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Study of the sigmoidal swelling kinetics of carboxymethylchitosan-g-poly(acrylic acid) hydrogels intended for colon-specific drug delivery

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ABSTRACT

The swelling kinetics of a series of carboxymethylchitosan-g-poly(acrylic acid) hydrogels pretreated under acidic buffer media has been studied. Sigmoidal swelling curves are exhibited when these pretreated hydrogels are subsequently immersed in the buffer solutions of pH 6.0–7.4. This phenomenon may be attributed to the disruption of a cooperative physical cross-linking (i.e. the hydrogen bonding and the ionic cross-linking) on the networks, which was proved by the change of FT-IR spectra of hydrogels during swelling. The buffer pH, the pretreating pH and the composition of hydrogels have an obvious influence on the sigmoidal effect. The profile of drug release at pH 7.0 from the hydrogel which was prepared in the pH 2.2 buffer containing 5-aminosalicylic acid (5-ASA) exhibits a sigmoidal release curve, namely, an initial slow release followed by a burst release. The swelling kinetics shows the potential in the design of the colon-specific drug delivery system.

1. Introduction

Hydrogels are very attractive materials for application in drug delivery systems because of their hydrophilic character and potential to be biocompatible (Saima, Saeid, & Kanchan, 2009). An important parameter to consider in the utilization of a hydrogel system as drug delivery system is the degree of swelling. While drug delivery is accomplished by the swelling of the hydrogel (Yin, Yang, & Xu, 2001), drug release is also related to this swelling behavior (Yin, Yang, & Xu, 2002). More and more studies have shown that the swelling behavior of hydrogels is influenced by the intermolecular weak interactions such as electrostatic interaction, hydrogen bonds et al. For example, more recently the swelling behavior of hydrogels based on sodium alginate-g-acrylic acid has been studied by us (Yin, Ji, Dong, Yi, & Zheng, 2008). The obtained results have revealed that the hydrogen bonds between carboxyl groups lead to some anomalous features. A swelling–deswelling process under acidic pH, which is actually known as overshooting effect, may be attributed to the dynamic hydrogen bond formation. Sigmoidal swelling behavior has been reported by some authors in different systems. Díez-Peña, Quijada-Garrido, and Barrales-Rienda (2002) proposes that the initial hydrophobic aggregates related to the hydrogen bonding of the gels constrain the water penetration, the disruption of hydrogen bond arrangements under swelling giving rise to the sigmoidal shape of the curves.

The utilization of natural polysaccharides in drug delivery continues to be a subject of intense investigation because of their biodegradability and biocompatibility. The major problem encountered with biodegradable chitosan is its solubility in acidic media and difficult solubility in neutral or basic media. Consequently, the hydrogels prepared with it will be unable to prevent the release of drugs during the transit through the stomach and the small intestine. Carboxymethylchitosan, an important derivative of chitosan, has good water solubility and biocompatibility (Zhao, Mitomo, & Naqasawa, 2003). However, the hydrogels prepared using it have the low swelling degree at pH 3.0 but not at other pH values (Sun, Du, Chen, Huang, & Cheng, 2004). Our study found that the incorporation of carboxymethylchitosan into PAA could provide a promising alternative due to the electrostatic and hydrogen bonding interactions between amide and carboxyl groups in acidic media, but drug release in the small intestine could not be avoided just on the basis of the pH-sensitivity of these hydrogels, because the pH of the small intestine and large intestine are almost the same (Ali & AlArifi, 2009; Mastiholimath, Dandagi, Jain, Gadad, & Kulkarni, 2007).

It is well known that the release characteristics of drug-loaded hydrogels are strongly dependent on the swelling behavior of the hydrogels (Berger et al., 2004). However, in the current literature, many investigations were dedicated to the study of the influence of the equilibrium swelling degree on the drug release; but few focused on the significant role of the swelling kinetics in the drug delivery. In this paper, the swelling kinetics of a series of

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Table 1
Molar composition and grafting percentage of the carboxymethylchitosan-g-poly(acrylic acid) gels.

