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Synthesis and properties of degradable hydrogels of konjac glucomannan grafted acrylic acid for colon-specific drug delivery

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Abstract

In this paper, we reported the synthesis and properties of novel hydrogel systems designed for colon targeted drug delivery. The gels were composed of konjac glucomannan (KGM), copolymerized with acrylic acid (AA) and cross-linked by *N*,*N*-methylene-bis-(acrylamide) (MBAAm). The influence of various parameters on the equilibrium swelling ratios of the hydrogels was investigated. The swelling ratio was inversely proportional to the content of MBAAm. It was possible to modulate the degree of swelling of the gels by changing cross-linking density of the polymer. The gels' swelling ratio has sensitive respondence to the environmental pH value variation. The results of degradation test show that the hydrogels retain the enzymatic degradation character of KGM and they can be degraded for 52.5% in 5 days by Cellulase E0240. In vitro release of model drug 5-aminosalicylic acid (5-ASA) was studied in the presence of Cellulase E0240 in pH 7.4 phosphate buffer at 37 °C. The accumulative release percent of 5-ASA reached 95.19% after 36 h and the drug release was controlled by the swelling and degradation of the hydrogels.

Keywords: pH-sensitive; Hydrogels; Colon-specific drug delivery

1. Introduction

In the past two decades, oral drug delivery systems for colon have been extensively investigated for the local treatment of a variety of bowel diseases [1–3] and for improving systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal tract [4]. Targeting of drugs to the colon can be achieved in several ways [5–10]. Prodrugs can provide site-specific drug delivery, but they are new chemical entities and detailed toxicological studies need to be performed before their use. The pH-sensitive delivery systems, such as enteric-coating, can be a simple and practical means for colon-specific drug delivery. However, such methods do not have sufficient site specificity because the large variations in the pH of the gastrointestinal tract. Although, the time-controlled release systems seem promising, the disadvantage of such systems is that the colon arrival time cannot be accurately predicted because the significant variations of gastric emptying time and small intestinal transit time between different patients [11], which result in poor colonic availability. Biodegradable matrix systems are very promising, because they can only be degraded by colonic bacterial enzymes and not be degraded in the stomach and small intestine.

Polysaccharides are polymers of monosaccharides. They are abundant, inexpensive and available. Their biodegradability and easily modified ability suggest their applications in colon-targeted drug delivery systems. Sinha and Kumria [8] reviewed that a large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextran, guar gum, inulin, amylose and locust bean gum. KGM is a high-molecular weight water-soluble non-ionic polysaccharides, it can be extracted from tubers of *Amorphophallus konjac* plant in large quantities. It is a linear random copolymer of β(1,4) linked D-mannose and D-glucose, the ratio of mannose and glucose is 1.6:1 [12]. There are some branching points at the C-3 position of the mannoses, an acetyl group is attached to one per 19 sugar residues [13]. KGM is not hydrolyzed by

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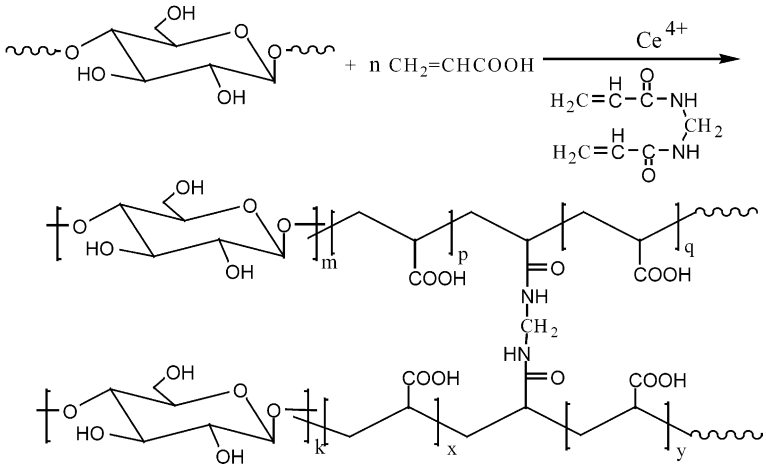

Scheme 1. Preparation of konjac glucomannan-*graft*-acrylic acid hydrogels.

digestive enzymes in upper gastrointestinal tract of human beings and is considered as an indigestible dietary fibre. However, it could be hydrolyzed by β-mannase to manufacture manno-oligosaccharides [14] or by other β-glycosidases to oligosaccharides. KGM could form strong, elastic, heat-stable gels when heated with mild alkali [15], and has also been studied as drug carriers [16]. In our previous work, we found that the graft copolymers of KGM and acrylic acid retain the enzymatic degradation specificity and potential for the colon-specific delivery of protein or peptide drugs [17].

