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Review

Preparation and characterization of konjac glucomannan–poly(acrylic acid) IPN hydrogels for controlled release

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ABSTRACT

In this paper, we reported the synthesis and properties of interpenetrating polymer network (IPN) hydrogel systems designed for colon targeted drug delivery. The gels were composed of konjac glucomannan (KGM) and cross-linked poly(acrylic acid) (PAA) by *N*,*N*-methylene-bis-(acrylamide) (MBAAm). It was possible to modulate the swelling degree of the gels. And the swelling ratio has sensitive respondence to the environmental pH value variation. The degradation tests show that the hydrogels retain the enzymatic degradation character of KGM. In vitro release of model drug VB_{12} was studied in the presence of Cellulase E0240 in pH 7.4 phosphate buffer at 37 °C. The accumulative release percent of the model drug reached 85.6% after 48 h and the drug release was controlled by the swelling and the degradation of the hydrogels. The results indicated that the IPN hydrogels can be exploited as potential carriers for colon-specific drug delivery.

1. Introduction

Konjac glucomannan (KGM) is a water-soluble non-ionic polysaccharide extracted from tubers of the *Amorphophallus konjac* plant (Ratcliffe, Williams, Viebke, & Meadows, 2005). It consists of 1,4-linked-β-D-mannopyranose and β-D-glucopyranose units in a molar ratio of 1.6:1 with a low degree of acetyl groups at the side chain C-6 position (Kaname et al., 2003). Different from many other biopolymers, its molecular weight distribution was fairly narrow, and the molecular chains were extending, semi-flexible, linear, little rigid and without branching (Li, Xie, & Kennedy, 2006). KGM is not hydrolyzed by digestive enzymes in human beings, thus it is considered as an indigestible dietary fiber. Also, it was reported that KGM has the ability to lower blood cholesterol and sugar level, helps with weight loss, promotes intestinal activity and immune function, etc. (He, Zhang, & Huang, 2001). Konjac is recognized as a safe material according to the FDA (Perols, Piffaut, Scher, Ramet, & Poncelet, 1997), and is also used as a functional health care drug for diabetics and adiposis in China. As one traditional food, KGM is deacetylated by alkali and can form a heat stable gel. Due to its biodegradability and heat gel-forming ability (Gao & Nishinari, 2004), many approaches are being explored to improve the efficiency of KGM in controlled release area.

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 (Ashford, Fell, Attwood, & Woodhead, 1993; Hardy et al., 1993; Kinget, Kalala, Vervoort, & van den Mooter, 1998) and for improving systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal tract (Saffran et al., 1986). Liu and co-workers (Chen, Liu, & Zhuo, 2005; Liu, Hu, & Zhuo, 2004), reported KGM gels for colon targeted drug delivery; the gels were copolymerized with acrylic acid and cross-linked by *N*,*N*-methylene-bis-(acrylamide); in their studies, the acrylic acid was grafted to the KGM. Pathak et al. (Pathak, Barman, & Philbrook, 2003) developed gel-forming macromers containing KGM, which was used as a hydrophilic block; the macromers are useful in variety of medical applications including drug delivery and tissue coating. Du and co-workers (Du et al., 2005; Du, Dai, Liu, & Dankovich, 2006) prepared carboxymethyl KGM (CKGM-CS) nanoparticles under very mild conditions via polyelectrolyte complexation. The CKGM-CS matrices not only exhibited pH-responsive properties, but ionic strength-sensitive properties. The pH-sensitivity of the polyelectrolyte complex could be used in protein delivery system.

In a chemical letter (Wen, Wang, Wang, Li, & Zhao, 2008), interpenetrating polymer network (IPN) hydrogels based on KGM and poly(acrylic acid) (PAA) was prepared by polymerization and cross-linking of acrylic acid (AA) in the pre-fabricated KGM gel. The IPN hydrogels were sensitive to environmental pH value. The gels were dried in an oven and maybe not suitable for delivery systems for colon. Recently, we proposed a novel method to prepare KGM hydrogels under mild conditions by deacetylated reaction and physically cross-linking method at a low temperature instead of heating gel-forming process, and the DNA release profiles were investigated (Nishinari, Williams, & Phillips, 1992).

