% in H_2O.

3.2 Swelling Behavior of CMC/AAc Hydrogels

The maintenance of the site specific drug carriers is largely dependent on the dynamics swelling and response to the external environment, in this case, pH of the swelling medium. By studying the factors affecting the swelling behavior of prepared hydrogels and their response in various pH solutions, performance of these hydrogels can be evaluated. Major factors that influence the degree of swelling of ionic polymers include the properties of the polymer (charge, concentration and pKa of the ionizable group, degree of ionization, crosslink density and hydrophilicity or hydrophobicity) and properties of the swelling medium (pH and ionic strength (15).

3.3 Effect of Irradiation Dose on the Equilibrium Swelling of CMC/AAc Hydrogels

Figure 3 show the time dependent swelling of CMC/AAc copolymer hydrogels prepared at different irradiation doses. The results show that the increase in the irradiation dose increases the degree of swelling. Such results might be attributed to the increase in the number of chain scission even after the formation of the network which leads to the formation of looser network. These results come in good agreement with that obtained from studying the effect of irradiation dose on the gelation of CMC/AAc copolymer.

3.4 Effect of CMC Content on the Equilibrium Swelling of CMC/AAc Hydrogels

Time dependent swelling is one of the important characteristic properties of the polymeric hydrogels. Figures 4 and 5 show the time course swelling of CMC/AAc copolymer hydrogels of different CMC content at pH 1 and pH 7, respectively. Generally, it is obvious that the swelling rates and degrees possessed in the buffer solution of pH 7 are much higher than that at pH 1. Such behavior is directly related to the presence of PAAc which is a pH-sensitive polymer within the polymeric matrix.

At pH 1, the increase in CMC content leads to an increase in the swelling degree and rate of the hydrogel. Whereas, at pH 7, the increase in CMC content within the hydrogel from 15 to 25 wt% leads to the decrease in the swelling rate and degree whereas, a further increase in the CMC content (from 25 to 50 wt%) leads to the increase in swelling rate and degree. The abnormal swelling behavior of the CMC/AAc hydrogel might be explained as follows: At pH 1, the contained PAAc chains are associated and forming inter- and intra-molecular hydrogen bonding, i.e., seem to be

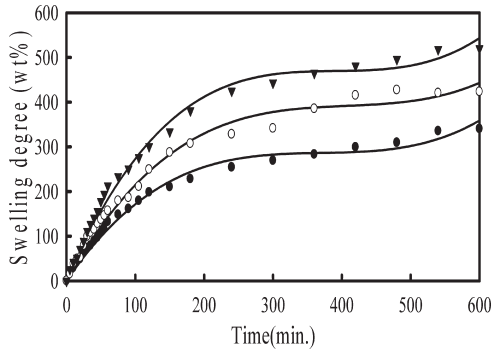

Fig. 3. Time dependent swelling of CMC/AAc copolymer hydrogels prepared at different irradiation doses; (●) 10, (○) 20 and (▼) 30 kGy. Total concentration; 20 wt% and CMC content; 25 wt%.

hydrophobic, whereas CMC, which is of pH independent swelling behavior, represents the hydrophilic counter part. The increase in the CMC content increases the hydrophilic character of the hydrogel, and as a result swelling degree increases. Contrary, at pH 7, the increase in the CMC content, which increases the efficiency and tightness of the formed network, restrict the swellability of the dissociated PAAc. The effect of CMC content on the swelling behavior of the prepared hydrogel at pH 7 might be attributed to the formation of a more perfect network by increasing the CMC content from 15 to 25 wt%. Meanwhile, the noticeable increase in the swelling degree observed by increasing the CMC content to 50 wt% may due to the damage which takes place in the network that results from radiation degradation within the CMC rich network which resulted in the increase in the pore size and available free volume within the matrix.

3.5 pH-Dependent Swelling CMC/AAc Copolymer Hydrogel

The response of the polymeric hydrogel to the change in the pH value of the surrounding environment is the most important evaluating character for the site specific drug carriers.

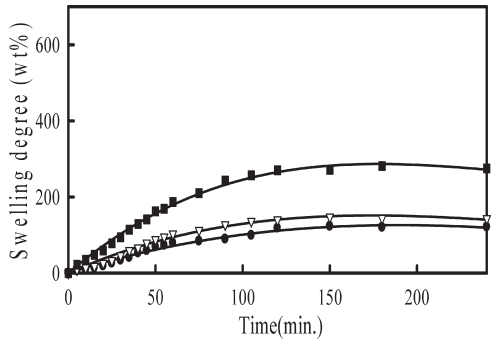

Fig. 4. Time dependent swelling of CMC/AAc copolymer hydrogels of different CMC contents; (●) 15, (▽) 25 and (■) 50 wt% content at pH 1. Total concentration; 20 wt% and irradiation dose; 20 kGy.