In this paper, a novel hydrogel was designed to take advantages of biodegradability of KGM and pH-dependence of poly(acrylic acid). The obtained gels are expected to have enhanced site-specificity to colon. In addition, the hydrogels can be prepared in aqueous medium under moderate temperature. We studied the dependence of swelling behavior of the hydrogels on the reaction conditions and pH value of external environment. The biodegradability of the hydrogels was also tested under Cellulase E0240 which contains β-glucosidases. In order to evaluate hydrogels' potential as colon-specific carriers, the drug release properties of the hydrogels was investigated by using 5-aminosalicylic acid (5-ASA), a drug for treatment of bowel diseases, as the model drug. The drug release test was conducted under conditions simulating pH values and courses likely to be encountered during drug transition from stomach to colon.

Table 1
Influence of concentration of CAN on hydrogel's swelling ratio (SR)

Entry	Molar ratio[a] KGM:CAN	SR (pH=7.4, 25 °C)
A1	60:1	9.23
A2	50:1	8.84
A3	40:1	9.14
A4	30:1	9.80
A5	20:1	10.39
A6	15:1	10.72
A7	10:1	12.65

KGM, 0.162 g; H_2O, 20 ml; MBAAM, 5×10^{-3} mol/l; AA, 2.0 mol/l.
[a] The molar content of KGM is calculated based on monosaccharide unit.

2. Experimental

2.1. Materials

Konjac glucomannan (KGM) was purified by extracting the refined konjac powder (purity of 95%, supplied by Shiyan Huaxianzi Konjac productions Co. Ltd, Hubei, China) with benzene-ethanol (4:1, v/v), then with chloroform-ethanol (5:1, v/v). Ceric ammonium nitrate (CAN), *N*,*N*-methylene-bis-(acrylamide) (MBAAm) and 5-aminosalicylic acid (5-ASA) were used without any further purification. Acrylic acid (AA, purchased from Shanghai Chemical Group, China) were purified by vacuum distillation. Cellulase E0240 was purchased from Shanghai Bio Life Science and Technology Co. Ltd, China (M_w= 52,000 g/mol, enzymatic activity $\geq$15 U/mg). Pancreatin was purchased from Wenjiang Tianyuan Biochemical Products Factory, Chengdu, China.

Table 2
Influence of molar content of AA on hydrogel's swelling ratio (SR)

Entry	Molar ratio[a] KGM:AA	SR (pH=7.4, 25 °C)
B1	1:10	11.15
B2	1:15	10.09
B3	1:20	11.94
B4	1:25	12.34
B5	1:30	10.36
B6	1:35	12.94
B7	1:40	14.14

KGM, 0.162 g; H_2O, 20 ml; MBAAM, 5×10^{-3} mol/l; CAN, 2.5×10^{-3} mol/l.
[a] The molar content of KGM is calculated based on monosaccharide unit.

2.2. Synthesis of hydrogels and drug loading

KGM (0.162 g) was dissolved in 20 ml water for 12 h and heated to 60 °C for 30 min, various of amount of CAN, AA and MBAAm were added to the solution. Before reaction, the solution was bubbled with nitrogen for at least 10 min to discharge oxygen. The reaction mixtures were stirred for 10 min and maintained 60 °C for 3 h. After reaction, the gels were washed several times with double distilled water to remove unreacted monomers, homopolymers and other small molecules. Then the gels were dried under 60 °C to constant weight and stored for further use.

The model drug 5-ASA was dissolved in 50 ml water to form saturated solution. The dry gels were dipped into the solution for 24 h. The gels were washed several times with double distilled water and dried under 45 °C to constant weight.

2.3. Fourier transform infrared spectroscope (FTIR) analysis

KGM and the hydrogels were analyzed by FTIR spectrometer to confirm grafting and cross-linking reactions. FTIR spectra were obtained on Perkin–Elmer-2 spectrometer (KBr, pellet).

2.4. Scanning electron microscope (SEM)

For SEM analysis, the samples were coated with gold–palladium for 70 s in an argon atmosphere before observing them under the microscope (HITACHI X-650, Japan).

2.5. Studies of the dynamic and equilibrium degree of swelling

The weighed mass of dry gels (W_0) were dipped in the swelling medium. At predetermined time intervals the gels were removed from the swelling medium, blotted with filter paper to remove excess water from the gel surface, and the weight of the swollen hydrogels (W_1) was weighed. The swelling ratio (SR) is calculated according to:

$$\mathrm{SR} = \frac{(W_1 - W_0)}{W_0}$$

The swelling ratio was considered to be the equilibrium swelling ratio when the hydrogel reached a constant weight.