Gels	Feed composition (mol%)[a]			Actual composition (mol%)			Grafting percentage
	AA	CMC	MBAA	AA	CMC	MBAA	
B_1	50.0	48.0	2.0	43.8	54.1	2.1	24.31
B_2	60.0	38.0	2.0	55.1	42.5	2.4	38.68
B_3	70.0	28.0	2.0	64.7	33.0	2.3	53.79

[a] The molar content of CMC is calculated based on monosaccharide unit.

carboxymethylchitosan-g-poly(acrylic acid) hydrogels pretreated under acidic or neutral media has been studied. Their application in colon-specific drug delivery was also reported.

2. Experimental

2.1. Materials

Chitosan, degree of deacetylation 91%, viscosity-average molecular weight 2.5×10^5 Da, was supplied by Zhejiang Yuhuan Biochemical Co., Ltd. (China), N′-methylene-bis-(acrylamide) (MBAA), potassium persulfate ($K_2S_4O_8$) and 5-aminosalicylic acid (5-ASA) were used without any further purification. Acrylic acid (AA) was used after distillation under reduced pressure. Deionized water was used for hydrogel preparation and swelling measurements and drug release. A phosphate–citric buffer system (0.2 mol/L Na_2HPO_4/0.1 mol/L $C_6H_8O_7$) was used for all experiments.

2.2. Preparation of carboxymethylchitosan (CMC)

Chitosan (3 g) was stirred with isopropanol (35 ml) for 6 h, and then filtered. NaOH solution (50%, wt%) was added into the beaker with filter residue, this solution was fully stirred to mix evenly, and then put in the refrigerator, where it froze overnight. Chloroacetic acid (4.5 g) dissolved in isopropanol (10 ml) then was dropped onto the frozen chitosan mixture. The mixture was stirred for 20 h at 15 °C. The solution was then filtered and the filter residue was washed with absolute ethanol, the crude product was purified and finally dried under vacuum. The total carboxymethyl substitution degree was determined using the ^{1}H NMR method according to literature (Chen & Park, 2003). The total carboxymethyl substitution degree was 0.7, Among the O-substitution degree was 0.5 and the N-substitution degree was 0.2. The viscosity-average molecular weight was 2×10^5 Da by calculation from the viscosity method (Nishimura, Nishi, Tokura, Nishimura, & Azuma, 1986).

2.3. Preparation of hydrogels

Hydrogels were prepared by radical graft copolymerization of carboxymethylchitosan (CMC) and acrylic acid (AA) with N,N′-methylene-bis-(acrylamide) as a cross-linking agent and $K_2S_4O_8$ as an initiator. The feed compositions of hydrogels are shown in Table 1. AA neutralized with 6.0 mol/L NaOH solution and MBAA were mixed. Then, $K_2S_4O_8$ and CMC was added to this solution, respectively, and dissolved at 20 °C. Mixed solution was degassed by centrifugation of samples at 8000 rpm/min for 15 min at 20 °C. After polymerization at 65 °C for 8 h, the solid copolymer slab was taken out and cut into circular disks, with a diameter of about 9.5 mm and a thickness of 0.8 mm. These disks were divided into two parts. One part was directly used for the determination of grafting percentage; the other part was immersed in deionized water for 4 days to remove the unreacted chemicals, during this time the water was changed once every 8 h, then was dried under vacuum at 30 °C until constant weight was obtained. This part was used for swelling kinetics and analysis of graft copolymer compositions. Each polymer composition estimated by elemental analysis is given in Table 1.

2.4. Determination of grafting percentage

The samples of the crude copolymers were weighed about 2.0 g; then extracted with acetone as solvent for 12 h to remove the homopolymers completely and finally the extractors were dried under vacuum at 60 °C until constant weight. The grafting parameters were calculated as

$$\text{Grafting percentage } (G\%) = \left[\frac{W_2 - W_1}{W_1}\right] \times 100\% \quad (1)$$

where W_1 is the weight of CMC; W_2 is the weight of the extractors. Grafting percentage ($G\%$) of each graft copolymer is also given in Table 1.