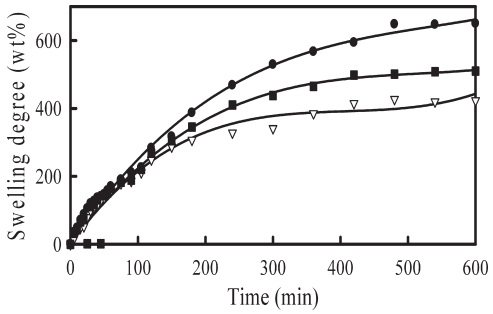

Fig. 5. Time dependent swelling of CMC/AAc copolymer hydrogels of different CMC content; (●) 15, (▽) 25 and (■) 50 wt% at pH 7. Total concentration; 20 wt% and irradiation dose; 20 kGy.

Figure 6 shows the pH dependent swelling behavior of CMC/AAc hydrogel of different CMC content. From the Figure, it is clear that all CMC/AAc hydrogels show pH dependent phase transition i.e. they possessed swelling degrees at buffer solution of high pH values (pH $>$ 4) much higher than that possessed at low pH values (pH $<$ 4). This behavior can be explained as follow: In aqueous media of appropriate pH i.e., at buffer solution of pKa higher than that of PAAc (pH 4.2), the pendant carboxylic groups ionize and develop fixed charges on the polymer network, generating electrostatic repulsive forces responsible for pH-dependent swelling of the hydrogel (16).

On the other hand, the data also show that the position and magnitude of such phase transition is directly related to the CMC content within the hydrogel. In other words, the increase in CMC content within the hydrogel shifts the position of the pH threshold to a lower values, as well as it reduces the magnitude of the phase transition. The effect of the increase of CMC content on position and magnitude of such phase transition might be attributed to the hydrophilic character of the CMC, as well as the crosslinking density.

3.6 Effect of Ionic Strength on the Equilibrium Swelling of CMC/AAc Hydrogels

Another factor, that may affect the equilibrium swelling of the site specific drug carrier and consequently, affect its

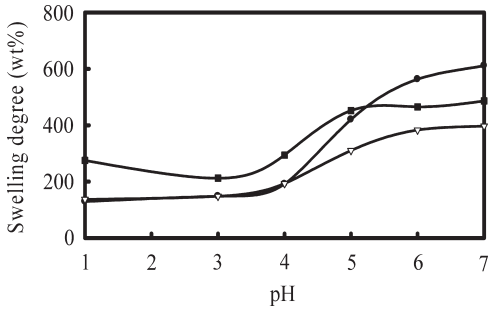

Fig. 6. pH dependent swelling behavior of CMC/AAc hydrogel of different CMC content; (●) 15, (▽) 25 and (■) 50 wt%. Total concentration; 20 wt% and irradiation dose; 20 kGy.

performance, is the change in the ionic strength of the swelling medium. To investigate such a parameter, CMC/AAc hydrogels of different CMC content were immersed in a buffer solution of different ionic strength and its swelling behavior was determined as shown in Figure 7. The data show that the equilibrium swelling degrees of all the hydrogels were affected by increasing the ionic strength of the swelling medium. The figure also shows that the samples of higher AAc content are more affected by the increase in the ionic strength. This may be due to, as the ionic strength increase, the electric shielding effect of the counter-ion on the carboxylate of the acrylic acid increases, consequently, the expansion of the gel network decreases. As a result, osmotic pressure difference between the gel network and the external solution decreased (17).

3.7 Swelling Kinetics

Most of the hydrogels are glassy in their dehydrated state, and drug release generally involves simultaneous absorption of water and desorption of drug via a swelling controlled mechanism (18). The rate-controlling factor mediating drug delivery is the resistance of the polymer to an increase in volume and change in shape (19). A glassy hydrogel, on coming into contact with water or any other thermodynamically compatible medium, allows solvent penetration into free spaces on the surface between the macromolecular chains. When enough water has entered the matrix, the glass transition temperature of the polymer drops to the experimental temperature. The presence of solvent in a glassy polymer causes the development of stresses that are accommodated by an increase in the radius of gyration and end-to-end distance of polymer molecules, which is seen macroscopically as swelling. The movement of solvent molecules into the dry (glassy) polymer matrix takes place with a well-defined velocity front and a simultaneous increase in the thickness of the swollen (rubbery) region with time in the opposite direction.

