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KGM and PMAA based pH-sensitive interpenetrating polymer network hydrogel for controlled drug release

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ABSTRACT

Sequential interpenetrating polymer networks (IPN) hydrogels based on konjac glucomannan (KGM) and poly(methacrylic acid) (PMAA) were prepared by immersion of a solution of methacrylic acid (MAA) monomer with cross-linker *N,N′*-methylenebisacrylamide (MBAAm) and initiating into a pre-fabricated dried KGM gel. Polymerization and cross-linking of MAA inside the KGM network resulted in a novel biodegradable pH-sensitive IPN hydrogel. The studies on the swelling behavior of IPN hydrogels reveal their sensitive response to environment pH value. It was possible to modulate the degree of swelling of the IPN gels by changing the KGM/PMAA ratio and the cross-linking density of the PMAA component. The KGM component in the IPN can be degraded by β-glycosidase Mannaway25L. *In vitro* drug release behavior of IPN hydrogels were investigated under different environments using model drugs 5-fluorouracil. The results suggested that such an IPN hydrogel can be exploited as carrier candidate for colon-specific drug delivery.

1. Introduction

Many scientific works in recent years have been dealing with hydrogels that are able to alter their volume and properties in response to environmental stimuli such as pH, temperature, ionic strength and electric field (Li, Wu, & Liu, 2008; Qiu & Park, 2012; Vashist, Gupta, & Ahmad, 2012; Wang & Wang, 2010; Zhang & Peppas, 2000). Because of their drastic swelling and syneresis in response to environmental stimuli, these polymeric hydrogels have been investigated for many biomedical and pharmaceutical applications, including controlled drug delivery (Liu, Chen, & Chen, 2010; Ramkissoon-Ganorkar, Gutowska, Liu, Baudyš, & Kim, 1999; Yang, Chen, Pan, Wan, & Wang, 2012), molecular separation (Feil, Bae, Feijen, & Kim, 1991; Gunavadhi, Maria, Chamundeswari, & Parthasarathy, 2012; Tokarev & Minko, 2010), artificial muscles (Peppas & Langer, 1994), sensors (Lin, Chang, Kuo, Magda, & Solzbacher, 2009; Monleón Pradas et al., 2001; Riedinger et al., 2011), *etc.* Among these "intelligent" polymers, pH-sensitive hydrogels have been widely studied to develop oral drug delivery system. The pH of physiological media is very precisely controlled because of its crucial importance in all functions of the human body. One example is the change of pH through the gastrointestinal tract, from the acidic pH of the stomach, namely, pH from 2 to 4, increasing progressively in the small intestine to neutral or slightly basic pH (Mc Gann, Higginbotham, Geever, & Nugent, 2009; Nguyen, Huynh, & Lee, 2009; Zhang, Shang, Zheng, Liang, & Chen, 2012). Hydrogels containing ionizable groups can take advantage of their ability to volume changes depending on the pH of the physiological medium. Poly(methacrylic acid) (PMAA) is an ionizable hydrophilic polymer (Fernyhough, Ryan, & Battaglia, 2009; Solhi, Atai, Nodehi, & Imani, 2012). Cross-linked PMAA is able to swell in water. Its swelling behavior is greatly pH-dependent due to the ionization/deionization of the carboxylic acid groups. At low pH, usually pH value less than 5.5, the —COOH groups are not ionized and keep the PMAA network at its collapsed state. At high pH values, usually pH value 5.5–7.4, the —COOH groups are ionized, and the charged COO^- groups repel each other, leading to PMAA swelling (Andersson Trojer, Wendel, Holmberg, & Nydén, 2012; Shalviri et al., 2012; Zhang et al., 2013). Hydrogel made of PMAA swells least in the stomach and the drug release is minimal.

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The extent of drug release increases due to the increasing swelling of hydrogel as it passes down the intestinal tract. Consequently, they can be used to release drugs in a neutral pH environment.