2.5. FT-IR spectroscopy

The FT-IR was performed by using Nicolet Fourier transform infrared spectroscopy (made by Thermo Nicolet), over the range 500–4000 cm^{-1}. The dried gels pretreated in the pH 2.2 buffer were immersed in the pH 7.0 at the experimental temperature. Then the samples were taken out at set time and treated by liquid nitrogen. The treated samples were dried in vacuum until constant weight. Each sample was ground with 2 mg of KBr and then pressed to form transparent disks. According to the swelling time, the adopted nomenclature for these samples is 0 min, 60 min, 240 min, and 600 min. For instance, "60 min", that is, a sample B_2 pretreated in the pH 2.2 buffer swelled for 60 min in the pH 7.0.

2.6. Pretreatment of hydrogels

The samples were soaked in three different buffer solutions (pH 2.2, 4.0, and 7.0) at 25 °C until the swelling equilibrium was reached and then dried. These samples were swelled again at pH 6.0–7.4 to carry out swelling kinetic experiments.

2.7. Swelling of hydrogels

Swelling degree was determined gravimetrically. Pretreated gel disks were left to swell in the buffer media at the experimental temperature. The samples were taken out at regular time intervals from the buffers, wiped superficially with filter paper, weighed and then placed again in the same immersion bath. Manipulate repeatedly until the swelling equilibrium was reached. The swelling degree is defined as the weight of water imbibed by the sample per unit weight of dry gel. The swelling degree Q_t at time t was calculated in grams of water per gram of dry gel using the following expression:

$$Q_t = \frac{m_t - m_0}{m_0} \quad (2)$$

where m_0 is the initial weight of the dried disk, namely, the weight at $t = 0$, and m_t is the weight after a time t. The equilibrium swelling

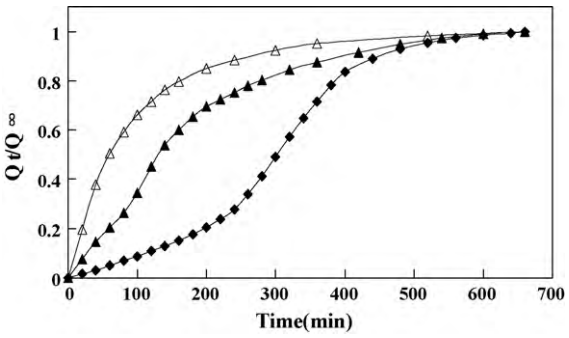

Fig. 1. Dynamic swelling curves at pH 7.0 for gel B_2 pretreated in different buffer solutions. (♦) pH 2.2, (▲) pH 4.0, and (△) pH 7.0.

degree Q_∞ is given by

$$Q_\infty = \frac{m_\infty - m_0}{m_0} \quad (3)$$

2.8. Drug loading and release

Drug loading was carried out as follows: first, the dried gels were swelled in deionized water until equilibrium; then the swollen hydrogels were immersed in the pH 2.2 or 7.0 buffer solution containing 5-ASA. After reaching equilibrium again, the hydrogels were taken out, dried and reweighed. The drug content in gels can be calculated by determining the content of 5-ASA in washing water and the original content with a UV–visible spectrophotometer at 331.0 nm. Of these drug-loaded gels, the sample prepared in the pH 7.0 buffer containing 5-ASA was used as a control sample of drug release.

Drug release from the drug-loaded hydrogels was carried out in a thermostatic rotary shaker at shaking speed of 45 rpm at 37 °C. The medium used for the release kinetics of 5-ASA was a 30 ml buffer of pH 7.0. The simulated gastrointestinal media used for the *in vitro* release of 5-ASA were 30 ml buffers (pH 2.2, 6.0 and 7.4). The samples were withdrawn from the buffer media at predetermined time intervals and the release rates of drug were measured by determining the 5-ASA concentrations in the buffers at 331.0 nm.

