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Hemicellulose-based pH-sensitive and biodegradable hydrogel for controlled drug delivery

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ABSTRACT

Hydrogels based on hemicellulose of wheat straw were prepared as a novel carrier for controlled drug delivery. The chemical structure and morphology of the hydrogels were characterised using FT-IR and SEM, respectively. The swelling ratios of the hydrogels were determined, and the results showed that the hydrogels were pH-responsive. The swelling kinetics of the hydrogels followed a Fickian diffusion process in media with a pH of 1.5, and water uptake was controlled collaboratively by hydrogel relaxation and water diffusion in media with pH values of 7.4 and 10.0. The degradation test of the hydrogels was conducted under simulated physiological conditions, and both hemicellulose content and the crosslinking density of the hydrogels were major factors that affected the biodegradability of the hemicellulose-based hydrogels. A comparison of the *in vitro* release of acetylsalicylic acid and theophylline indicated that the drug release was controlled both by the hydrogel and by the intrinsic character of the drug. According to the results presented here, hemicellulose-based hydrogels can be used in biomedical fields, especially for controlled drug release.

1. Introduction

In recent years, intelligent hydrogels have been widely studied because of their responsiveness to environmental stimuli, such as pH, ionic strength, solvent composition, temperature and electric and magnetic fields (Qiu & Park, 2001). Because of their special properties, hydrogels could be widely used in biomedical fields, including biological scaffolds for tissue engineering (Hoffman, 2002), biosensors, immobilised carriers for the encapsulation of living cells (Sefton, May, Lahooti, & Babensee, 2000), barrier materials to regulate biological adhesions (Bennett, Melanson, Torchiana, Wiseman, & Sawhney, 2003) and controlled delivery systems for drugs (Lin & Metters, 2006; Qiu & Park, 2001). pH-responsive hydrogels have received considerable attention in the field of oral drug delivery, not only because the hydrogels could protect the drug against acidic denaturation and reduce the noxious stimulation of drugs on the stomach, but also because they could prolong the residence time of drugs and reduce dosing frequency (Qiu & Park, 2001). Furthermore, because of the excellent biocompatibility and biodegradation of natural polymers, a variety of natural polysaccharides have been used to prepare hydrogels as harmless controlled release systems for drug delivery (Coviello, Matricardi, Marianecci, & Alhaique, 2007; Lindblad, Sjöberg, Albertsson, & Hartman, 2007).

Hemicellulose (HC), the second most abundant renewable natural polymer compared to cellulose, exists widely in plants. More and more attention has been concentrated on the development and application of hemicellulosic products because of their numerous inherent advantages, which include non-toxicity, biocompatibility, biodegradability and anti-cancer effect (Ebringerová, Hromadkova, & Heinze, 2005; Oliveira et al., 2010). HC has been used as fermentation feedstock in the production of ethanol, butanol and xylitol (Ebringerová et al., 2005; Saha, 2003) and as raw materials in the preparation of food packaging films (Hansen & Plackett, 2008; Hartman, Albertsson, & Sjöberg, 2006). Xylan, the major HC isolated from grass and hardwood, has many beneficial effects, including anti-phlogistic effects, immune function (Ebringerová, Hromádková, Alföldi, & Hřibalová, 1998; Ebringerová, Kardosova, Hromadkova, Malovikova, & Hribalova, 2002), inhibitory action on the growth rate of tumours (Whistler, Bushway, Singh, Nakahara, & Tokuzen, 1976) and mutagenicity activity (Tsutomu, 1992). Some reports have noted that xylan was digested little in the physiological stomach environment but was consumed by anaerobic bacteria in the colon (Ebringerová & Heinze, 2000; Sinha & Kumria, 2001; Sinha, Mittal, Bhutani, & Kumria, 2004; Yang, Chu, & Fix, 2002). This unique property of xylan has advantages in the preparation of pH-responsive hydrogels for the controlled release of oral drugs.

Over the last decade, a few reports on the synthesis of HC-based hydrogels have appeared. Gabrielii et al. (Gabrielii & Gatenholm,

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1998; Gabrielii, Gatenholm, Glasser, Jain, & Kenne, 2000) prepared a hydrogel by mixing HC (which contained glucuronic acid functional groups) with chitosan in acidic solution. Most of the studies on the synthesis of HC-based hydrogel focused on the introduction of alkenyl-functional groups onto the HC structure and their subsequent covalent cross-linking to form a hydrogel (Albertsson, Voepel, Edlund, Dahlman, & Söderqvist-Lindblad, 2010; Lindblad, Albertsson, Ranucci, Laus, & Giani, 2005; Lindblad, Ranucci, & Albertsson, 2001; Yang, Zhou, & Fang, 2011). In our study, a series of HC-based hydrogels were synthesised using various HC/acrylic acid monomer ratios (diverse neutralisation degree) and various amounts of initiator and crosslinker, to examine factors that affect the swelling behaviour and pH-sensitivity of the resulting hydrogels. The prepared hydrogels were characterised using scanning electronic microscopy (SEM), Fourier-transform infrared (FT-IR) spectrophotometry, and swelling tests. Degradation tests were conducted under simulated physiological conditions. Finally, an *in vitro* drug release study was performed using acetylsalicylic acid and theophylline as model drugs.