Konjac glucomannan (KGM) is a neutral polysaccharide isolated from the konjac tuber. It consists primarily of a linear chain of β-1,4 linked D-glucose and D-mannose units with a glucose to mannose ratio of approximately 1:1.6 (Kato & Matsuda, 1969; Lin, Li, & Zhu, 2013). There has been a suggestion that there are some branches on the C_3 on mannose; the length of the branched chains being in the range of 11–16 mannose units and 5–10% of the backbone residues being acetylated (Dea et al., 1977). In the presence of alkali, konjac glucomannan will deacetylate and form a heat stable gel. Alkali gelation is considered as a consequence of the formation of associations between acetyl free regions of the backbone (Gao & Nishinari, 2004; Penroj, Mitchell, Hill, & Ganjanagunchorn, 2005). It is worth noting that KGM can be used as a colon-targeting drug-delivery system because it can only be degraded by colonic bacterial enzymes (β-mannase or β-glycosidases) and not be degraded in the stomach and small intestine (He, Zhang, & Huang, 2001; Liu et al., 2010, 2012). In order to improve and exploit the properties of KGM and PMAA for colon-targeting delivery, the interpenetrating polymer networks (IPN) are utilized instead of synthesizing new types of polymers. IPN is defined as a mixture of two or more cross-linked networks which are dispersed within each other at a molecular segmental level. In general, no significant degree of covalent bonds exists between the constituent networks (Klempner, Frisch, & Frisch, 1970). Since there is no chemical bonding between them, each polymer network may retain its own property like its homopolymer. Meanwhile, because of IPN physically interlocked structure, when one component swells or shrinks, the other component can be enforced to cooperate by attractive and repulsive interactions of whole network (Liu et al., 2006). Interpenetration of the two networks may lead to an enhanced mechanical strength due to the physical entanglements and network interaction (Chivukula et al., 2006). There are two basic synthetic routes for IPN: sequential and simultaneous IPN. When the second network formation proceeds in the presence of the already formed network, the IPN is called sequential networks; the both polymers grow simultaneously with non-interfering modes, the IPN is known as a simultaneous IPN (Ilavský, Mamytbekov, Hanyková, & Dušek, 2002).

In this paper, we synthesized sequential IPN based on KGM and PMAA. It is expected that these IPN hydrogels will exhibit good pH-dependent swelling behavior and biodegradability. The enzymatic degradation and drug release experiments were carried out to test whether the IPN hydrogels can be used for colon specific controlled drug delivery.

2. Materials and methods

2.1. Materials

Konjac glucomannan (KGM) (purity of 95%) was supplied by Shiyan Huaxianzi Konjac productions Co. Ltd., Hubei, China. Methacrylic acid (MAA) purchased from Fuchen Shiji Co. Ltd., China was purified by vacuum distillation before use. *N,N′*-methylenebisacrylamide (MBAAm), ammonium persulfate (APS) and other chemicals bought from Shanghai Chemical Group, China were of analytical reagent grade and used without any further purification. Mannaway25L (endo-1,4-β-mannanase, CAS number: 37288-54-3) was purchased from Novozyme Co. Ltd., China. Pancreatin was provided by Wenjiang Tianyuan Biochemical Products Factory, Chengdu, China. Fluorouracil injection (250 mg 5-fluorouracil in 10 mL aqueous solution) was purchased from Tianjin Jinyan Amino Acids Co. Ltd.

Table 1
Feed compositions of the different KGM/PMAA IPN hydrogels.

Entry	Mass ratio KGM:MAA	Molar ratio APS:MAA	Molar ratio MBAAm:MAA
A	30:70	1:40	1:50
B	50:50	1:40	1:50
C	70:30	1:40	1:50
D	70:30	1:40	1:100
E	70:30	1:60	1:50
PMAA	–	1:40	1:50

2.2. Synthesis of the KGM hydrogels

KGM power was dispersed in 1.5 mol/L sodium carbonate solutions, and then the mixture was stirred with a magnetic stirrer to uniform at room temperature. The obtained KGM dispersion was placed in a thermostated bath at 60 °C for 12 h. Afterwards, the gelated sample was immersed into large volume of deionized water at room temperature for at least 96 h to remove the unreacted reactants and alkali. The water was replaced every several hours until its pH value was neutral. Then the KGM hydrogels were obtained by lyophilization for further use.