3. Results and discussion

3.1. Sigmoidal effect of hydrogels

The dynamic swelling curves for gel B_2 pretreated in different buffer solutions (pH 2.2, 4.0, and 7.0), and subsequently immersed in a buffer pH 7.0, are shown in Fig. 1. The dynamic swelling curve for gel B_2 pretreated at pH 2.2 (see pH 2.2) displays a remarkable sigmoidal shape. The whole swelling process shows three stages: initially a slow swelling stage; subsequently an accelerated swelling stage; and finally a gradual swelling until the equilibrium (see Fig. 2).

The sigmoidal swelling effect was given many interpretations. For instance, Siegel et al. (Firestone & Siegel, 1991; Siegel, 1993) found this anomalous behavior for a hydrophobic weak polyelectrolyte of poly[(methyl methacrylate)-co-(N,N-dimethylaminomethacrylate)]. They attributed this effect to a swelling front separating the glassy core from the rubbery periphery. This rigid core constrains the swelling of the outer part. Only when the front reaches the core is the swelling permitted in three dimensions, leading to swelling acceleration. The sigmoidal swelling based on the thermoresponsive hydrogels of poly[(N-iPAAm)-co-(n-butylmethacrylate)] was firstly reported by Okano and co-workers (Okuyama, Yoshida, Sakai, Okano, & Sakurai, 1993; Yoshida, Sakai, Okano, & Sakurai, 1994). They suggested that the acceleration was due to a rapid increase in swelling with disappearance of the glassy core which had constrained swelling. Recently, this similar phenomenon has also been observed by Díez-Peña et al. (2002) in the case of thermoresponsive poly(N-iPAAm-co-MAA) hydrogels. They assumed that the main factor responsible for the effect is the disruption of a cooperative physical cross-linking (i.e. chemical cross-linking and physical cross-linking coexist and are cooperative) caused by the hydrogen bonds between the carboxyl groups and the amide groups of the hydrogels in a neutral solution.

On the basis of that there exist pendant carboxyl groups and amine groups on the network structure for hydrogels studied here, we proposed the sigmoidal swelling kinetics behavior at pH 7.0 for carboxymethylchitosan-g-poly(acrylic acid) hydrogels pretreated in acidic buffer media is also related to the disruption of a cooperative physical cross-linking caused by the hydrogen bond cross-linking between the neighbouring carboxyl groups and the ionic cross-linking between ionized carboxyl groups and protonated amine groups (see Fig. 2). This disruption process was demonstrated by the IR spectra of the hydrogel under swelling.

The sigmoidal swelling processes for the pretreated hydrogels may be divided into the three stages: the initial slow swelling stage, and subsequently the accelerated swelling stage and finally the gradual swelling until equilibrium. The FT-IR spectra in the different swelling stages in the pH 7.0 buffer for hydrogel B_2 pretreated at pH 2.2 are shown in Fig. 3. The relatively strong characteristic absorption band at 1720 cm^{-1} (see curve 0 min) before swelling indicates presence of hydrogen bonds between the protonated carboxyl groups. The similar results have also been reported in the literature (Bures & Peppas, 2000; Devine & Higginbotham, 2003; Yin et al., 2008), which were attributed to the formation of

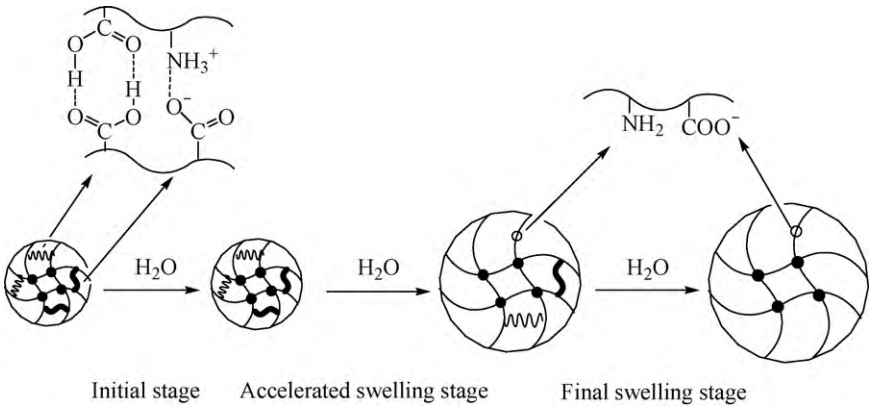

Fig. 2. Schematic picture of the sigmoidal swelling kinetics for carboxymethylchitosan-g-poly(acrylic acid) hydrogels.