2. Materials and methods

2.1. Materials

Wheat straw, from the Changan Region in the Shanxi Province of China, was ground to pass a 1 mm size screen, and HC was extracted from the wheat straw. Acrylic acid (AAc) was obtained from Shanghai Chemical Reagent Co. (China). Potassium persulfate, anhydrous sodium sulfite, and *N*,-*N*-methylene bisacrylamide (MBA) were purchased from Tianjin Fuchen Chemical Reagent Co. (China). Acetylsalicylic acid and theophylline as model drugs were provided by J&K Chemical (China branch). All chemicals used were of analytical grade.

2.2. Isolation of hemicellulose

The isolation of HC from wheat straw was divided into four steps (Scheme 1) according to our previous study (Sun, Sun, Tomkinson, & Baird, 2003). First, the cut wheat straw was dewaxed with toluene and ethanol at a ratio of 2:1 (v/v) in a Soxhlet extractor for 12 h. Second, the dewaxed straw was delignified with sodium chlorite at pH 4.0 (adjusted with acetic acid) at 75 °C for 2 h. The obtained holocellulose was treated with 10% KOH (w/w) at room temperature for 10 h and then filtrated to separate the HC and cellulose. The filtrate was neutralised to pH 5.5, concentrated under reduced pressure, and then precipitated in 3 volumes of ethanol to yield the HC.

The obtained HC sample was hydrolysed with 2 M trifluoroacetic acid for 2 h at 120 °C. The neutral sugar composition in the hydrolysate solution was determined using gas chromatography (GC) analysis.

2.3. Preparation of hydrogels

HC-based hydrogels have been successfully prepared by other methods (Peng, Ren, Zhong, Peng, & Sun, 2011; Yang et al., 2011). In this study, hydrogels were prepared from wheat straw hemicelluloses with a redox initiation system, and all experiments were performed at 50 °C in a water bath. HC was first dissolved in distilled water at a concentration of 5% (w/w). As the redox initiation system, potassium persulfate and anhydrous sodium sulfite were added to the hemicellulosic solution. AAc was added slowly, followed by the solubilised crosslinker (*N*,-*N*-methylene bisacrylamide) after 5 min. The reaction system became progressively thicker until it could not be stirred. The sample was removed, cut into cuboids (approximately 8 mm long, 4 mm wide and 2 mm thick) and dried under vacuum at 50 °C to a constant weight. The dried hydrogel samples were immersed in deionised water for 48 h, and the deionised water was refreshed every 4 h to remove the impurities, especially the acrylic acid homopolymer. The swollen hydrogel samples were subsequently dried in vacuum oven at 50 °C to a constant weight. The AAc/HC ratio, the amounts of initiator and crosslinker, and the degree of AAc neutralisation will affect the chemical structure and properties of the synthesised hydrogel. These conditions were varied to study the influences of these factors on the physic-chemical properties of HC-based hydrogels, such as the swelling behaviour, morphology and degradation, and a of total 17 hydrogel samples were prepared, as shown in Table 1.

2.4. FT-IR and SEM analysis

The hydrogel samples were dried in a vacuum oven at 50 °C for 24 h to a constant weight. The dried hydrogels were analysed in KBr discs by FT-IR performed on a Nicolet 510 spectrophotometer.

The swollen hydrogels in pH 1.5, 7.4 and 10.0 buffer solutions (see Section 2.5) were freeze-dried to maintain their porous structures without any collapse. The surface and inner pore structure of oven-dried and freeze-dried hydrogels were observed on a scanning electron microscope (SEM, S-2460N, Hitachi, Tokyo, Japan) at 400×.

2.5. pH dependence of the swelling ratio

Swelling experiments were conducted by a gravimetric method at room temperature in buffer solutions of desired pH (1.5–10.0) in which the ionic strength was kept constant at $I = 0.05$ M. The swollen hydrogels were removed from the solutions, wiped with filter paper, and then weighed as soon as possible. The tests of all samples were conducted in triplicate. The swelling ratio (S) at time t and the equilibrium swelling ratio (S_{eq}) were calculated as follows:

$$S = \frac{W_t - W_d}{W_d} \quad (1)$$

$$S_{eq} = \frac{W_e - W_d}{W_d} \quad (2)$$

where the term W_d is the initial weight of the dry hydrogel, and W_t and W_e are the weight at time t and the equilibrium weight during the swelling process, respectively.

2.6. Drug loading and release

Acetylsalicylic acid and theophylline were used as model drugs for drug loading and release experiments. The drug was first dissolved in distilled water, and the drug solution was added into the hydrogel when the reaction system became thick during the hydrogel preparation process. The amounts of acetylsalicylic acid and theophylline in the dry gels were 2% and 1.5% (w/w), respectively.