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KGM is a traditional food, and easy to be accepted as for oral drug delivery. Thus, in the present study, IPN hydrogel was designed to take advantages of biodegradability of KGM and pH dependence of PAA. KGM hydrogel was prepared under mild conditions by deacetylated reaction and physically cross-linking method at a low temperature, and then IPN gel was prepared by polymerization and cross-linking of AA under moderate temperature. The gels are expected to have enhanced site-specificity to colon. We studied the dependence of swelling behavior of the hydrogels on the preparation conditions and pH value of external environment. The biodegradability of the hydrogels was also tested under Cellulase E0240 and steapsin which contain β-glucosidases. The drug release properties of the hydrogels were investigated by using vitamin B_{12} (VB_{12}) as a 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.

2. Experimental

2.1. Materials

Konjac glucomannan (KGM) was purified by extracting the refined konjac powder (purity of 95%, supplied by Bete Co. Ltd., ChengDu, China). Acrylic acid (AA), *N*,N′-methylene-bis-(acrylamide) (MBA) and vitamin B12 (VB_{12}) are obtained from Chengdu Kelong Chemical Reagent Company. 2,2′-Azo-bis-isobutyronitrile (AIBN) was purchased from *Shanghai* No.4 Reagent & H.V. Chemical Co., Ltd. The phosphate buffer solution was supplied by Boster biotechnology Co. Ltd., Wuhan, China. All the other chemicals are of AR grade, and are used without further purification unless otherwise described.

2.2. Preparation of KGM/PAA-IPN hydrogels

2.2.1. Preparation of KGM tablet

KGM was dissolved in 50 ml NaOH (0.025 M) solution to obtain different concentration solutions (1%, 2%, 3% and 5%, w/w); then the deacetylated reaction simultaneously occurred in the solutions. After the reaction, equivalent acetic acid (1%, v/v) was added to the solution slowly to neutralize the solution. Then the solution was centrifuged to remove the bubbles. After 1.5 ml of ethanol was dropped into the solution; massive gels were obtained. The gels were washed several times, followed freeze-dried, and then three-dimensional porous KGM foam was obtained. The foam was then cut into cylinder tablets for further use; the tablets had average diameter and thickness of about 5.0 and 1.0 mm, respectively.

2.2.2. Preparation of KGM/IPN-IPN hydrogel

The cylinder tablets were immersed in AA aqueous solutions containing initiator (AIBN) and cross-linker (MBA) with different concentrations, as shown in Table 1, until the liquid was absorbed into the hydrogel. Then, the system was warmed up to 50 °C for 12 h for polymerization. The IPN hydrogels obtained were washed with double distilled water to remove the unreacted monomers and the small molecules. Then the IPN gels were freeze-dried.

2.2.3. Preparation of drug-loaded gels

Drug loading was accomplished by swelling the hydrogels in pH 7.4 phosphate buffer solution containing model drug vitamin B12 (VB_{12}) with the concentration of 2% (*W/W*). Then the drug-loaded hydrogels were wiped to remove the surface water, and dried at 50 °C.

2.3. Characterization of KGM/PAA-IPN hydrogels

For the FT-IR analysis, the obtained KGM/PAA-IPN hydrogels (Sample K1A1 and K3A1) were dried and ground into a powder form. The powders were then mixed with KBr (1:100) and pressed into a disk. Analysis was performed by using a FT-IR spectrometer (Nicolet FT-IR170, Japan).

For scanning electron microscope (SEM) observation, the KGM/PAA-IPN hydrogels (Sample K2 and K2A2) were freeze-dried. Then cut with a single-edged razor blade, attached to the sample supports and coated with a gold layer. The SEM images were recorded using an S-2500C microscope (Hitachi, Japan).

Table 1
Feed composition for the preparation of the KGM/PAA-IPNs hydrogels.