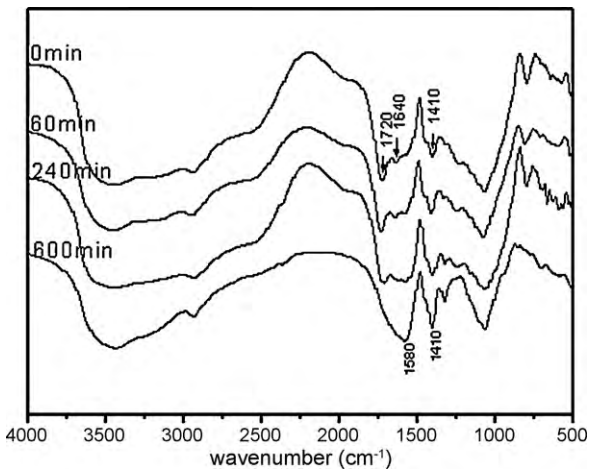

Fig. 3. FT-IR spectra at set time during swelling in the pH 7.0 buffer for gel B_2 pretreated at pH 2.2.

dimers between the carboxyl groups. The NH_3^+ absorption band at 1640 cm^{-1} and the COO^- symmetrical extension vibration at 1410 cm^{-1} (Chen et al., 2007; Sun et al., 2004) indicate the presence of ionic cross-linking between amine groups and some carboxyl groups. Compared with that before swelling, the significant differences are not observed in the spectrum (see curve 60 min). This indicates the cooperative physical cross-linking remain stable in this swelling stage (during the initial swelling). However, in the spectrum (see curve 240 min), the bands at 1720 cm^{-1} and 1640 cm^{-1} decrease; and the COO^- absorption bands at 1410 cm^{-1} and 1580 cm^{-1} become strong. These indicate that the degree of cooperative physical cross-linking becomes weak in the accelerated swelling stage. When the hydrogel swelled for 600 min (during the final swelling), the bands at 1720 cm^{-1} and 1640 cm^{-1} disappear (see curve 600 min), the bands at 1410 cm^{-1} and 1580 cm^{-1} become stronger. These indicate the complete ionization of carboxyl groups on the network at this time.

When the gels pretreated under acidic buffer media and dried are swelled again at pH 7.0, first, the cooperative physical cross-linking on the networks hinder or restrict the penetration of water inside the hydrogel and resulting in a slow initial swelling stage. With the progress of swelling, the degree of cooperative physical cross-linking becomes weak owing to the ionization of carboxyl groups at pH above pK_a and the loss of protons of NH_3^+ groups at pH 7.0; the swelling begins to accelerate. When the ionization of the carboxyl groups reaches a certain degree, at which the cooperative physical cross-links disrupt completely, the swelling begins to become slow until the maximal ionization of the carboxyl groups, the swelling reaches equilibrium.

3.2. Dependence of sigmoidal effect on the pretreating pH

The influence of the pH of the pretreating buffer solution on the sigmoidal effect is also shown in Fig. 1. The shape of the swelling curves depends strongly on the pretreating pH. The sigmoidal effect of hydrogel becomes unremarkable with the increase of pH value. Compared with that for hydrogel pretreated at pH 2.2, the time of accelerated swelling is earlier for hydrogel pretreated at pH 4.0, the swelling rate of initial stage increases. On the contrary, the dynamic swelling curve does not display sigmoidal shape for the hydrogel pretreated at pH 7.0.