In vitro release studies of the drug from the hydrogels were performed in a shaker incubator at a shaking speed of 50 rpm at 37 °C. The drug-loaded hydrogels (0.1 g) were immersed in a defined volume of pH 1.5, pH 7.4 or pH 10.0 buffer solutions. Five millilitres of each solution was collected at 1 h intervals for the determination of drug content using a UV spectrophotometer (acetylsalicylic acid: 294 nm; theophylline: 273 nm), and an equal volume of the same solution medium was added back to maintain a constant volume. The *in vitro* release tests of all samples were conducted in triplicate. The concentration of the drug in the different buffer solutions was calculated from the following calibrated standard curves.

Table 1
Synthesis of hydrogels under various reaction conditions.

Sample code	Reaction conditions			
	AAc/CH (g/g)	Initiator (g)	Crosslinker (g)	Degree of AAc neutralisation (%)
gel-1	6:1	0.032	0.024	0
gel-2	8:1	0.032	0.024	0
gel-3	10:1	0.032	0.024	0
gel-4	12:1	0.032	0.024	0
gel-5	8:1	0.016	0.024	0
gel-6	8:1	0.048	0.024	0
gel-7	8:1	0.064	0.024	0
gel-8	8:1	0.032	0	0
gel-9	8:1	0.032	0.012	0
gel-10	8:1	0.032	0.036	0
gel-11	8:1	0.032	0.048	0
gel-12	8:1	0.032	0.072	0
gel-13	8:1	0.032	0.024	20
gel-14	8:1	0.032	0.024	40
gel-15	8:1	0.032	0.024	60
gel-16	8:1	0.032	0.024	80
gel-17	8:1	0.032	0.024	100

For acetylsalicylic acid:

pH 1.5: $y = 0.25711 + 0.00369x$ ($r = 0.9997$);
pH 7.4: $y = 0.2521 + 0.0029x$ ($r = 0.9992$);
pH 10.0: $y = 0.22354 + 0.01641x$ ($r = 0.9989$).

For theophylline:

pH 1.5: $y = 0.041 + 0.055x$ ($r = 0.9989$);
pH 7.4: $y = 0.04771 + 0.05562x$ ($r = 0.9992$);
pH 10.0: $y = 0.05581 + 0.05343x$ ($r = 0.9987$).

The cumulative release ratio of the drug was calculated from the following equation:

$$\text{Cumulative release}\,(\%) = \frac{W_{dt}}{W_\infty} \times 100 \quad (3)$$

where W_{dt} is the weight of released drug at time t and W_∞ is the total weight of loaded drug in the hydrogel.

2.7. Degradation test

Degradation tests were performed in phosphate buffered solution with 50 U/ml trypsin (pH 7.4, simulated intestinal fluid) and 50 U/ml pepsin (pH 1.5, simulated gastric fluid) and without any enzymes at 37 °C. The mass loss of swollen hydrogels was monitored at certain intervals. The tests of all samples were conducted in triplicate. The degradation ratio was determined with the following formulas:

$$\text{Wet mass change}\,(\%) = \frac{W_t}{W_e} \times 100 \quad (4)$$

$$\text{Dry mass loss}\,(\%) = \frac{W_d - W}{W_d} \times 100 \quad (5)$$

where W_e and W_t represent the weights of hydrogels in their original equilibrium swollen states and at time t in the test solutions, respectively; and W_d and W are the weights of the dry hydrogels before and after degradation, respectively.

3. Results and discussion

3.1. Hemicellulose from wheat straw and synthesis of hydrogel

According to our previous study, the HC extracted from wheat straw in this study was mainly arabinoxylan (Sun, Sun, Fowler, & Baird, 2005). GC analysis showed that xylose was the major sugar in the isolated HC, comprising approximately 80.44% (w/w) of the total sugars, and arabinose (12.47%) was the second most abundant sugar. Glucose (4.28%) and galactose (2.81%) appeared as minor constituents, and mannose was not detected.

As illustrated in Scheme 2, the pH-sensitive hydrogels were synthesised by radical copolymerisation of the hemicellulosic polymer with AAc. The backbone of the gel network was made up of the HC component, and AAc was grafted onto the backbone by fixing one end structurally. The linear PAAc and the intrinsic side chain on the HC backbone served as the free mobile chains. Within the hydrogel, cross-linking points were formed in both the HC backbone and the ends of the grafted chains.

3.2. FT-IR spectra of the hemicellulose and the prepared hydrogel

The FT-IR spectra of HC and the HC-based hydrogel (gel-2) are shown in Fig. 1. The prominent band at 1037 cm^{-1} originated from the C—O—C stretching of pyranoid-ring xylans. The occurrence of a small band at 1166 cm^{-1} was due to the presence of arabinose residues. A sharp band at 891 cm^{-1}, which arose from the C1 group frequency or ring frequency, was observed, and this band is characteristic of β-glucosidic linkages between sugars units. The broad band at 1618 cm^{-1} was most likely due to absorbed water. The weak