The influence of pH on the swelling behavior of gels was studied by immersing the gels in buffer solutions with different pH values at room temperature. And the change of swelling ratio of gels with time from the beginning to the equilibrium state was also studied at 37 °C.

2.6. Degradation

The enzymatic degradation of the hydrogels were carried out in a flask filled with 25 ml phosphate buffer (pH = 7.4, 0.1 mol/l, 37 °C) which contained determined content of Cellulase E0240 or pancreatin and 0.6 mg NaN_3. The degradation experiments were conducted by immersing the dry gel mass in buffer placed in a thermostatic rotary shaker (Grant CS200G, England) and by the determination of the weight loss after recovery of the samples at predetermined time intervals. The buffer solution was changed every day to maintain enzymatic activity. After a predetermined time, the samples were removed from the solution, washed thoroughly with double distilled water, and then dried under 60 °C.

Table 3
Influence of molar content of MBAAm on hydrogel's swelling ratio (SR)

Entry	Molar ratio AA:MBAAm	SR (pH = 7.4, 25 °C)
C1	3200:1	35.50
C2	2000:1	26.70
C3	1600:1	22.41
C4	1200:1	21.18
C5	800:1	18.43
C6	400:1	13.52
C7	200:1	11.29

KGM, 0.162 g (0.001 mol); H_2O, 20 ml; CAN, 5×10^{-3} mol/l; AA, 2.0 mol/l.

2.7. Estimation of drug loading and in vitro drug release

With UV–vis spectrophotometer (Shimadzu UV-240) at 331.2 nm, we can calculate the drug loading in gels by determining the content of 5-ASA in washing water and the original content.

In vitro drug release from the hydrogels was carried out in a thermostatic rotary shaker at shaking speed of 45 rpm at 37 °C. One of the dissolution media used for the release of 5-ASA was 25 ml phosphate buffer solution. Another was 25 ml phosphate buffer solution added with 3.33 mg

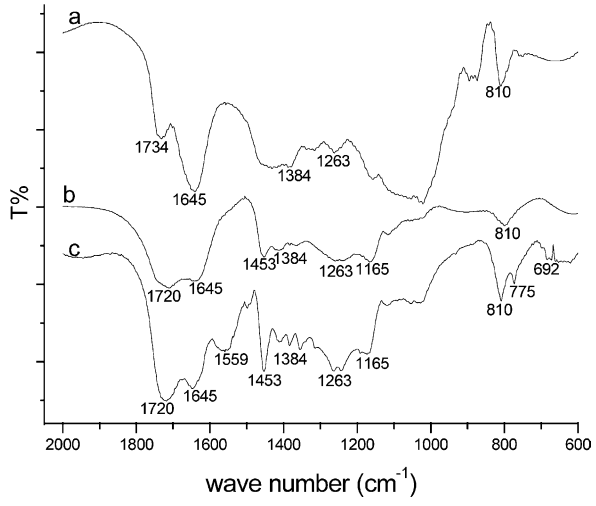

Fig. 1. FTIR spectra of KGM (a), hydrogel (b), and hydrogel-loaded 5-ASA (c).

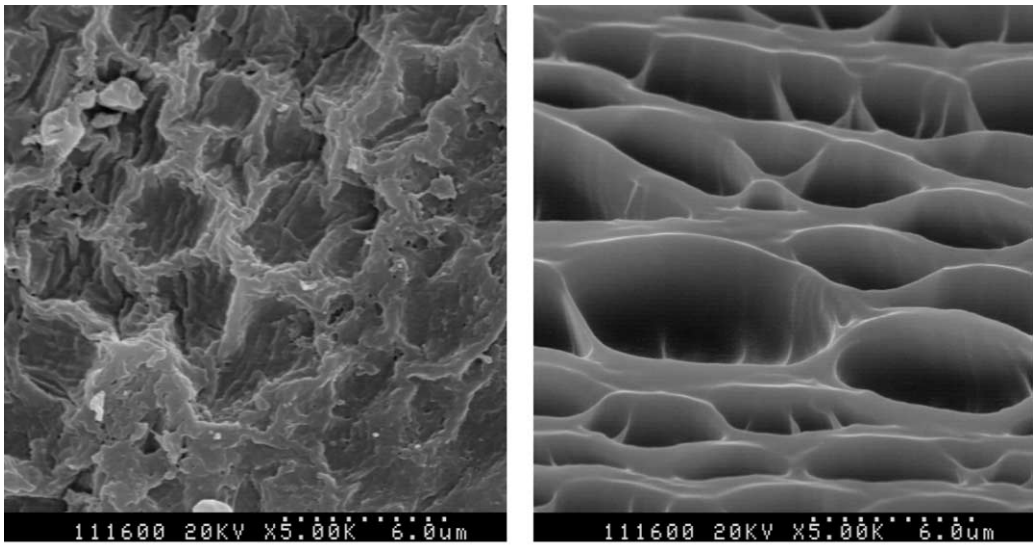

Fig. 2. SEM photographs of KGM powder (a) and cross-section of heating dried hydrogel C1 (b) (the scale bar 6 μm).