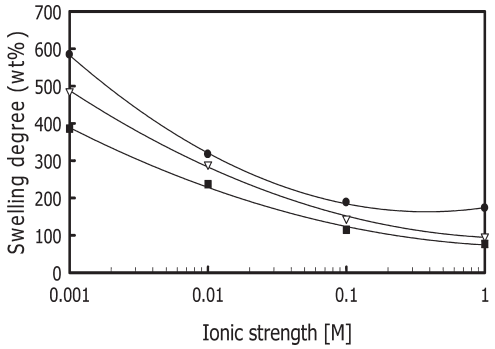

Fig. 7. Effect of the ionic strength of the swelling medium on the equilibrium swelling of CMC/AAc hydrogels of different CMC contents; (●) 15, (▽) 25 and (■) 50 wt%. Swelling medium; buffer solution of pH 7.

It is important to understand the mechanism of transport through hydrogels. In most polymeric systems, water uptake and release can be explained in terms of simple diffusion. The mechanism of drug release from the CMC/AAc hydrogels was studied by fitting the swelling data to an empirical equation of the following type (20, 21):

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

The ratio M_t/M_∞ represents the fractional absorbed water at time t, k is a constant characteristic of the drug polymer system, and n is the diffusional exponent. Diffusion of water to the glassy polymeric matrix generally exhibits behavior ranging from Fickian to Case II extremes depending on the experimental conditions and thermodynamic compatability between water and copolymer hydrogel. For $n = 0.5$, water follows the well-known Fickian diffusion mechanism. For $n > 0.5$, non-Fickian diffusion behavior is generally observed. Finally, for $n = 1$, Case-II transport mechanism is followed.

In the present study, the statistical values of n at the 95% confidence limit are presented in Table 1, which are estimated from figures similar to Figure 8, show the effect of CMC content, and pH of the surrounding medium on diffusional exponent (n) of the CMC/AAc hydrogels. It is clear that, CMC/AAc hydrogels possesses Fickian diffusion at pH 1 and turned to non-Fickian at high pH values (pH 7) which indicates the ability of the prepared hydrogels to protect the loaded drug at pH 1 i.e., stomach medium and to release it at higher pH values, i.e., intestine medium.

3.8 Colon-Specific Drug Delivery of CMC/AAc Hydrogel

Variations in pH are known to occur at several body sites, such as the gastrointestinal tract and these can provide a suitable base for pH-responsive drug release (22). In addition, local pH changes in response to specific substrates can be generated and used for modulating drug release. The pH-responsive drug delivery systems have been targeted for per-oral controlled drug delivery (23, 24). Colon-specific drug delivery is useful in several therapeutic areas such as topical treatment of colonic diseases and oral delivery of proteins and drugs destroyed in the upper gastrointestinal track. To accept the copolymer as a carrier for colon-specific

Table 1. Effect of CMC content on the diffusion parameters

CMC content (wt%)	pH 1		pH 7	
	n	r^2	n	r^2
15	0.42	93	0.63	99
25	0.36	95	0.61	98
50	0.39	95	0.66	97

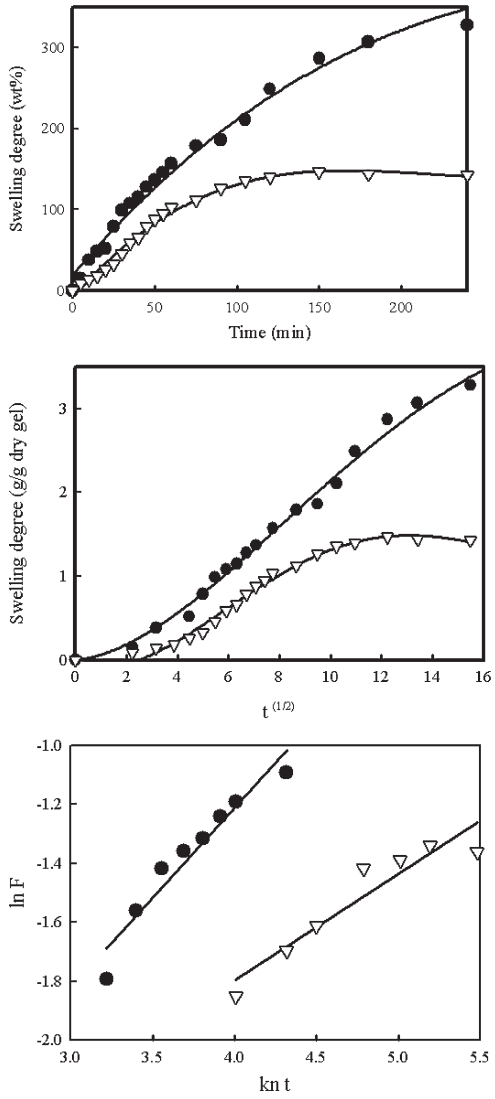

Fig. 8. Swelling kinetics curves of poly (CMC/AAc) hydrogels at pH 1 and pH 7 of CMC content 30 wt% at (▽) pH 1 and (●) pH 7.