Sample	KGM concentration to prepare hydogels			Component of PAA to prepare hydrogels			
	m_{KGM}	V_{H2O}/mL	%	m_{AA}/g	m_{MBA}/g	m_{AIBN}/g	V_{H2O}/mL
K1A1	0.5	49.5	1	6	0.1	0.018	23.9
K1A2	0.5	49.5	1	6	0.15	0.018	23.8
K2A1	1	49	2	6	0.1	0.018	23.9
K2A2	1	49	2	6	0.15	0.018	23.8
K2A3	1	49	2	6	0.2	0.018	22.8
K3A1	1.5	48.5	3	6	0.1	0.018	23.9
K3A2	1.5	48.5	3	6	0.15	0.018	23.8
K5A1	2.5	47.5	5	6	0.1	0.018	23.9
K5A2	2.5	47.5	5	6	0.15	0.018	23.8

2.4. Swelling and pH sensitivity of KGM/PAA-IPN hydrogels

2.4.1. Swelling studies

The water-sorption capacity of the KGM/PAA-IPN hydrogels was determined by swelling dry gels in media at 37 °C. At predetermined time intervals, the swollen gels were blotted with filter paper to remove the surface water and then weighed immediately. The media for the swelling studies were either 0.1 N HCl (pH 1.0), 10 mM acetic acid–sodium acetate (pH 3.0, 4.0 and 5.0), 10 mM phosphate-buffered solution (pH 6.0, 7.4, 8.0 and 9.5), or phosphate-buffered solutions containing enzyme (0.133 mg/g cellulose enzyme or 0.25% pancreatin). The ionic strength of above buffered solutions was carefully adjusted to 0.2 M by adding an appropriate amount of sodium chloride. The swelling ratios (*SR*) of the tested samples were calculated from the following expression:

$$SR_e = \frac{(M_e - M_d)}{M_d}$$

$$SR_t = \frac{(M_t - M_d)}{M_d}$$

where M_d is the initial weight of the dry gels; M_e is the weight at equilibrium after the water sorption; and M_t is the weight at any time t during water sorption.

2.4.2. Shrinking studies

The KGM/PAA-IPN hydrogels were dipped into PBS solution (pH 7.4) at 37 °C to reach the equilibrium swelling for 8 h (the time was determined by preliminary experiments). Then the gels were removed from the PBS solution, blotted with filter paper to remove the surface water; and then applied to 0.1 N HCl solutions (pH 1.0). At predetermined time intervals, the wet weight of the swollen gels was determined. And the shrinking ratios (*WR*) of the tested samples were calculated from the following expression:

$$WR_t = SR_e - \frac{(M_e - M_t)}{M_e}$$

where M_e is the weight at swelling equilibrium, M_t is the weight at any time t.

To study the pH sensitivity, the gels were dipped into 0.1 N HCl solutions (pH 1.0) to reach the swelling equilibrium firstly; then

the swelling ratio was determined. After that, the gels were applied to PBS solution (pH 7.4) to reach the swelling equilibrium; and then the swelling ratio was determined. And then the gels were applied to 0.1 N HCl solutions (pH 1.0). This process was repeated for several times.

2.5. Degradation of KGM/PAA-IPN hydrogels

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 solutions, and placed in a thermostatic shaker (37 °C, 50 r/min). The degradation of the gels was expressed by the weight loss 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. The degradation ratios (*DR*, or weight loss) of the test samples were calculated from the following expression:

$$DR_t = \frac{(M_i - M_t)}{M_i}$$

where M_i is the initial weight of the dry gels, M_t is the weight at time t.

2.6. Estimation of drug loading and in vitro drug release

Freeze-dried IPN hydrogels were placed in VB_{12} aqueous solution, and were incubated at 4 °C for 2 days in a shaker at 120 rpm. The loading amount of the drug in the hydrogels was calculated from the decrease in the concentration of the VB_{12} solution which was determined using a UV–vis spectrophotometer 752 (Shanghai Spectrum Instruments Co., Ltd., China) at 361 nm.

In vitro drug release from the hydrogels was carried out in a thermostatic shaker at shaking speed of 50 r/min at 37 °C. One of the media used for the release of VB_{12} was 25 ml phosphate buffer solution. Another was 25 ml phosphate buffer solution containing 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 VB_{12} concentration was determined with UV–vis spectrophotometer at 361 nm.