Cellulase E0240 (or 5.0 mg pancreatin) and 0.6 mg NaN_3, and the solution was changed at predetermined time intervals to measure the released drug. The 5-ASA concentration was determined with UV–vis spectrophotometer at 331.2 nm.

3. Results and discussion

3.1. Synthesis of hydrogels

Graft copolymerization of konjac glucomannan with acrylic acid was performed by free-radical polymerization initiated by Ce(IV). Ce(IV) can effectively initiate saccharide units to generate free-radical sites, which react with AA monomers to form graft copolymer. The hydrogels were obtained by incorporating of cross-linker MBAAm. The gel formation is shown in Scheme 1.

In order to optimize hydrogel synthesis and to find the relation between the reaction conditions and the swelling ratio of resultant hydrogels, the influence of the parameters, such as concentration of CAN, AA, and MBAAm on the water uptake of gels was investigated (Tables 1–3). In a certain range of concentrations, the molar content of CAN or AA does not significantly affect the equilibrium degree of swelling (Tables 1 and 2). Contrastively, the molar content of cross-linker in feed has an evident influence on the swelling ratio of the gels. From Table 3, it can be clearly seen that the equilibrium degree of swelling decreased with increasing molar content of MBAAm in the gels, which can be explained as the consequence of the lower hydrophilic nature of MBAAm in combination with the increased cross-linking density.

Table 4
Influence of the content of the cross-linking reagent on hydrogel's drug-loading

Entry	C3	C4	C5	C7
Ratio of drug to dry gel (wt%)	9.46	7.70	5.71	3.61

The hydrogel symbols are designated in Table 3.

3.2. FTIR characterization of KGM films and hydrogels

From IR spectrum of KGM (Fig. 1), it can be seen that the absorption band of carbonyl of acetyl groups was at 1734 cm^{-1} [18] and the band at 1645 cm^{-1} was the intramolecular hydrogen bonds. For the IR spectra of the hydrogels, comparing with spectrum of KGM, some peaks disappeared or became stronger due to interaction or superposition of peaks among groups of MBAAm, AA, and KGM. It can be seen that 1720 cm^{-1} was assigned to the absorption of carbonyl group of poly(acrylic acid) moieties. The band at 1263 cm^{-1} was characteristic absorption of C–O stretching. The peaks at 1453 and 1165 cm^{-1} were absorption bands of poly(acrylic acid) backbone chain. The peaks of 1559, 775 and 692 cm^{-1} was attributed to trisubstituted benzene (5-ASA).

3.3. SEM micrographs of KGM and the hydrogel

The graft copolymerization of glucomannan with acrylic acid was further confirmed by SEM micrographs of KGM and the heating dried hydrogel (Fig. 2). Before graft copolymerization, the surface of KGM was rough and compact. After reaction, the surface of the hydrogel was