2.3. Synthesis of the IPN hydrogels

The hydrogels of KGM/PMAA interpenetrating polymer networks were synthesized by sequential cross-linking technology. Predetermined amounts of monomer MAA, cross-linker MBAAm and initiator APS were dissolved in suitable amount of water. Nitrogen was bubbled through the monomer/solvent mixture for 30 min to remove oxygen dissolved in the reaction mixture. A known weight dried KGM hydrogel synthesized previously was then immersed into the solution until almost all the solution was absorbed into the hydrogel network. In the course of absorption, the system was maintained at lower temperature (5 °C) to allow swelling of the KGM gel. Then, the system was warmed up to 60 °C to start the polymerization reaction to form second network within the original KGM gel network. A PMAA network was formed within a swollen KGM hydrogel to generate the IPN hydrogel. In the course of formation, the PMAA network entangled through the existing KGM gel network chains to form an IPN structure. The reaction was carried out for 24 h in a sealed glass vessel. Thereafter, an IPN, consisting of KGM and PMAA network components, was formed and named as IPN hydrogel. The prepared IPN hydrogels were washed with double-distilled water, as described above, to remove the unreacted monomers and other small molecules. The IPN gels were dried first in air and then dried in a vacuum oven.

In order to find the relationship between polymerization condition and the swelling properties of IPN gels, the influence of the parameters, such as the ratio of the two hydrogel networks, the feed concentration of MBAAm and APS were investigated (Table 1).

2.4. Fourier Transform Infrared (FT-IR) spectroscopic analysis

KGM and the IPN hydrogels were analyzed by FT-IR spectrometer to confirm cross-linking and interpenetrating network constructure. FT-IR spectra were obtained on Perkin-Elmer-2 spectrometer (KBr, pellet).

2.5. Measurement of the dynamic and equilibrium degree of swelling

The gravimetric method was employed to study the hydrogel's swelling ratio. Briefly, the weighed mass of dried IPN hydrogels was immersed in the swelling medium. At a predetermined time,

the gels were removed and soaked up with filter paper to remove excess water on the hydrogels surface and weighted. The swelling ratio was calculated by the following equation:

$$SR = \frac{W_S - W_d}{W_d} \quad (1)$$

where W_s is the weight of the swollen hydrogel and W_d is the weight of dry hydrogel.

When the hydrogel reached a constant weight, the swelling ratio was defined as to be the equilibrium swelling ratio (ESR).

The influence of pH value on the swelling behavior of the IPN hydrogels was investigated by immersing the gels in buffer solutions with a different pH value at 37 °C. Each sample was tested in triplicate.

2.6. Degradation

The enzymatic degradation of the hydrogels was carried out in a flask filled with 20 mL phosphate buffer (pH 7.4, 0.1 mol/L, 37 °C) which contained 0.1 mL Mannaway25L or pancreatin in the presence of 0.5 mg sodium azide (NaN_3). The degradation experiments were carried out by immersing the dry IPN hydrogels in buffer solution placed in a thermostatic rotary shaker (Grant CS200G, England). Then the samples were taken out from the solution over predetermined time intervals, washed thoroughly with deionized water, and dried in a vacuum oven. The buffer-enzymatic solution was changed every day to maintain enzymatic activity. The degradation rate was measured by the weight loss which is defined as follows:

$$\text{Weight loss } (\%) = \left[\frac{w_0 - w_1}{w_0}\right] \times 100 \quad (2)$$

where w_0 is initial weight and w_1 is weight after degradation at different time intervals.