drug delivery system, it should not release the drug and protect it at the stomach, pH 1, and start to release the drug at colon and small intestine, pH 7. Theophylline, which is a bronchodilator, was chosen as a suitable drug for investigation of the formations showing sustained release characteristics because some dosage forms with slow release are commercially available.

3.9 Release of Theophylline from CMC/AAc Hydrogels

The release experiments were carried out at a buffer solution of pH 1 which is almost similar to that of the 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. Figures 9 and 10 show the drug release profile of CMC/AAc copolymer hydrogels of different CMC content prepared at different

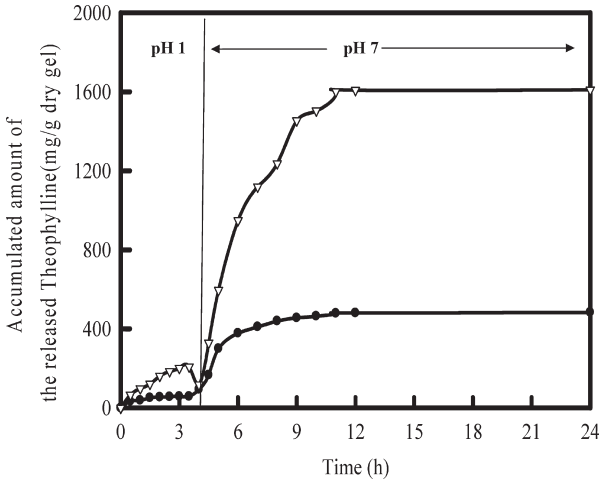

Fig. 9. Release profile of Theophylline as model drug from CMC/AAc hydrogel of different CMC contents; (●) 25 and (▽) 50 wt%.

irradiation doses, respectively, as a function of time at pH 1 and pH 7. The figures generally show that there is no significant drug release at pH 1, whereas the drug release occurs as soon as the copolymer transferred to a 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 and irradiation dose on the release rate and total released drug. It is clear from the figures that the increase in CMC content within the hydrogel from 25 to 50 wt% increases the amount of the drug released up to about 4 times, i.e., about 1.6 instead about 0.4 gram drug per gram of dry hydrogel. On the other hand, the increase in the total exposure dose during preparation also increases the amount of drug released. Such a release profile is directly related to the swelling behavior of the prepared hydrogels.

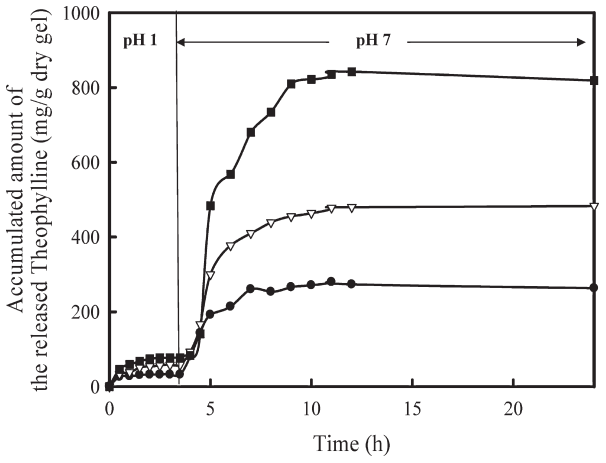

Fig. 10. Release profile of Theophylline as a model drug from CMC/AAc hydrogel prepared at different irradiation doses; (●) 10, (▽) 20 and (■) 30 kGy.

4 Conclusions

A novel natural polymer-based site specific drug carrier was synthesized by γ-radiation induced copolymerization and crosslinking carboxymethyl cellulose and acrylic acid. The influence of preparation conditions such as; irradiation dose and CMC content on the equilibrium swelling were investigated. Swelling kinetics studies show that the hydrogel possesses Fickian diffusion in the stomach-like medium i.e., pH 1, whereas it possesses non-Fickian diffusion in the intestine-like medium i.e., pH 7. SEM studies also clearly showed the effect of pH on the topgraphical structure of CMC/AAc hydrogels. The aforementioned characteristics recommended the hydrogel to serve as a site specific drug carrier.