3. Results and discussion

3.1. FT-IR analysis

The recent studies on KGM reveal that the KGM gelation is promoted by adding coagulants and heating due to the deacetylation reaction. The thermal processing induced strong inter-chain interactions such as hydrogen bonding. And these interactions indicated that there are enough molecules with non-acetylated blocks to form network (Nishinari et al., 1992).

Fig. 1 shows the FTIR spectra of cross-linked PAA and the KGM/PAA-IPN hydrogels. As shown in the figure, all the spectra show very broad bands between 3600 and 2500 cm^{-1}. The O–H stretching vibration of the carboxylic groups occurs between 3600 and 3300 cm^{-1}; and the stretching of –OH groups of the methyl in the KGM also occurs at 3422 cm^{-1}. The sharpest band of PAA spectrum is 1715 cm^{-1}, it corresponds to the carbonyl stretching vibration. With the addition of KGM, the intensity of the peak becomes weaker. The characteristic absorption bands of the mannose in the KGM appeared at 895 and 808 cm^{-1}. The peak at 1742 cm^{-1} was assigned to the stretching of the C=O of the carbonyl of acetyl

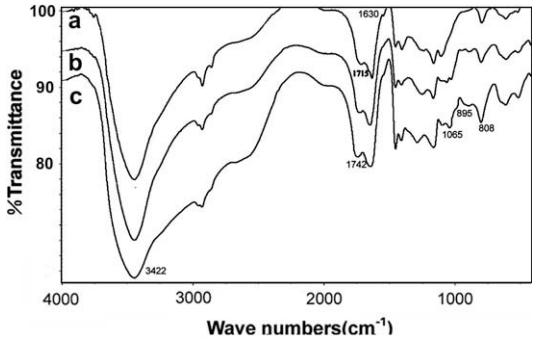

Fig. 1. FTIR spectra of the cross-linked PAA (a), the K1A1 hydrogel (b), and the K3A1 hydrogels (c).

groups and the C–O of the intermolecular hydroxy groups. The peaks at 1065 cm^{-1} were assigned to the characteristic absorption band of C6–OH in the KGM. The concentration of the substrate in the composite materials has great effect on the intensity of the IR spectrum; and with the increase of the KGM content in the IPN hydrogels, the characteristic absorption bands of the KGM increased, as shown in the Figure. These further demonstrated the present of KGM.

3.2. SEM of the hydrogels

The cross-sectional morphology of the freeze-dried KGM hydrogel and the KGM/PAA-IPN hydrogel is shown in Fig. 2. A porous honeycomb-like structure with many large pores is clearly shown for the KGM hydrogel, which seems to indicate a high accessibility of water to the amorphous regions of the hydrogel. For the KGM/PAA-IPN hydrogel, the pore size becomes smaller, since the acrylic acids entered into the pores of the KGM hydrogel, and cross-linked to form the IPN structure. Certainly, the average pore diameter of the IPN gels decreases with the increasing of the cross-linking density. In the KGM/PAA-IPN hydrogels, there existed not only IPN system but also the hydrogen bonding when combined the results of 1 (Gousse, Chanzy, Cerrada, & Fleury, 2005).

3.3. Swelling kinetics of KGM/PAA-IPN hydrogels

The swelling behavior of the hydrogels at different pH values could be easily investigated (data not shown), the swelling ratios increased shapely at the first 8 h. With the increase of the pH values, the swelling ratios increased. As we known, the swelling ratios at various pH environments depend upon the available free volume of the expanded polymer matrix, polymer chain relaxation, and availability of ionizable functional groups such as –COOH able to form hydrogen bonds with water (Huang, Yu, & Xiao, 2007). At the pH value of 7.4, the system has a basic pH, thus the swelling ratio exhibited the largest value due to the electric interaction. Such pH-dependent properties of the hydrogels come from the polyelectrolyte nature of poly(acrylic acid) segments in the hydrogel network.