2.7. Estimation of drug loading and in vitro drug release

5-Fluorouracil was used as the model drug of hydrophilic small molecules. The fluorouracil injection solution was added in the aqueous solution of second reactant system, and reaction continued as described in the section of IPN hydrogels' synthesis. After synthesis, the drug-loaded IPN gels were washed several times with deionized water and dried to constant weight for *in vitro* release kinetic study. With a UV-vis spectrophotometer (PERKIN ELMER UV/vis Spectrometer Lambda Bio 40) at 265.7 nm, we can calculate the drug loading in IPN hydrogels by determining the content of 5-FU in washing water and the original content.

The *in vitro* release experiments were carried out by immersing the drug-loaded IPN hydrogels in a flask filled with dissolution media and placed in a thermostatic rotary shaker at shaking speed of 45 rpm at 37 °C. One of the dissolution media used for the drug release was 20 mL phosphate buffer solution. Another was 20 mL phosphate buffer solution with 0.1 mL Mannaway25L and 0.5 mg sodium azide, and the solution was changed every 24 h to maintain the enzymatic activity. At predetermined time intervals, 5 mL aliquots of the buffer medium was withdrawn and replaced with an equal volume of the same dissolution medium. The percentage of drug release was calculated by measuring the UV absorbance of the aliquot. All release experiments were conducted in triplicate. The results were presented in terms of cumulative release:

$$\text{Cumulative release } (\%) = \left(\frac{M_t}{M_\infty}\right) \times 100 \quad (3)$$

where M_t is the amount of drug released from the hydrogels at time t and M_∞ is the estimated amount of drug loaded in the hydrogels.

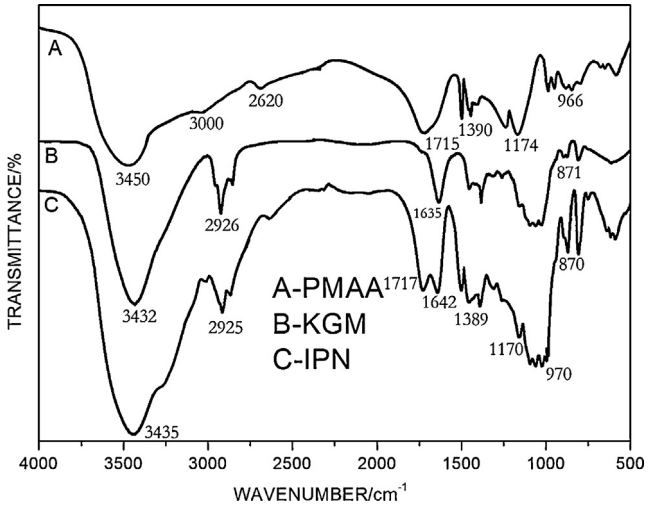

Fig. 1. FT-IR spectra of PMAA, KGM and IPN hydrogels.

3. Results and discussion

3.1. FT-IR characterization of the IPN hydrogels

Fig. 1 shows the FT-IR spectra of PMAA, KGM gels and the IPN hydrogels. For the IR spectra of the IPN hydrogels, new peaks appeared and some peaks became stronger due to interaction or superposition of peaks among groups of MBAAm, MAA and KGM moieties. The band at 1635 cm^{-1} is the intramolecular hydrogen bonds of KGM. The peaks at 808 cm^{-1} and 871 cm^{-1} are the absorption of pyran ring and β-D glucosidic bond. The peaks at 1715, 1390 and 966 cm^{-1} were assigned as absorption bands of PMAA moieties. These experimental observations confirm that the IPN hydrogel retains the primary structure of backbone chain of KGM and PMAA.

3.2. Dynamic and equilibrium swelling studies

Fig. 2a shows the swelling kinetics of the different feed compositions' IPN hydrogels in pH 7.4 buffer solution at 37 °C. The time to reach the equilibrium swelling ratio was about 12 h for most samples, although the IPN hydrogels exhibited different equilibrium swelling ratios. Comparing IPN hydrogels A, B and C, the swelling ratio increased with the increase of PMAA content in IPN network because the PMAA hydrogel has much higher swelling ratio than KGM hydrogel. The content of cross-linker and initiator also has influence on the equilibrium degree of swelling: decreasing the feed amount of MBAAm or APS increased the swelling ratio. These phenomena were due to the decreased cross-linking density of PMAA and the reduced interpenetration through the molecules.