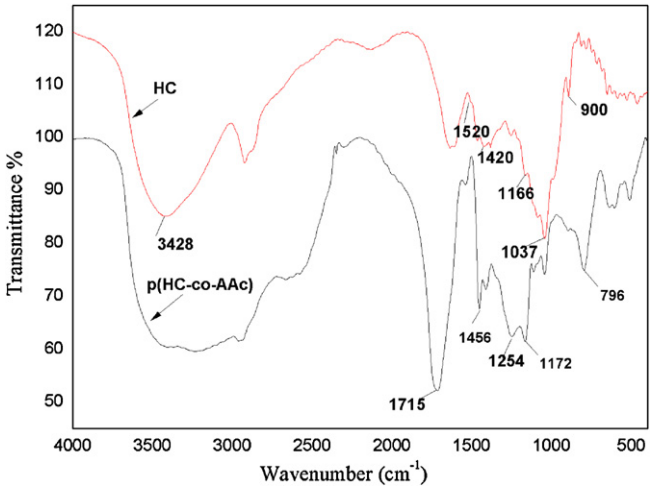
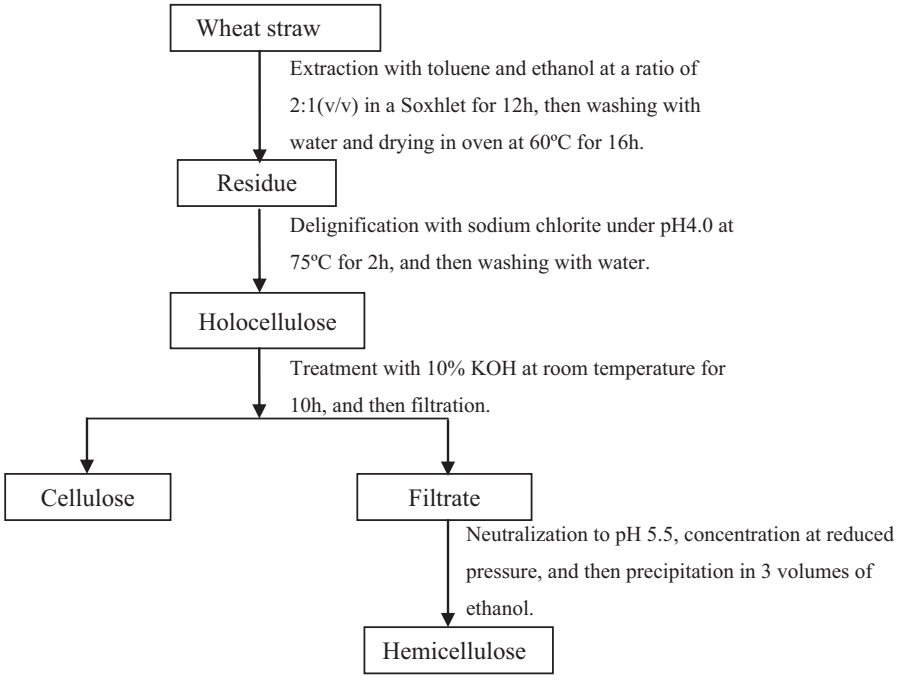


Fig. 1. FT-IR spectra of hemicellulosic polymer and HC-based hydrogel.



Scheme 1. Extraction of hemicellulosic polymers from wheat straw.

bands at 1520 cm^{-1} and 1420 cm^{-1} were indicative of the presence of trace amount of lignin in the HC (Sun et al., 2005).

The two strong absorption peaks at 1715 cm^{-1} and 1456 cm^{-1} in FT-IR spectrum of gel-2 were attributed to asymmetric stretching vibration of COOH and bending vibrations of COO^- groups, respectively. The symmetric stretching vibration of COO^- groups overlapped at 1254 cm^{-1} and 1173 cm^{-1}. The characteristic absorption band of HC at 1037 cm^{-1} was obviously weakened. These results indicated that AAc chains were grafted onto the HC backbone. The absorption band of a C=C stretching vibration that typically appears at approximately 1600 cm^{-1} was not observed, which suggested that the gel did not contain the AAc monomer.