The water uptake character of the hydrogels in pharmaceutics is similar to the swelling of the hydrogel in polymer science (Vergnaud, 1993). In the present study, the Vergnaud model can also be used to describe the swelling ratio, and the model is shown as follows:

$$M_t = kt^n$$

where M_t is the amount of the liquid transferred at time, t; k is the rate constant characteristic of the system; n is the transfer exponent indicating the mechanism of swelling. The values of the exponent,

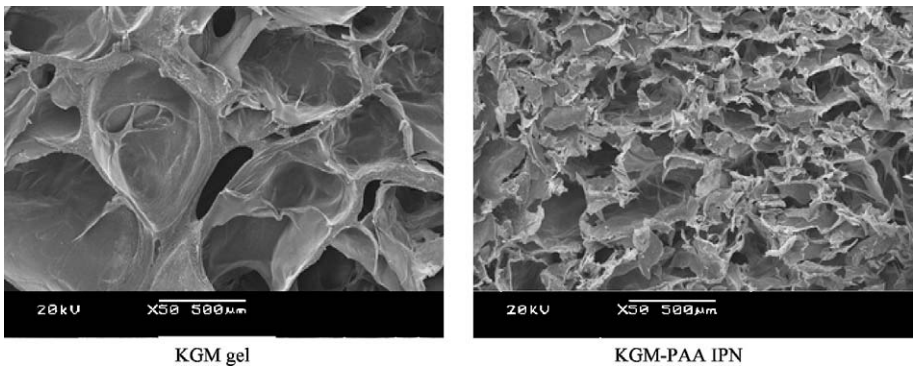

Fig. 2. SEM pictures of the cross-section of the freeze-dried KGM hydrogel and KGM/PAA-IPN hydrogel. Magnification 50×.

$n \leqslant 0.5$, $0.5 < n < 1.0$, $n = 1.0$, indicate the diffusion controlled, anomalous diffusion and stress relaxation-controlled mechanism, respectively (Ebube, Hikal, Wyandt, & Beer, 1997; Roy & Rohera, 2002). The data calculated according to the Vergnaud model indicated that the swelling kinetic for the hydrogel was in agreement with the model, for which the value of the correlation coefficient, R^2, was about 0.98; and the value of the exponent (n) suggested that the diffusion rate of the liquid was much less compared with the rate of the relaxation of the polymer segment. With the increase of the pH values, the exponent (n) increased (but not more than 0.5). These results indicated that the swelling process was diffusion controlled mechanism, and with the increase on the pH values, the effect of the relaxation of the polymer segment on the swelling increased.

3.4. Effect of the composition of the hydrogels and enzyme in the solution on the swelling

The effect of the composition of the IPN hydrogels on the swelling ratios (SR) at a temperature of 37 °C and different pH values is investigated (data not shown). With the increase of the KGM content, the equilibrium swelling ratios of the hydrogels decreased from about 24 to about 12. KGM is a non-ionic polysaccharide, which has no pH sensitivity. In the hydrogels, the pH sensitivity comes from the PAA. When the KGM content increased, the PAA ratios in the hrdrogels decreased. The less the PAA content in the hydrogels, the smaller the affinity of the hydrogels to water and the lower the swelling ratio of the hydrogels. The swelling phenomenon of the IPN hydrogels is the result of the swelling after the water uptake of the two components and the restriction of the two components in the network each other.

Many types of enzyme are known to co-exist in the stomach and intestine (Schacht et al., 1996). Therefore, the effect of enzyme on the swelling is very important in drug release. Fig. 3 shows the swelling ratios of the hydrogels in enzyme solutions. As shown in the figure, there is no significant difference at the first 24 h. After that the swelling ratios increased rapidly with time, especially in the cellulase solution; and the swelling ratio was 80 after 60 h. The cellulase could degrade the KGM, thus the swelling ratio was the largest, and these will be further investigated in the next section. Since pancreatin is a mixture containing trypsinogen, lipase and amylase, and could not degrade the KGM molecule chain, thus the swelling ratio was similar to that in PBS solution.