The gel which was pretreated at buffer pH 2.2 and dried has the compact structure and strong hydrophobicity due to strong hydrogen bonds and ionic cross-linking, so exhibiting a slow initial water uptake when swelled at pH 7.0. However, with the increase of pre-

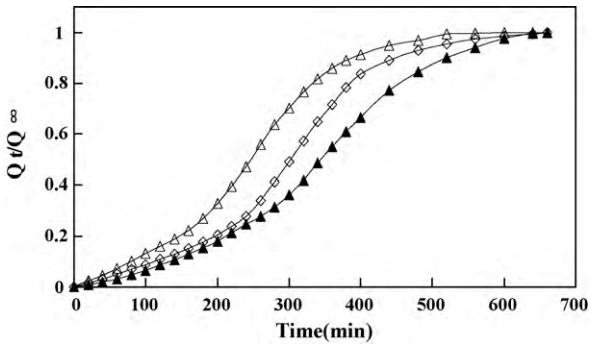

Fig. 4. Dynamic swelling curves in the pH 6.0–7.4 buffer solutions for gel B_2 pretreated at pH 2.2. (▲) pH 6.0, (◊) pH 7.0, and (△) pH 7.4.

treating pH value, the swelling time in the initial stage is shortened and the accelerated swelling shifts to an earlier time. This is obviously attributed to the degree of hydrogen bond cross-linking being weakened because of the decrease in the protonated degree of carboxyl groups. For the hydrogel pretreated at pH 7.0 and dried, the carboxyl groups on the network being in the complete ionization state, the hydrogel swelling directly accelerates due to the repulsive interaction between ionized carboxyl groups, therefore the hydrogel does not display sigmoidal shape swelling behavior.

3.3. Influence of the buffer pH on sigmoidal effect

The dependence of sigmoidal swelling kinetics on the pH of buffer solution is shown in Fig. 4: the remarkable sigmoidal dynamic swelling curves at pH 6.0–7.4 are observed for hydrogels B_2 pretreated at pH 2.2. The accelerated swelling stage appears earlier with the increase of pH, which can be attributed to the faster ionization of carboxyl groups causing an earlier disruption of the hydrogen bond cross-linking.

As mentioned in the introduction, the hydrogels based on carboxymethylchitosan-g-poly(acrylic acid) could not avoid the release of drugs in the small intestine because their equilibrium swelling degree is very high in the small intestinal pH media. However, the sigmoidal swelling kinetics behavior of the hydrogels shows potential for avoiding release of the drugs in the small intestine. In the pH 6.0–7.0 buffers, there exists a slow initial swelling stage close to the small intestinal residence time for the hydrogels pretreated at pH 2.2 (see Fig. 4), so no release of the drugs or a limited release in the small intestine may be achieved. Subsequently an accelerated swelling of the hydrogels can trigger the immediate release of drug from the delivery system to reach the colon.

3.4. Influence of composition of hydrogels on sigmoidal effect

The effect of composition of hydrogels B_1–B_3 on the swelling kinetics is shown in Fig. 5. Remarkable sigmoidal dynamic swelling curves for these hydrogels, especially for hydrogel B_2, are observed. This may be attributed to the higher degree of hydrogen bond cross-linking on the network. Moreover, compared with hydrogel B_2, the weaker sigmoidal swelling curve of hydrogel B_3 with the highest molar ratio of AA may be attributed to the higher hydrophilicity of PAA.

3.5. Kinetics model for interpretation of sigmoidal effect

Although the sigmoidal effect has been reported earlier, much attention is paid to the qualitative explanation of this phenomenon. Up to recent years, a quantitative kinetics equation was given by Díez-Peña et al. (2002) for the sigmoidal curves appeared in the swelling processes of poly(N-iPAAm-co-MAA). It can be expressed

Table 2
Eqs. (4) and (6) kinetic parameters at pH 7.0 for gels B_1–B_3 pretreated in pH 2.2 and 7.0 buffer solutions.