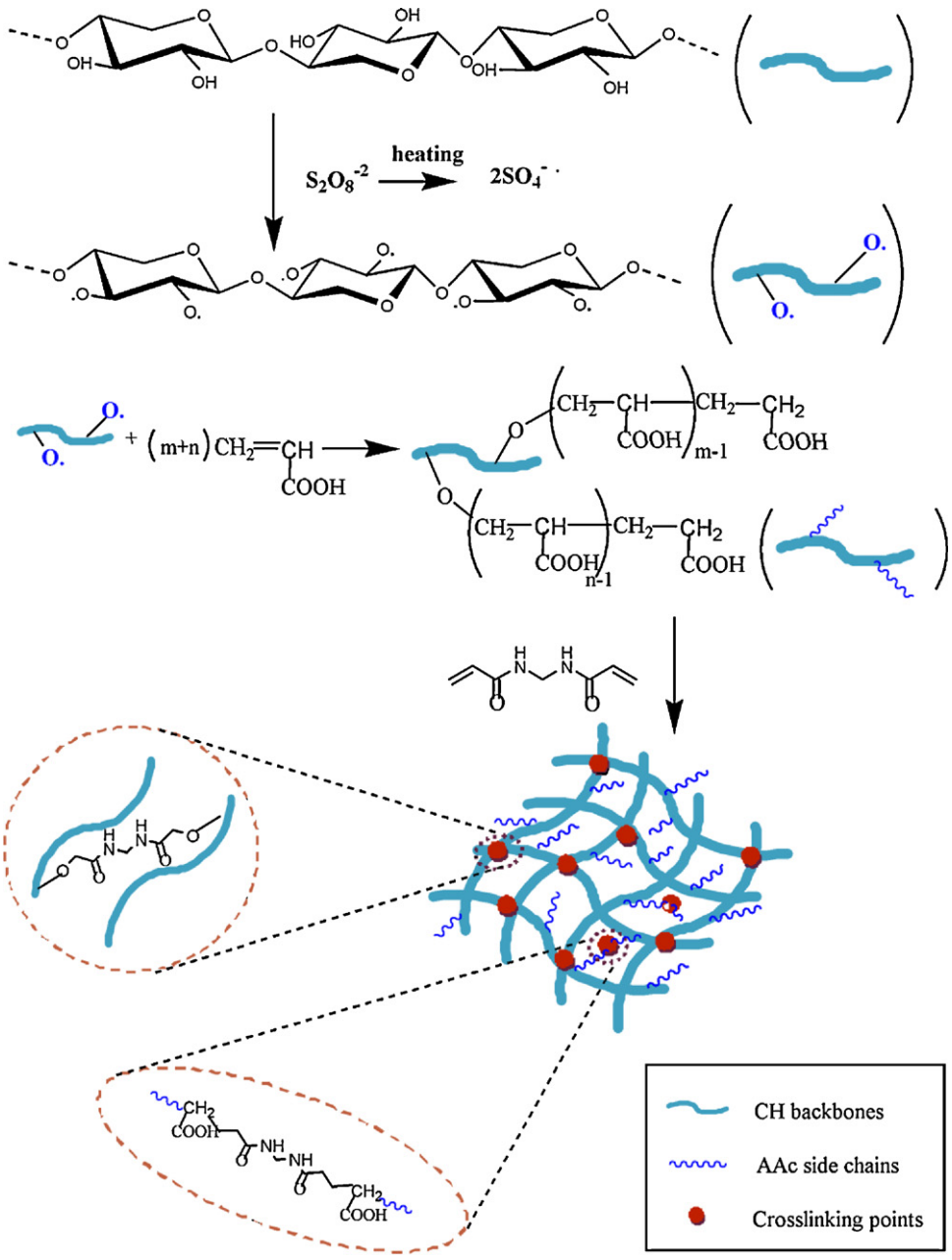
3.3. Swelling behaviour of hydrogels

The hydrogels prepared *via* the grafting of acrylic acid onto HC represent anionic hydrogels with obvious pH-sensitivity. The carboxylic group in the hydrogels is ionisable, and the degree of ionisation strongly depends on the pH; in addition, the degree of electrostatic repulsion within the hydrogel also depends on pH. Major factors (Swann, Bras, Topham, Howse, & Ryan, 2010) that influence the degree of swelling of ionic polymers include the properties of the polymer itself (*i.e.*, charge, concentration and pK_a of the ionisable group, degree of ionisation, cross-link density, and hydrophilicity or hydrophobicity) and properties of the swelling medium (*i.e.*, pH, ionic strength, the nature of the counterion, and its valency). In our study, the buffer systems at a given pH value were identical and the ionic strength was kept constant; therefore, the swelling behaviour of the hydrogel at various pH values mainly depends on the ionised pendant groups, the fixed charges on the polymer network, and the electrostatic repulsive forces (Schneider & Linse, 2003).

Fig. 2 illustrates the effect of pH on the equilibrium swelling ratio (S_{eq}) of the HC-based hydrogel. The swelling behaviour of the hydrogel at various pH values was divided into three parts: the low-lying area (pH 1–3), the increasing area (pH 4–7.4), and the slowing down area (pH 8–10.0). The hydrogels in the low-lying area maintained a shrinking state, and the swelling ratio increased slightly with increasing pH value. Under acidic conditions, most of the carboxyl groups were unionised, so no significant differences were created in the ion concentrations; these conditions resulted in little electrostatic repulsion, and a low swelling ratio was observed in the low-lying area. A sharp increase in S_{eq} appeared when the pH value was changed from pH 3 to pH 4 because of the ionisation of carboxyl groups. When the pH value of the buffer solution was higher than the pK_a of the hydrogel, the COOH groups dissociated to COO^-, and the fixed charge density in the network increased significantly, which accounted for the higher swelling ratio. Because of the increase in the fixed charge density, the cation concentration difference in and out of the hydrogel became greater. The osmotic pressure between the hydrogel and the external solution would cause the external solution to easily penetrate into the network; therefore, the swelling ratio increased sharply. In addition, because of the increased fixed charge, the electrostatic repulsion among the polyanions was enhanced, which accelerated the expansion of the macromolecular chains until the swelling equilibrium was reached. However, the swelling ratio of the hydrogels declined slightly in the alkaline buffer solution. The concentration of free ions (such as Na^+) increased in the alkaline buffer solution, and the free ions surrounded the fixed charges, which were on the end groups of the hydrogel chains, to produce a weak-ion environment. This environment led to a slight decrease in the electrostatic repulsion among the macromolecular chains and to a decrease in the osmotic pressure, which caused a decrease in the swelling ratio.