Equilibrium swelling studies indicated that IPN gels were capable of responding to environmental pH. As shown in Fig. 2b, the swelling curve of the IPN hydrogels exhibited a sharp transition at approximately pH 5.5, the pK_a of pure PMAA. This transition was due to the local ionization of the pendant carboxylic acid group. At a pH above the pK_a of the network, the pendant groups were ionized, and the gels swelled to a large degree due to the development of a large osmotic swelling force due to the presence of the ions. The swelling ratio reached the maximum at pH 7.4, after that it decreased. Such pH-dependent properties of the hydrogels might come from the polyelectrolyte nature of PMAA segments in the hydrogel networks. The swelling ratio of the IPN was not as high as that of the pure PMAA gel (Fig. 2b). This was because the incorporation of the second network increased the apparent crosslinking density of the IPN. In addition, the existence of the second network decreased the carboxylic group density of the system compared to

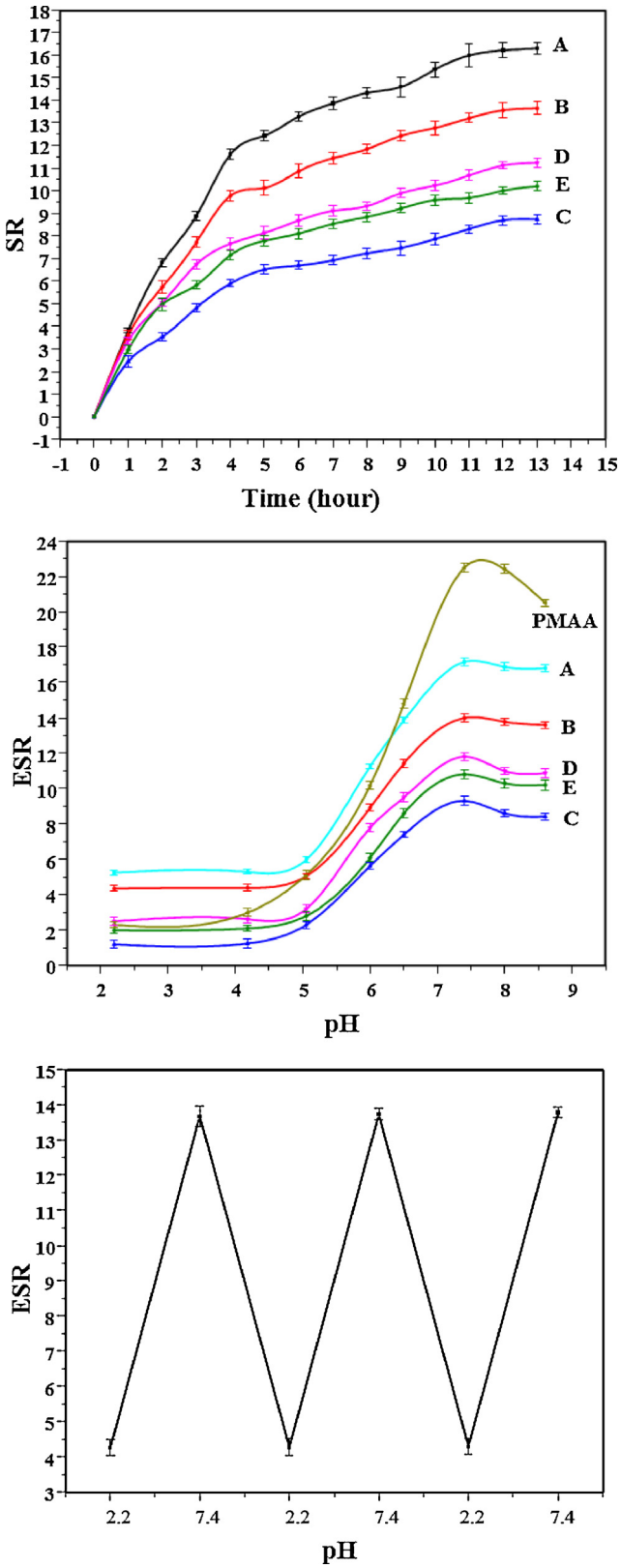

Fig. 2. (a) Swelling kinetics for different IPN hydrogels in phosphate buffer solution of pH 7.4 at 37 °C. (b) The influence of pH values of phosphate buffer solution on equilibrium swelling behavior of IPN hydrogels and pure PMAA at 37 °C. (c) Equilibrium reswelling behavior of IPN hydrogel B. Sample was transferred from pH 2.2 buffer solution to pH 7.4 buffer solutions for three cycles at 37 °C. The IPN hydrogel symbols are designed in Table 1.