Pretreating pH	pH 2.2				pH 7.0	
Kinetic equation	Eq. (4)				Eq. (6)	
Kinetic parameters	10^3k_1	10^3k_2	k_1/k_2	R^2	10^3K	R^2
Gel (B_1)	1.0	15.1	0.0662	0.9995	3.747	0.995
Gel (B_2)	0.1	16.6	0.0060	0.9995	1.601	0.998
Gel (B_3)	0.4	13.6	0.0294	0.9990	0.836	0.995

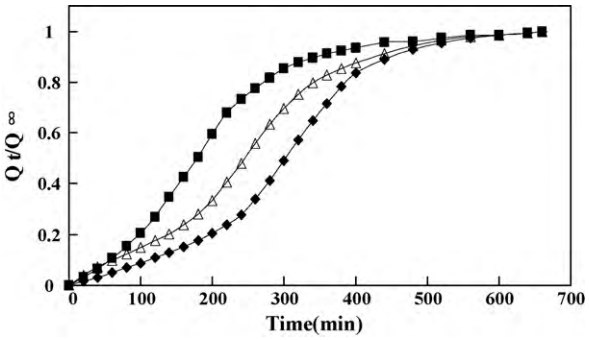

Fig. 5. Dynamic swelling curves in the pH 7.0 buffer for gels B_1–B_3 pretreated at pH 2.2. (■) B_1, (♦) B_2, and (△) B_3.

as follows:

$$\ln\left[\frac{(k_1/k_2)+(Q_t/Q_\infty)}{1-(Q_t/Q_\infty)}\right] = \ln\left[\frac{k_1}{k_2}\right] + (k_1+k_2)t \quad (4)$$

where k_1 is a first-order rate constant, corresponding to the initial penetration of water, and k_2 is the accelerative rate constant. Values for rate constants k_1, k_2, their ratio k_1/k_2, and determination coefficient R^2 from the best fitting of the experimental values for hydrogels B_1–B_3 pretreated in the pH 2.2 buffer to Eq. (4) are gathered in Table 2. As it can be seen, the values of the determination coefficients are quite good, $R^2 \geq 0.999$.

The shape of swelling kinetics curve depends on the relative value of the two rate constants k_1 and k_2 or k_1/k_2. Compared with those for hydrogels B_1 and B_3, the swelling process in the pH 7.0 for hydrogel B_2 pretreated in the pH 2.2 buffer has the lower value of k_1 and the higher value of k_2 or the lower value of k_1/k_2 (see Table 2), and display a more remarkable sigmoidal swelling effect (see Fig. 5).

When $k_1 \gg k_2$, Eq. (4) can be simplified to a first-order kinetics form:

$$\frac{Q_t}{Q_\infty} \approx 1 - e^{-k_1 t} \quad (5)$$

At the initial swelling stage, because of the higher cooperative physical cross-linking degree, the difficult diffusion or penetration of water into gel and the sample volume almost remaining constant, the swelling process is controlled by a first-order swelling kinetics.

3.6. Swelling kinetics for hydrogels pretreated in the pH 7.0 buffer

As it is seen from Fig. 1 the gel B_2 pretreated in the pH 7.0 buffer and dried does not show a sigmoidal swelling kinetics when it swelled again in the solution. This is attributed to the cooperative physical cross-linking not being formed due to the complete ionization of carboxyl groups in the pretreated buffer. We assume that the swelling process of hydrogel should follow the second-order swelling kinetics proposed by Schott (1992). The swelling kinetics equation may be expressed as follows:

$$\frac{t}{Q_t} = \frac{1}{KQ_\infty^2} + \frac{t}{Q_\infty} \quad (6)$$

where K is a second-order rate constant and t is swelling time. By the application of the swelling data of hydrogels B_1–B_3 at pH 7.0 to Eq. (6), rate constant K and determination coefficient R^2 are obtained and collected in Table 2: the values of the determination coefficients are quite good, $R^2 > 0.99$. This result demonstrates that the swelling processes of hydrogels pretreated in the pH 7.0 follow Schott's swelling theoretical model.