3.3.1. Effect of HC content on the swelling ratio

Fig. 2a demonstrates that the ratio of AAc/HC (g/g) affected the subsequent equilibrium swelling ratio in various pH buffer solutions. With an increase in the AAc/HC ratio from 6:1 to 8:1, the equilibrium swelling ratios of the hydrogels increased from 33 to 79. In this case, one of the major factors that affects the pH sensitivity of the swelling ratio is the content of carboxyl groups in the hydrogels. Within a certain range of AAc/HC ratio, a higher AAc content will result in a more ionisable carboxyl group in the hydrogels and in a higher swelling ratio of the hydrogels. In addition, the hydrogen bonds that exist in the HC may increase the density of



Scheme 2. Synthesis of hemicellulose-*co*-PAAc hydrogel by radical copolymerization.

cross-linking points in the hydrogel and restrain the swelling. The increase in the degree of ionisation of the carboxyl groups undermine hydrogen bonds and promote the swelling of the hydrogels. However, when the AAc/HC ratio was greater than 8:1, the equilibrium swelling ratio decreased. The mass loss of the hydrogels with higher AAc concentrations (greater than 8:1) was found to be greater when the hydrogel samples were immersed in deionised water for 48 h. This result indicated that the acrylic acid homopolymers were easily generated due to the high AAc concentration and that the graft rate of the hydrogel decreased, which resulted in the decreased swelling ratio. The optimum AAc/HC ratio with respect to water absorrption of the hydrogels was 8:1.

3.3.2. *Effect of crosslinking degree on the swelling ratio*

A comparison of the swelling ratios of gel-2, gel-9, gel-10, and gel-12 in solutions with the same pH value (Fig. 2b) reveals that the equilibrium swelling ratio (S_{eq}) decreased as the amount of crosslinker was increased. This result was attributed to the increased cross-linking degree, which decreased the distance between crosslinking points and reduced the space for water absorption; thus, less free water would be retained in the network. However, the hydrogel without crosslinker would slowly dissolve in the solution media because only physical crosslinking forces existed in the hydrogels. In our follow-up study, we found that a moderate cross-linking density was important for drug release and degradation.

3.3.3. *Effect of initiator amount on the swelling ratio*

Fig. 2c shows the effect of the initiator on the equilibrium swelling ratio of hydrogels. When the initiator concentration was low, the number of graft points on HC decreased, which resulted in the incomplete grafting reactions, and the equilibrium swelling ratio was low. When the initiator concentration was increased, more free radicals were generated, which promoted the grafting