In the present study, the cellulase concentration (2 U/ml) was smaller than that in human body (6.8 U/ml). Therefore, the swelling ratio change caused by the KGM degradation in cellulase solution was observed. These indicated that the KGM could easily be degraded under intestinal tract environment according to the relationship between the enzyme activity and substrate. Furthermore, we found that the PAA was very weak after adsorbing large amount of water, and would easily be ruptured. These results suggested that the IPN hydrogels would not be degraded in upper alimentary tract; however, in intestinal tract where there is glycosidic enzyme and with high pH value, the hydrogels would be rapidly degraded and be ruptured. These indicated that the hydrogels might have potential to be used as oral drug delivery systems for colon.

3.5. Shrinking kinetics of KGM/PAA-IPN hydrogels

The shrinking kinetics of the hydrogels after reaching the swelling equilibrium under pH 7.4 was investigated under pH 1.0 buffer solutions (data not shown). The shrinking ratios decreased from about 28 to 8 with in 1 h for the sample which had low amount of KGM; while for the sample which had high amount of KGM, the shrinking ratios decreased from about 18 to 12. These indicated that the shrinking speed increased when the KGM amount decreased.

To evaluate the reswelling ability and the pH-sensitivity of the hydrogels, the equilibrium reswelling behavior of the K2A1 sample is illustrated in Fig. 4. The samples were put in pH 1.0 buffer solution, and then transferred to a pH 7.4 buffer solution, and then transferred to pH 1.0 buffer solution, this process was repeated for three cycles. The KGM/PAA-IPN hydrogels are stable in the acidic condition due to the interpenetrating polymer network system, though the KGM might be hydrolyzed in the acidic condition for a long time. The *SR* values almost remained unchanged in pH 1.0 buffer solution or pH 7.4 buffer solution again. The results show that the KGM/PAA-IPN hydrogels have good reswelling ability and maintain the high sensitivity to pH. And the pH sensitivity shows

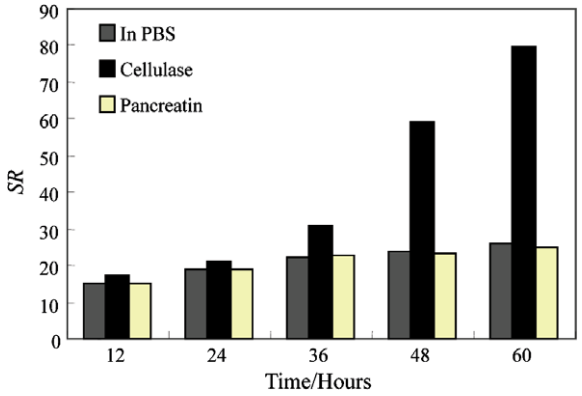

Fig. 3. Swelling ratios of the hydrogels (K2A1) in buffer solution of pH 7.4 with Cellulase or Pancreatin. Duplicate experiments gave the similar results.

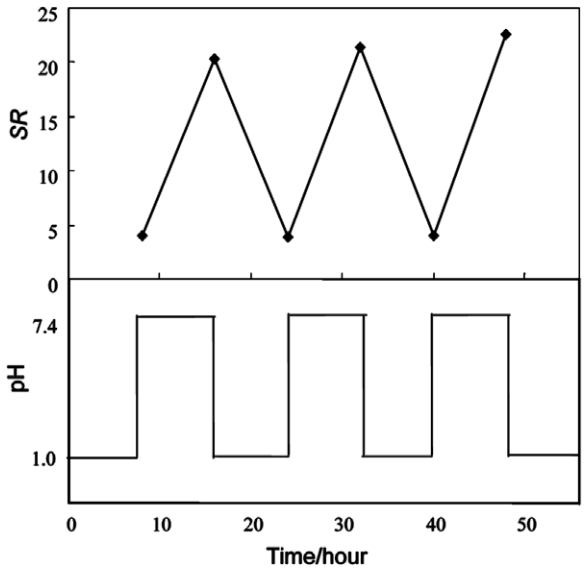

Fig. 4. Equilibrium reswelling behavior of hydrogel K2A1 sample was transferred from pH 1.0 solution to pH 7.4 buffer solutions for several cycles. Duplicate experiments gave the similar results.

no difference compared to the PAA grafted KGM hydrogels (Chen et al., 2005).