5 References

1. Wurzburg, O.B. *Modified Starches: Properties and Uses*; CRC Press: Boca Raton, p. 277, 1986.
2. Brandt, L. *Cellulose Ethers*; Campbell, F.T., Pfefferkorn, R. and Rounsaville, J.F. (eds.); in Ullmann's Encyclopedia of Industrial Chemistry, VCH Verlagsgesellschaft: Weinheim, p. 461, 1986.
3. Suo, A., Qian Yao, J.Y. and Zhang, W. (2007) *J. Appl. Polym. Sci.*, **103(3)**, 1382–1388.
4. Silva, A., Santos, D., Ferreira, D. and Souto, E. (2007) *J. Biotech.*, **131(2)**, S67–S68.
5. El-Hag Ali, A. (2005) *Biomaterials*, **26**, 2733–2739.
6. El-Hag Ali, A. and Hegazy, E.A. (2007) *J. Biomed. Mater. Res., Part B: Appl. Biomater.*, **81B(1)**, 168–174.
7. Peppas, N.A. (Ed.) *Hydrogels in Medicine and Pharmacy*; CRC Press: Boca Raton, FL, Vols. I–III, 1986–1987.
8. Nugent, M.J.D. and Higginbotham, C.L. (2007) *Euro. J. Pharm. Biopharm.*, **67(2)**, 377–386.
9. Bouwstra, J.A. and Junginger, H.E. Hydrogels. In *Encyclopaedia of Pharmaceutical Technology*; Swarbrick, J. and Boylan, J.C. (eds.); Marcel Dekker: New York, 441–465, 1993.
10. Yoshii, F., Suhartini, M., Nagasawa, N., Mitomo, H. and Kume, T. (2003) *Nucl. Inst. Meth. Phys. Res. Sec. B.*, **208**, 370–373.
11. Leavitt, F.C. (1961) *J. Polymer Sci.*, **51**, 349–357.
12. Rokhade, A.P., Agnihotri, S.A., Patil, S.A., Mallikarjuna, N.N., Kulkarni, P.V. and Aminabhavi, T.M. (2006) *Carbohyd. Polym.*, **65(3)**, 243–252.
13. Pourjavadi, A., Barzegar, Sh. and Mahdavinia, G.R. (2006) *Carbohyd. Polym.*, **66(3, 2)**, 386–395.
14. Liu, P., Peng, J., Li, J. and Wu, J. (2005) *Radiat. Phys. Chem.*, **72(5)**, 635–638.
15. Kim, S.W. and Bae, Y.H. Stimuli-modulated delivery systems, In *Transport Processes in Pharmaceutical Systems*; Amidon, G.L. et al. (eds.); Marcel Dekker: New York, 547–573, 2000.
16. Kost, J. Intelligent drug delivery systems. *Encyclopaedia of Controlled Drug Delivery*; Mathiowitz, E. (ed.); John Wiley & Sons: New York, 445–459, 1999.
17. Lin, Z., Wu, W., Wang, J. and Jin, X. (2007) *React. Func. Polym.*, **67(9)**, 789–797.
18. Huang, Y., Yu, H. and Xiao, C. (2007) *Carbohyd. Polym.*, **69(4)**, 774–783.
19. Bouwstra, J.A. and Junginger, H.E. Hydrogels. In *Encyclopaedia of Pharmaceutical Technology*; Swarbrick, J. and Boylan, J.C. (eds.); Marcel Dekker: New York, 441–465, 1993.
20. Fujita, H. (1961) Diffusion in polymer-diluent systems. *Fortschr Hochpolym-Forsch*, **3**, 1–47.
21. Peppas, N.A. (1985) *Pharm. Acta Helv.*, **60**, 110–111.
22. Guyton, A.C. and Hall, J.E. Secretory functions of the alimentary tract. In *Textbook of Medical Physiology*; Guyton, A.C. and Hall, J.E. (eds.); W.B. Saunders Co., 815–832, 1998.
23. Kumar, A., Lahiri, S.S., Punyani, S. and Singh, H. (2008) *J. Appl. Polym. Sci.*, **107(2)**, 863–871.
24. Sakata, S., Uchida, K., Kaetsu, I. and Kita, Y. (2007) *Radiat. Phys. Chem.*, **76(4)**, 733–737.