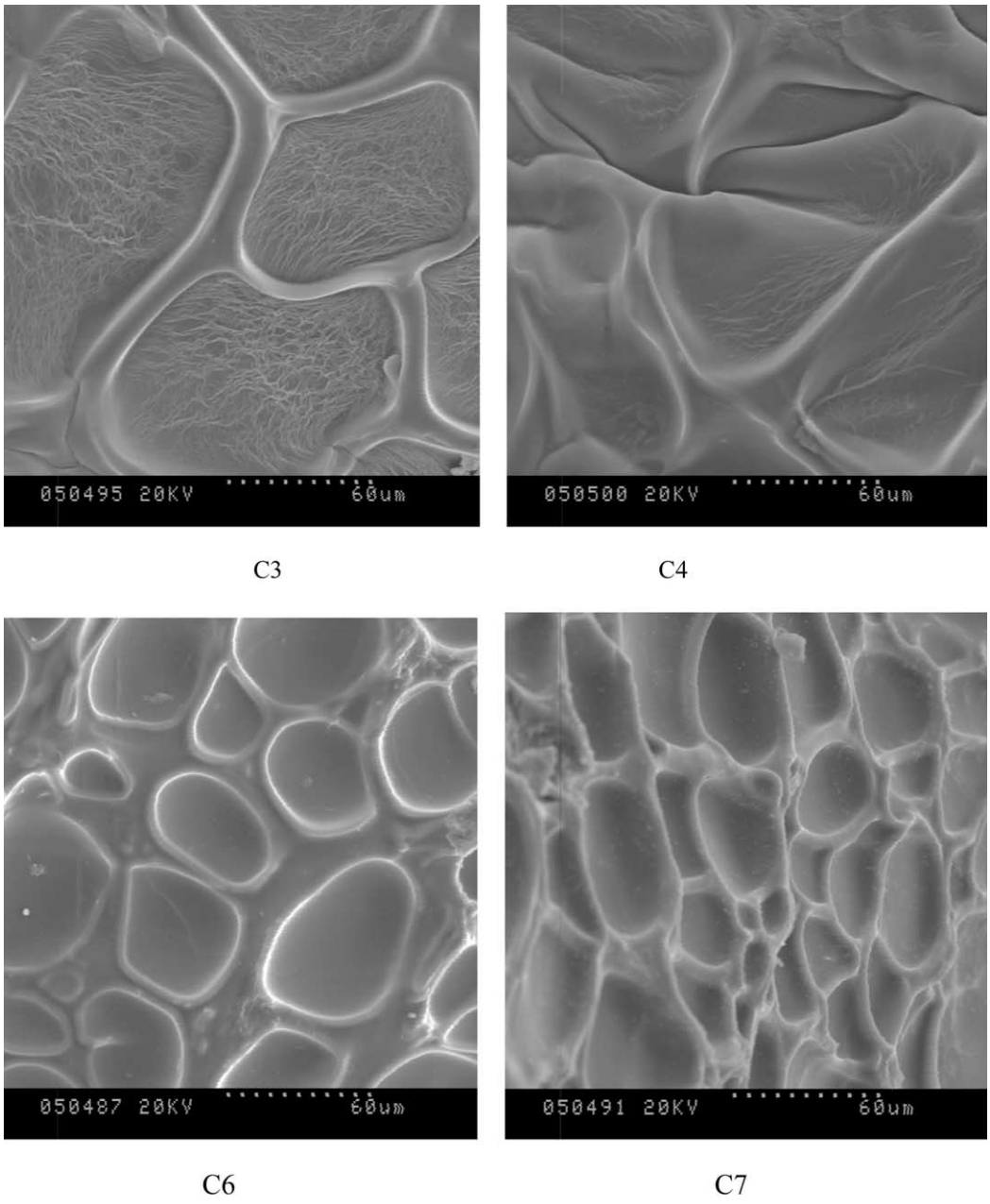

Fig. 3. SEM photographs of the freeze dried hydrogels surface with different cross-linking density (the scale bar 60 μm). The hydrogel symbols are designated in Table 3.

smooth and porous, and there are caves and holes inside the hydrogel. The significant texture difference between the KGM and the hydrogel reflected apparently that cross-linking network was formed.

The morphology of the freeze dried gels' surface is observed using SEM (Fig. 3). The average pore diameter of hydrogel C3 is about 117 μm when the molar ratio of acrylic acid to cross-linker is 1600:1. However, the average pore diameter of hydrogel C7 decreases to 27 μm when the molar ratio of acrylic acid to cross-linker is decreased to 200:1. From Fig. 3, it can be seen that the average pore diameter of the gels decreases with the increasing cross-linking density.

3.4. Dynamic and equilibrium swelling studies

The swelling kinetics of the hydrogel was studied in pH 7.4 buffer solution at 37 °C. The time to achieve the equilibrium swelling were about 24 h for most samples (Fig. 4). The different swelling ratios owe to the different cross-linking densities of the hydrogels [19].

Environmental pH value has a large effect on the swelling behavior of these gels [20]. From Fig. 5, it is clear that in the lower pH values the gel swelled less; the swelling ratio increases with pH values elevated and reaches the maximum at pH 7.4; after that it decreases.

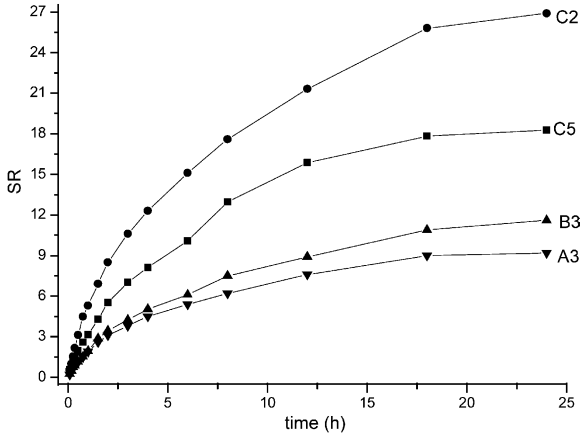

Fig. 4. Swelling kinetics for different hydrogels in phosphate buffer solution of pH 7.4 at 37 °C. The hydrogel symbols are designated in Tables 1–3.

Such pH-dependent properties of the hydrogels come from the polyelectrolyte nature of poly(acrylic acid) segments in the hydrogel network.