3.6. Degradation

To estimate the biodegradability of the KGM/PAA-IPN hydrogels, the enzymatic hydrolysis experiment was carried out in pH 7.4 buffer solution with Cellulase E0240 at 37 °C. Since the hydrogels were not degrade in pancreatin solution, thus not mentioned in this section.

Fig. 5 shows the weight loss of the hydrogels (sample K2A1) in cellulase solutions at different concentrations. The results indicated that the KGM/PAA-IPN hydrogel could not be degraded in pH 7.4 buffer solution, but it could be degraded by Cellulase E0240, which contains b-glycosidases, and the weight loss was 12% (the total amount of KGM in the IPN hydrogel was about 15%) for 5 days. The effect of KGM contents on the degradation was also investigated. With the increase of the KGM amounts in the hydrogels, the weight loss increased, which suggested that the KGM/PAA-IPN hydrogels can be degraded by the enzymes

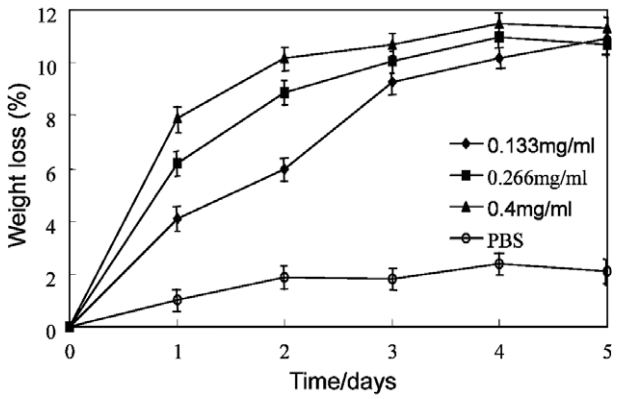

Fig. 5. Degradation of the IPN hydrogel (K2A1) in buffer solution of pH 7.4 with different concentrations of cellulose.

(Gao & Nishinari, 2004; He et al., 2001), i.e. the hydrogels retain the biodegradability characters of KGM.

3.7. In vitro drug release

The effects of KGM concentration and the effect of the cross-linking reagent on the drug loading were investigated. The results indicated that with the decrease of the KGM concentration used to prepare the hydrogels, the drug loading amount increased. Also, the drug loading amount decreased with the increase of the amount of the cross-linking reagent. In this work, the drug was not chemically attached to the polymer and the only likely interactions are intromolecular attraction and entrapment within the polymer matrix. Therefore, the drug should remain in a biologically active form and could perform its function once released from the polymer matrix. Obviously, the major advantage of this formulation is that the drug in the polymer matrix is unaltered, and hence the efficacy of the released drug should be closed to that of its native form.

3.7.1. Effect of pH on the drug release

The drug release was firstly investigated using drug-loaded hydrogels in buffer solutions with two different pH values (pH 1.0 and 7.4) at 37 °C. There was almost no bursting release in the two medium, and there was no significant difference for the accumulative release percent at the first 5 h, since the diffusion of the VB_{12} from the hydrogel played the most important role. After that, the drug release was controlled by the relaxation of the polymer segment, and the accumulative release percent was much higher in the pH 7.4 medium than that in pH 1.0 medium. Since the swelling ratio of the hydrogels was much higher in the pH 7.4 medium than that in pH 1.0 medium. The accumulative release percents were 95% and 60% in the pH 7.4 medium and pH 1.0 medium in the experiment times, respectively.

3.7.2. Effect of KGM content on the drug release

As discussed above, the pH value had great effect on the drug release, thus, the effect of KGM content on drug release were investigated at two different pH values, pH 1.0 and pH 7.4. The result showed that the drug release decreased with the increase of the KGM concentration used to prepare the IPN hydrogels both in the two mediums.

The drug release from the IPN hydrogels was controlled by diffusion, since almost no degradation occurred. The data could be analyzed according to Huguchi equation.

$$M_t/M_\infty = Kt^{1/2}$$

where M_t/M_∞ is the drug released fraction at time t, K is a constant, which related to the properties of the gels. Data are summarized in Table 2.