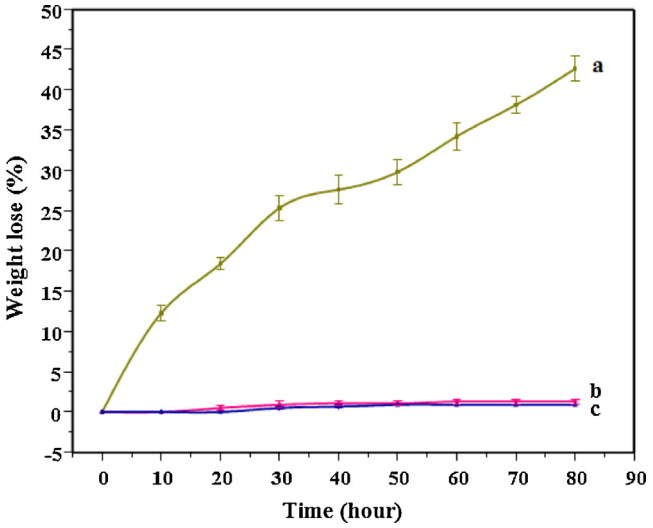

Fig. 3. Weight loss of IPN hydrogel B during degradation in phosphate buffer solution of pH 7.4 with Mannaway25L (a), with pancreatin (b) or without enzymes (c) at 37 °C.

that of the pure PMAA hydrogel, thus resulting in a lower swelling ratio.

To evaluate the reswelling ability and the pH-sensitivity of the IPN, the hydrogel samples were put in pH 2.2 buffer solutions, and then transferred to pH 7.4 buffer solutions, such operations for three cycles. The gel was incubated in one buffer solution for at least 15 h before being transferred to the other buffer solution. We can see from Fig. 2c that the swelling ratio almost remained unchanged in pH 2.2 buffer solutions and pH 7.4 buffer solutions. The result shows that the IPN has good reswelling ability and maintain its sharp respondence to pH variation.

3.3. Degradation

The enzymatic hydrolysis experiments of IPN hydrogels were carried out in pH 7.4 buffer solutions at 37 °C with Mannaway25L or pancreatin. The biodegradation properties of the IPN hydrogels were evaluated by the weight loss during degradation. The results are presented in Figs. 3 and 4. From Fig. 3, it is clear that

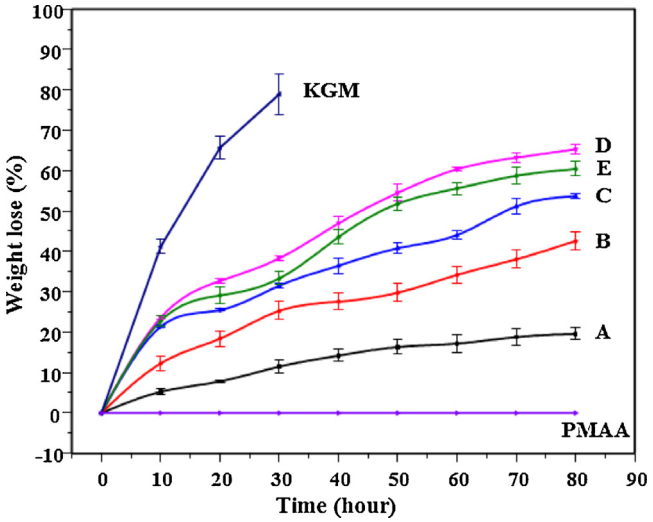

Fig. 4. Weight loss of different IPN hydrogels during degradation in phosphate buffer solution of pH 7.4 with Mannaway25L at 37 °C. The IPN hydrogel symbols are designed in Table 1.