To evaluate the reswelling ability and the pH-senstivity of the hydrogels, the gel examples were put in pH 2.2 buffer solution, then transferred to pH 7.4 buffer solution, such operations for three cycles. The gels were incubated in one buffer solution for at least 36 h before being transferred to the other buffer solution. We can see from Fig. 6 that SR values almost remained unchanged in pH 2.2 buffer solution and pH 7.4 buffer solution. The results show that the hydrogel has good reswelling ability and maintain its sharp respondence to pH variation.

3.5. Degradation

To estimate the biodegradability of the obtained hydrogels, the enzymatic hydrolysis experiment was carried out in pH 7.4 buffer solution at 37 °C with Cellulase E0240 concentration of 0.133 mg/ml. To test the specificity to

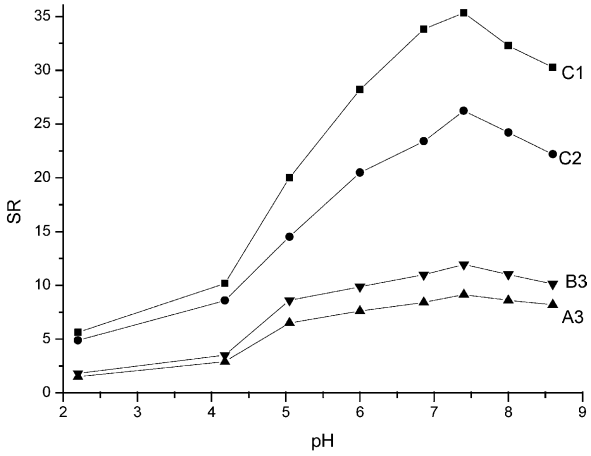

Fig. 5. The influence of pH values of phosphate buffer solution on equilibrium swelling behavior of hydrogels at 25 °C. The hydrogel symbols are designated in Tables 1–3.

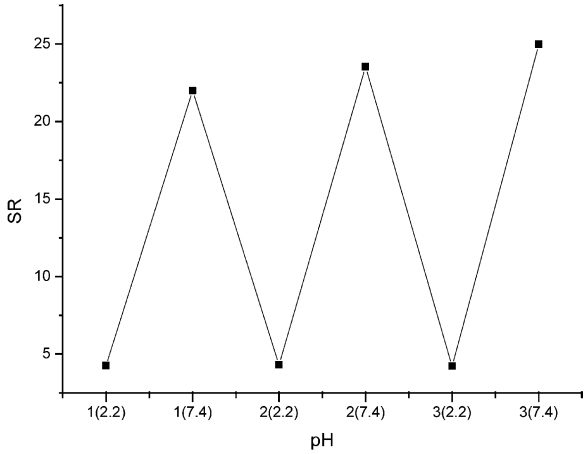

Fig. 6. Equilibrium reswelling behavior of hydrogel C2. Sample was transferred from pH 2.2 buffer solution to pH 7.4 buffer solution for three cycles at 25 °C.

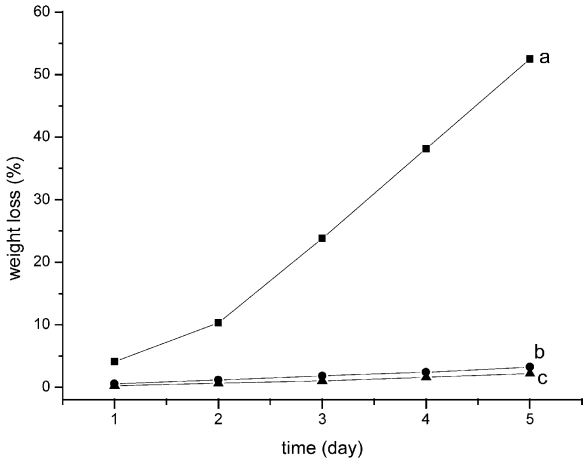

Fig. 7. Degradation of heating dried hydrogel C3 in buffer solution of pH 7.4 with Cellulase E0240 (0.133 mg/ml) (a), with pancreatin (0.2 mg/ml) (b) or without enzymes (c) at 37 °C.