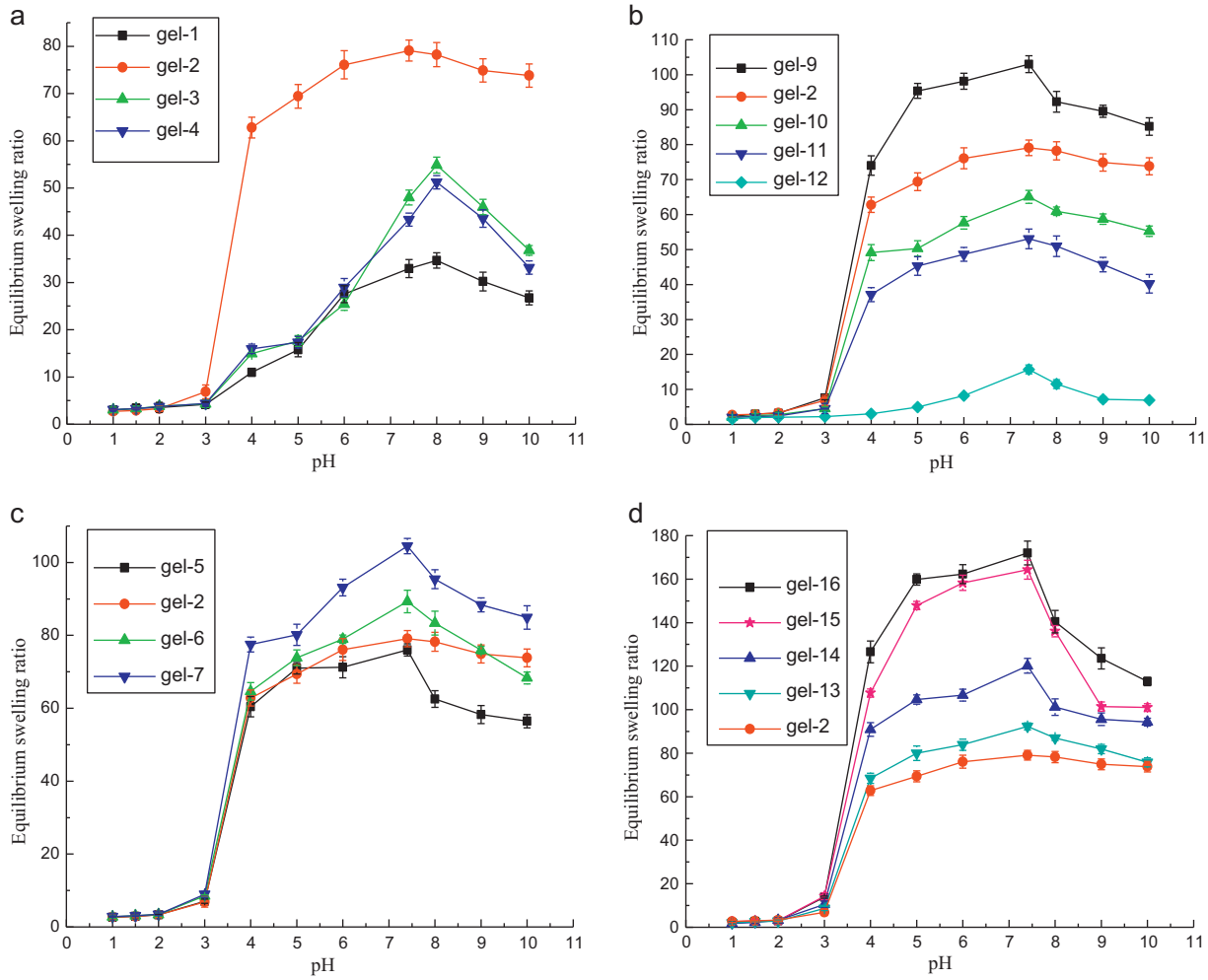


Fig. 2. Effect of pH on the equilibrium swelling ratio of hydrogels prepared under various reaction conditions: (a) effect of HC content; (b) effect of crosslinking degree; (c) effect of initiator amount; (d) effect of AAc neutralisation degree.

and copolymerisation reaction, and the equilibrium swelling ratio increased.

3.3.4. *Effect of AAc neutralisation degree on the swelling ratio*

The degree of AAc neutralisation also strongly influenced the water absorption of the hydrogel, as is clearly shown in Fig. 2d. The optimum degree of AAc neutralisation with respect to the water uptake capacity ranged from 60% to 80%. The COOH groups on the neutralised PAAc dissociated into COO^-, and then the number of fixed ionised groups within the hydrogel increased. This increase in the number of ionised groups generated electrostatic repulsion forces between the adjacent ionised groups in the polymer network, which facilitated the diffusion of water into the network. In contrast, when the degree of AAc neutralisation was 100% (gel-17), gel formation was practically impossible.

3.4. *Morphological analysis*

To investigate the change in the surface morphology of the hydrogels in various pH buffer solutions, SEM images of the oven-dried and freeze-dried gel-2 were collected; the results are shown in Fig. 3. The hydrogel sample dried in a vacuum oven showed a smooth and dense surface, but a porous honeycomb-like structure was clearly observed for all of the freeze-dried hydrogels. The pore size increased as the amount of water absorbed into the hydrogel increased. At pH 7.4 or 10.0, the electrostatic repulsions caused by COO^- groups enlarged the space within the networks of the hydrogels, which favoured the enhancement of water absorption to form large pores. The SEM images of freeze-dried gel-1 and gel-9 swollen in pH 7.4 buffer solution are also shown in Fig. 3; these gels also exhibited regular macro-porous architectures, and the pore size of the hydrogels decreased in the order gel-2 > gel-1 and gel-9 > gel-2. With the decrease in the HC content and crosslinking density, the pore size increased, which created more open and loose structures. The SEM observation revealed that HC was sufficiently rigid to act as a backbone in the hydrogel. As the crosslinking degree decreased, the number of crosslinking points was decreased, which was convenient for the penetration of water into the polymeric network and the follow-up degradation.

3.5. *Analysis of water absorption mechanism*

To evaluate the dynamic swelling properties of the HC-*co*-PAAc hydrogels, Fick's diffusion kinetics model was adopted; according to the literature, this model can be expressed as Eq. (7) (Kim, Flamme, & Peppas, 2003; Ritger & Peppas, 1987):