As shown in the table, all the regression coefficients (R^2) were larger than 0.97, which indicated that the data were in agreement with Huguchi equation. Also, at high pH value, the Huguchi release constant was larger than that at lower pH value. This suggested that the release rate was higher at higher pH value once again.

Table 2
Coefficient and exponents of VB_{12} release kinetics based on Higuchi equation.

Entry		K	R^2
K1A1	pH 1.0	1.671	0.972
	pH 7.4	2.815	0.992
K2A1	pH 1.0	1.138	0.975
	pH 7.4	2.098	0.993
K3A1	pH 1.0	1.002	0.973
	pH 7.4	1.967	0.996

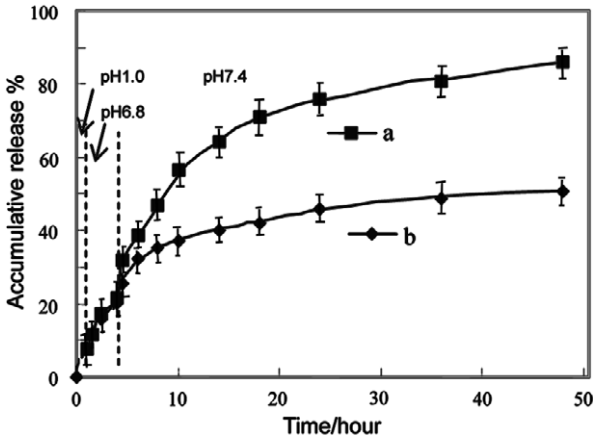

Fig. 6. In vitro release profile of VB_{12}-loaded gels K2A1 with enzymes (a) and without enzymes (b) under different conditions: 0–1 h, pH 1.0; 1–4 h, pH 6.86; 4–60 h, pH 7.4.

Furthermore, we investigated the amount of the cross-linking reagent on the release of the model drug. With the increase of the cross-linking amount, the accumulated release percent decreased. The loaded drug amount decreased, thus the actual release rate decreased, since the swelling ratio decreased.

3.7.3. Drug release in simulated gastrointestinal internal environment

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 (Chen et al., 2005; Gupta, Beckert, & Price, 2001), First, the drug loaded dry gels were put in pH 1.0 buffer solution for 1 h, then in pH 6.8 buffer solution with pancreatin for 3 h, finally in pH 7.4 buffer solution with Cellulase E0240, the buffer solution without enzymes as control (Fig. 6). From Fig. 6, we can see that there was only a little release and there was no significant difference in the first 4 h when buffer solutions did not contain b-glycosidase. The little release (accumulative release 21.4%) was observed at the initial stage (within 4 h) and the reason was as same as mentioned above. Contrastively, the model drug release increased evidently and there was remarkable difference between the buffer solutions with and without b-glycosidase in the succedent course. The accumulative release percent was much higher in the medium with b-glycosidase than in the medium without b-glycosidase, and they were 85.6% and 48.9% after 48 h, respectively. These results indicated that the KGM/PAA-IPN hydrogels could be used for the oral drug delivery systems for colon.

4. Conclusions

Biodegradable pH-sensitive interpenetrating polymer network (IPN) hydrogels designed for colon targeted drug delivery system, were synthesized and studied in this paper. The IPN hydrogels were prepared by polymerization and cross-linking of acrylic acid (AA) in the pre-fabricated KGM gel. Both the content of KGM and cross-linker *N*,*N*-methylene-bis-(acrylamide) had significantly influence on the swelling ratio and drug release of the obtained hydrogels. The studies on the swelling behavior of hydrogels revealed their sensitive response to environmental pH values change. Furthermore, the gels retained the biodegradability and specificity to enzymatic degradation character of konjac glucomannan. The results of in vitro model drug VB_{12} release indicated that the release was controlled by both swelling and degradation of the hydrogels. The in vitro release profile of the model drug implied that the IPN hydrogels could be exploited as potential carriers for colon-specific drug delivery.

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