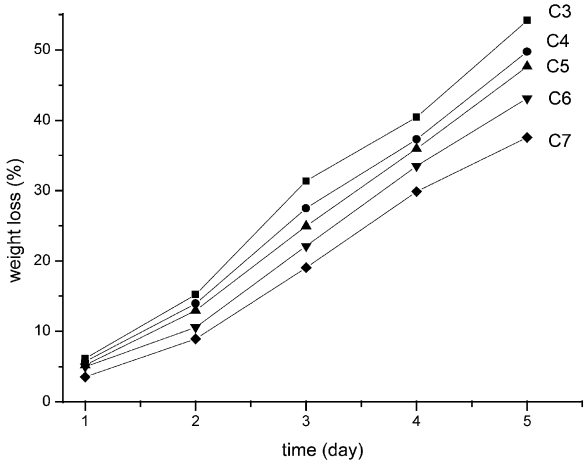

Fig. 8. Degradation of different freeze dried hydrogels in buffer solution of pH 7.4 with 0.133 mg/ml Cellulase E0240 37 °C. The hydrogel symbols are designated in Table 3.

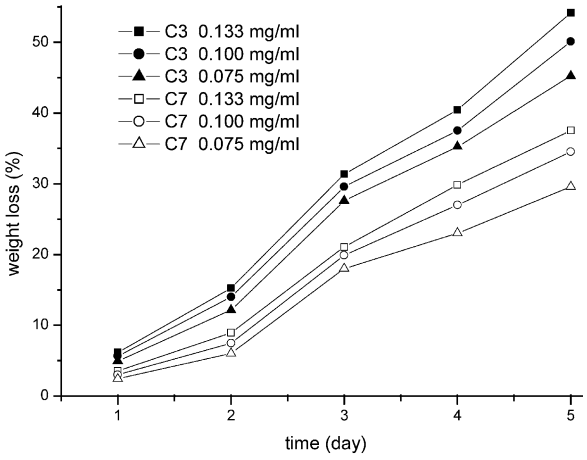

Fig. 9. Degradation of freeze dried hydrogels in buffer solution of pH 7.4 with different concentrations of Cellulase E0240 at 37 °C. The hydrogel symbols are designated in Table 3.

enzymatic degradation, pancreatin, which occurs in the upper gastrointestinal tract, was used as positive control, and buffer solution without enzymes was used as negative control. The results (Fig. 7) indicated that KGM-*graft*-AA gel could not be degraded in pH 7.4 buffer solution, or by pancreatin, but it could be degraded by Cellulase E0240, which contains β-glycosidases, and the weight loss was 52.5% for 5 days. The results suggested that KGM grafted copolymers can be degraded by the enzymes which can degrade KGM itself [14], i.e. KGM-*graft*-AA gels retain the biodegradability characters of KGM.

The cross-linking density of the gels can significantly affect the degree of the gels' degradation (Fig. 8). The weight loss decreases from 52.5 to 37.6% after degradation by Cellulase E0240 for 5 days when the molar ratio of acrylic acid to cross-linker is decreased from 1600:1 (C3) to 200:1 (C7). The rate and the degree of the gels' degradation both decrease with the increasing cross-linking density.

The concentration of the Cellulase E0240 can significantly affect the rate of the gels' degradation (Fig. 9). When the concentration of Cellulase E0240 increases from 0.075 to 0.133 mg/ml, the weight loss of hydrogel C3 increases from 45.2 to 52.5%, at the same time, the weight loss of hydrogel C7 increases from 29.6 to 37.6%. That is, the rate of the gels' degradation increases with the increasing concentration of Cellulase E0240.

3.6. In vitro drug release

The dried hydrogel was soaked in buffer solution containing 5-ASA at ambient temperature for 2 days, and then dried under 45 °C to constant weight. The maximal drug loading can arrive 9.46% (wt%) and it is found to be the cross-linking density dependent (Table 4), it decreases with the increasing cross-linking density.

The drug release was investigated using drug-loaded hydrogels in buffer solution of pH 7.4 with different concentrations of Cellulase E0240 at 37 °C (Fig. 10). There is a little bursting release (about 9%) at the initial stage, which is due to desorption of 5-ASA from the gel surface. The accumulative release percent is much higher in the medium with β-glycosidase than in the medium without β-glycosidase, they are 94.0 and 37.1% after 36 h, respectively. The former is mainly due to the degradation of the gel networks, the latter may be the result of diffusion of hydrophilic 5-ASA from the hydrogel when the gel becomes swollen. The release rate can be affected by the concentration of Cellulase E0240, the accumulative release percent increases from 86.8 to 94.0% after 36 h when the concentration of Cellulase E0240 increases from 0.075 to 0.133 mg/ml, i.e. the release rate increases with the increasing concentration of Cellulase E0240.