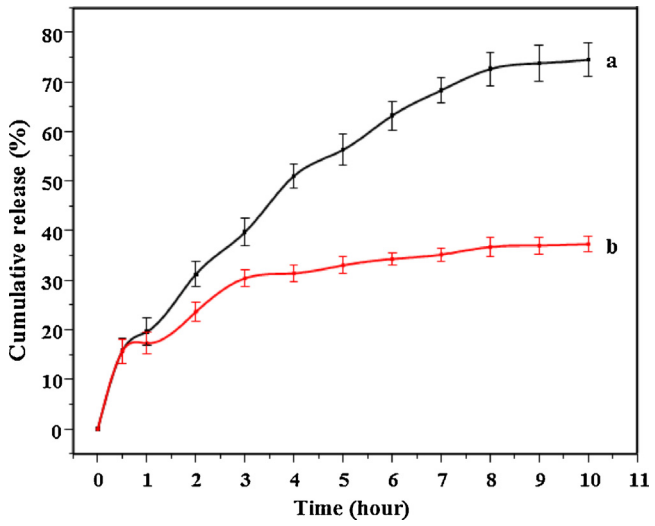

Fig. 5. *In vitro* release profile of 5-FU-loaded IPN hydrogel B in phosphate buffer solution of pH 7.4 with Mannaway25L (a) and without enzymes (b) at 37 °C.

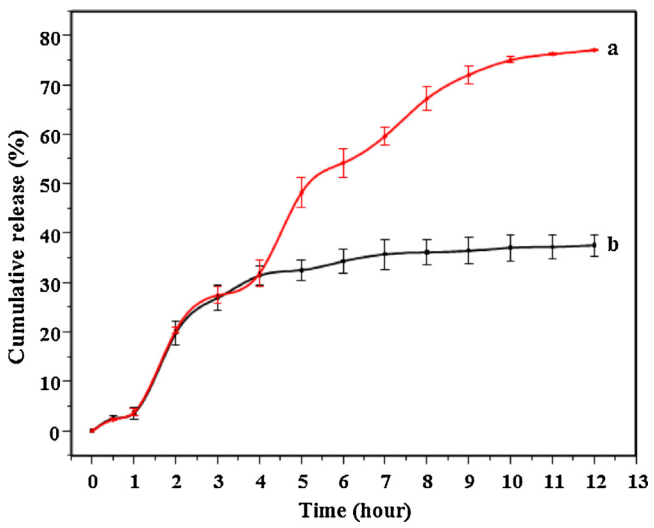

Fig. 6. *In vitro* release profile of 5-FU-loaded IPN hydrogel B with enzymes (a) or without enzymes (b) at 37 °C under different conditions: 0–1 h, pH 2.2; 1–4 h, pH 6.86; 4–36 h, pH 7.4.

the IPN hydrogel could not be degraded in pH 7.4 buffer solutions, or by pancreatin, which occurs in the upper gastrointestinal tract, but it could be degraded by Mannaway25L, a β-glycosidase and here served as a representative enzyme in colon. The enzymatic degradation specificity indicates that the KGM/PMAA IPN hydrogels retain the biodegradability of KGM.

The mass ratio of the two components of the IPN hydrogels can significantly affect the hydrogels' degradation extent, and Fig. 4 shows that the degradation rate increased with increasing the content of KGM. The weight loss increased from 19.6% to 65.3% after degradation by Mannaway25L for 80 h when the mass percentage of KGM increased from 30% to 70%. The main reason for the fact may be the increasing content of degradable KGM component and the reducing of chains entanglement of IPN.