3.7. Drug release of hydrogels

The profiles of drug release at pH 7.0 from the drug-loaded gel samples are shown in Fig. 6. The sample (Gel-1) prepared using hydrogel B_2 in the pH 7.0 buffer containing 5-ASA was used as a control. As compared with the control, the release profile of the sample (Gel-2) prepared in the pH 2.2 buffer containing 5-ASA exhibits an obvious sigmoidal shape, while a burst release appears at the start for the control. This is obviously attributed to a cooperative physical cross-linking (the hydrogen bond cross-linking between the neighbouring carboxyl groups and the ionic cross-linking between ionized carboxyl groups and protonated amine groups) in the loading medium of pH 2.2.

The profile of drug release during the conditions simulating the pH and time intervals likely to be encountered during transit from stomach to colon was also illustrated in Fig. 6 (see Gel-3). First, the sample (Gel-3) prepared in the pH 2.2 loading medium was put in the pH 2.2 buffer for 2.0 h, then at pH 6.0 for 3 h, finally at pH 7.4 for 30 h. From Fig. 6 we can see that there is a little bursting release (about 9.86%) in the initial 5 h, which may be ascribed to desorption of 5-ASA from the gel surface. However, the 5-ASA release was accelerated when the drug-loaded hydrogel was exposed to the pH 7.4 medium, and is nearly complete at 20 h.

The release mechanism of hydrophilic drug is based on the diffusion process by means of water as a medium. The pore size and number in hydrogel control the speed of drug release. When the

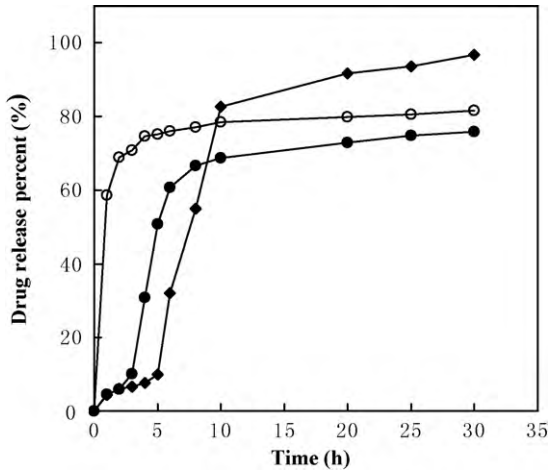

Fig. 6. Release of 5-ASA in the pH 7.0 buffer and during simulating gastrointestinal conditions from the drug-loaded gels prepared with hydrogel B_2. Gel-1 (○): a control sample; Gel-2 (●): pH 7.0; and Gel-3 (♦): simulating gastrointestinal conditions.

gels pretreated in acidic buffer media and dried are swelled again at pH 7.0, first, as mentioned before, the cooperative physical cross-linking on the networks hinder or restrict the penetration of water inside the hydrogel and resulting in a slow initial release stage. With the progress of swelling, the disruption of cooperative physical cross-linking leads to the increase of pore diameter and number in the hydrogel, and thus the release of drug accelerates.

4. Conclusions

The dynamic swelling curves in the pH 6.0–7.4 buffers for carboxymethylchitosan-g-poly(acrylic acid) hydrogels pretreated in acidic buffer media display sigmoidal shape. This anomalous phenomenon can be attributed to the disruption of a cooperative physical cross-linking on the networks. The cross-linking increases the hydrophobicity of hydrogels and leading to a slow initial swelling stage. Subsequently the gradual disruption of cross-linking triggers an accelerated swelling. The swelling kinetics of the hydrogels depends on their composition, the buffer pH, and the pretreating pH. The increase of pretreating pH leads to a weakening of the sigmoidal effect. The hydrogels pretreated in neutral buffer do not show a sigmoidal shape swelling.

The profile of drug release in the simulating gastrointestinal conditions from the gel prepared in the pH 2.2 buffer solution containing 5-ASA exhibits a sigmoidal release curve, namely, an initial slow release followed by a burst release. The hydrogels show the suitability for the delivery of 5-ASA to the colon.

Acknowledgments

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