The drug release was also tested in the conditions chosen to simulate the pH and time interval likely to be encountered during transit from stomach to colon [21]. First, the drug-loaded dry gels were put in pH 2.2 buffer solution for 1 h, then in pH 6.8 buffer solution with pancreatin for 3 h, finally

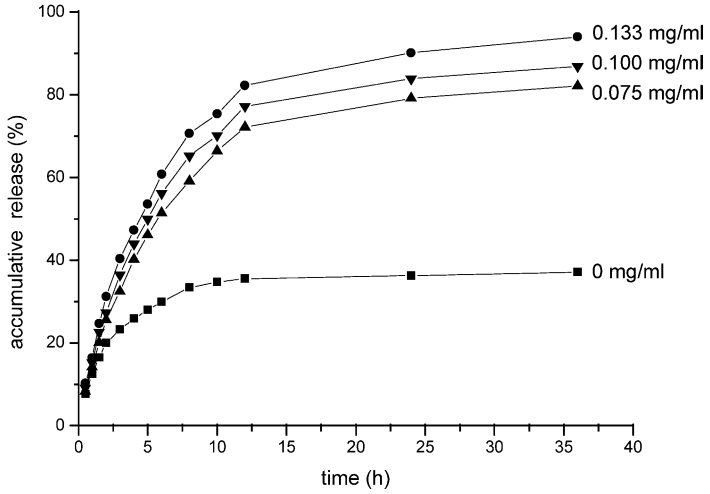

Fig. 10. In vitro release profile of 5-ASA-loaded gels C3 in buffer solution of pH 7.4 with different concentrations of Cellulase E0240 at 37 °C.

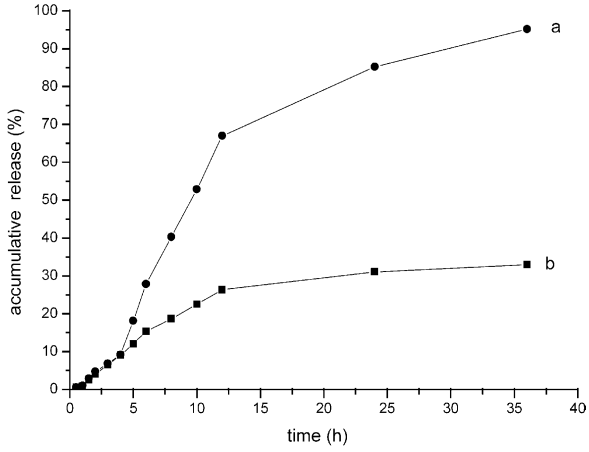

Fig. 11. In vitro release profile of 5-ASA-loaded gels C3 in different pH values with enzymes(a) or without enzymes(b) at 37 °C under different conditions: 0–1 h, pH = 2.2; 1–4 h, pH = 6.86; 4–36 h, pH = 7.4.

in pH 7.4 buffer solution with Cellulase E0240 for about 32 h, and the buffer solution without enzymes as control (Fig. 11). From Fig. 11, we can see that there is only a little release and there is no differences in the first 4 h when buffer solutions did not contain β-glycosidase. The little release (accumulative release percent $\leq$9.14%) was observed at the initial stage and the reason is as same as mentioned above. Contrastively, the model drug release increased evidently and there is remarkable differences between test and control buffer solutions in the succedent course. The accumulative release percent is much higher in the medium with β-glycosidase than in the medium without β-glycosidase, they are 95.19 and 32.95% after 36 h, respectively.

Comparing the drug release profile with the degradation results, it can be seen that the drug release nearly reach completed when the weight loss of hydrogel matrix is only about 15%. The possible explanation is that the release mechanism of small molecules, especially hydrophilic small molecules is diffusion from the pores in the hydrogel. Enzymatic degradation of the matrix to some extent results in (a) the appearance of new pores, (b) partial damage of networks, and (c) increase of pore diameter, all these promote diffusion of small molecules. Thus, small molecules can diffuse via these pores and release completely when the matrix is not degraded completely.

The fact that release profile of 5-ASA coincides with the designed release profile, namely, the drug releases in colon but not in upper intestinal tract and the release could be completed before emptying of delivery system, suggests that the KGM-*graft*-AA can be chosen as candidate for colon-specific drug delivery matrix.

4. Conclusion

Novel biodegradable pH-sensitive hydrogels designed for colon targeted drug delivery system were synthesized and studied in this paper. The hydrogels were prepared by graft copolymerization of acrylic acid to konjac glucomannan, cross-linking with *N*,*N*-methylene-bis-(acrylamide). The molar content of cross-linker has a significant influence on swelling ratio of the obtained hydrogels, while the concentration of acrylic acid or initiator has slight effects. The studies on the swelling behavior of hydrogels reveal their sensitive response to environmental pH values change. Furthermore, the gels retain the biodegradability and specificity to enzymatic degradation character of konjac glucomannan. The results of in vitro model drug 5-ASA release indicate that the release is controlled by swelling and degradation of the hydrogels. The in vitro release profile of model drug implies that hydrogels KGM-*graft*-AAs can be exploited as potential carriers for colon-specific drug delivery.

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