3.4. *In vitro* drug release

In order to evaluate the properties as drug delivery matrix of obtained IPN hydrogels, *in vitro* release of 5-FU was conducted under different conditions. The drug loading was about 5% (w/w) with the loading efficiency about 90%. The release profile of 5-FU released from the IPN hydrogels in buffer solution of pH 7.4 at 37 °C are shown in Fig. 5. For both samples, about 15% of the 5-FU was released within the first 0.5 h. For the sample in buffer solution without enzyme, after the burst period, the release rate slowed down and gradually reached a plateau. At the same time, the release rate of 5-FU enhanced obviously in the medium containing Mannaway25L.

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 (Gupta, Beckert, & Price, 2001). First, the drug-loaded dry gels were put in pH 2.2 buffer solutions for 1 h, then in pH 6.8 buffer solutions with pancreatin for 3 h, finally in pH 7.4 buffer solutions with Mannaway25L for about 8 h, and the buffer solution without enzymes as control. The results are shown in Fig. 6. It can be seen that there was little release in acidic condition within 1 h because of the little swelling ratio. During the next 3 h, there was seldom difference between the releases when buffer solutions contained pancreatin or not. Within the first 4 h, the cumulative 5-FU release was about 31% for both samples. However, the 5-FU release increased rapidly in solution contained endo-1,4-β-mannanase and there was distinct difference between test and control buffer solutions in the following course. The accumulative release percent was much higher in the medium with Mannaway25L than in the control solution, they were 77% and 37.5% after 10 h, respectively.

For the release of hydrophilic small molecules drug in buffer solution without enzyme which degrades KGM, the concentration gradient is the driving force for drug diffusion. In Fig. 5, the observed initial burst release is possibly due to those 5-FU near the hydrogel surface. During the very early stage of contact between the hydrogel surface and the release medium, high 5-FU concentration gradient leads to a high initial burst and fast release rate. The 5-FU located near surface could be released immediately from the hydrogel to the surrounding medium as soon as the hydrogel swelled in a buffer solution. Beyond the burst period, the release rate slowed down and gradually reached a plateau, which was the result of diffusion of hydrophilic 5-FU from the hydrogel when the gel became swollen. For the IPN hydrogel in medium with Mannaway25L, the rapid release resulted from the degradation of the KGM gel networks.

The *in vitro* drug release from hydrogel maybe involves two mechanisms. One is the diffusing of drug molecules, especially hydrophilic small molecules, through aqueous pores or channels formed during preparation. Such a release usually occurs near the surface of the hydrogel. The other mechanism involves degradation of the hydrogel matrix. Enzymatic degradation of the matrix to some extent results in the appearance of new pores, partial damage of networks, and increase of pore diameter. The drug molecules that are previously not accessible to release medium can diffuse out and be released completely, which causes the rapid increase in the release rate. The endo-1, 4-β-mannanase in Mannaway25L degraded KGM component in IPN hydrogel and spoiled the IPN structure, which resulted in the rapid and complete release.

4. Conclusion

A novel biodegradable and pH-sensitive IPN hydrogels of KGM and PMAA were synthesized by polymerization of MAA in the KGM network. The mass ratio of KGM to PMAA has significant influence on the properties of resultant IPN hydrogels. The studies on the swelling behavior of hydrogels reveal their sensitive response to pH change. The equilibrium swelling ratios increase with increasing PMAA content. KGM network in the IPN hydrogels can be degraded under the action of β-glycosidase, such as Mannaway25L, but not under α-glycosidase such as pancreatin which occurs in the upper

gastrointestinal tract. The degradation rates increase with increasing KGM content in IPN gels. The results of *in vitro* drug release of 5-FU confirm that the release is controlled by swelling and degradation of the hydrogels. The properties of the IPN hydrogels, that is, the pH sensitivity and the specificity to enzymatic degradation, suggest that they are desirable in colon-specific drug delivery applications.

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