$$\frac{W_t}{W_\infty} = kt^n \tag{6}$$

$$\mathrm{Ln}\left(\frac{W_t}{W_\infty}\right) = n\ln t + \ln k \tag{7}$$

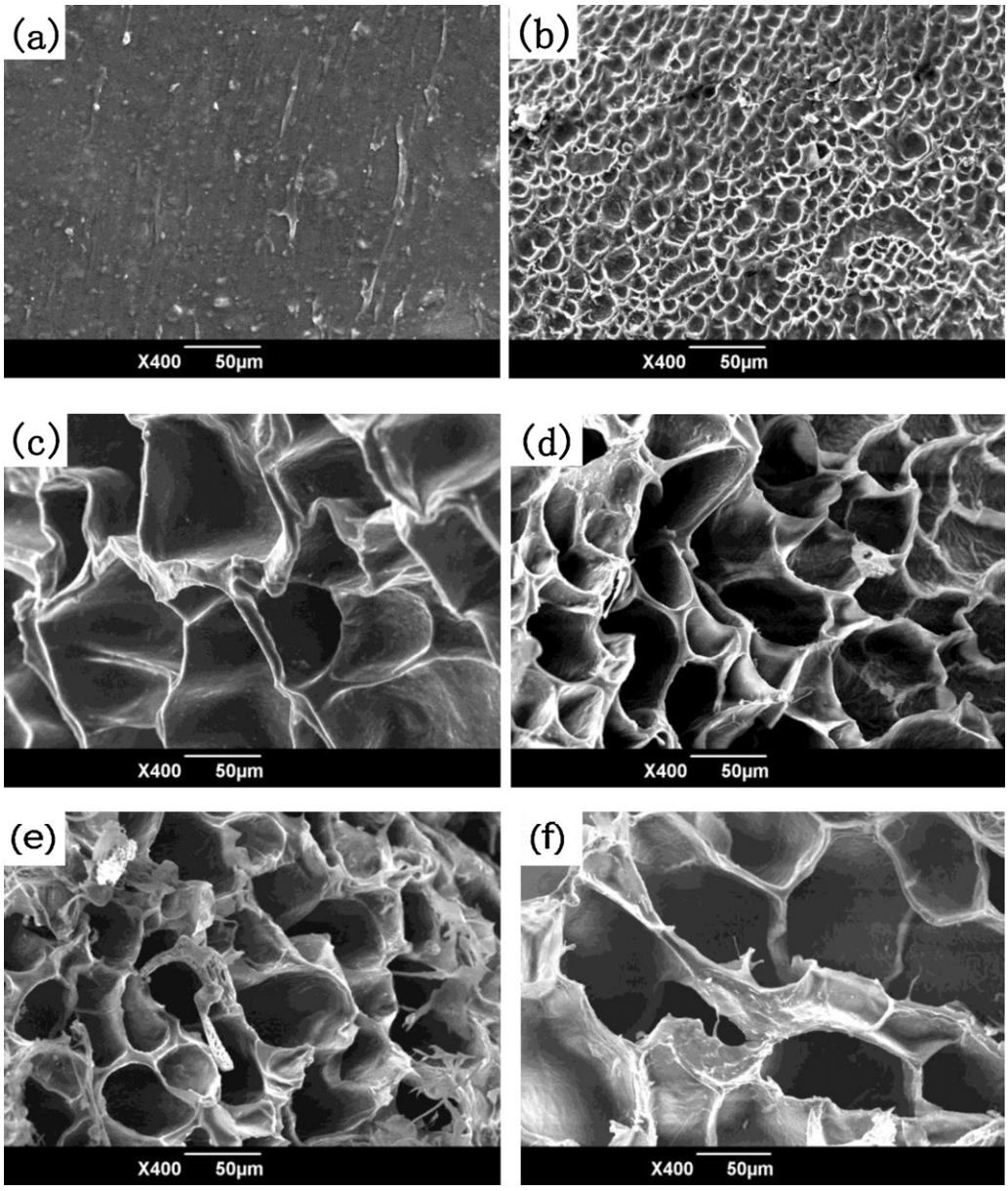


Fig. 3. SEM images of gel-2 dried in vacuum oven (a) and in a freeze dryer after swelling in pH 1.5 (b), pH 7.4 (c), pH 10.0 (d) buffer solutions, and images of the freeze-dried gel-1 (e) and gel-9 (f) after swelling in pH 7.4 buffer solution.

Table 2
Swelling exponents of different hydrogel samples.

Sample code	pH					
	1.5		7.4		10.0	
	Swelling exponent n	Corr. coeff. r	Swelling exponent n	Corr. coeff. r	Swelling exponent n	Corr. coeff. r
gel-1	0.212	0.995	0.867	0.993	0.792	0.984
gel-2	0.298	0.987	0.896	0.988	0.863	0.993
gel-3	0.256	0.990	0.872	0.990	0.856	0.993
gel-5	0.285	0.993	0.851	0.982	0.800	0.990
gel-6	0.309	0.991	0.922	0.987	0.865	0.989
gel-10	0.201	0.990	0.775	0.981	0.698	0.986
gel-9	0.320	0.994	0.924	0.990	0.901	0.996
gel-15	0.306	0.992	1.119	0.984	1.054	0.998
gel-16	0.356	0.986	1.264	0.985	1.102	0.992

where W_t is the mass of the water absorbed by the hydrogel at a specified time, t; W_∞ is the mass of the water absorbed by the hydrogel at the equilibrium state; k is a characteristic constant of the hydrogel; and n is the diffusional exponent, which was often used to determine the transport mechanism mode. For $n < 0.5$, the swelling behaviour fits Fickian diffusion, in which the water transport is governed by a simple concentration gradient. For $0.5 < n < 1$, the water uptake conforms to an anomalous diffusion, where the

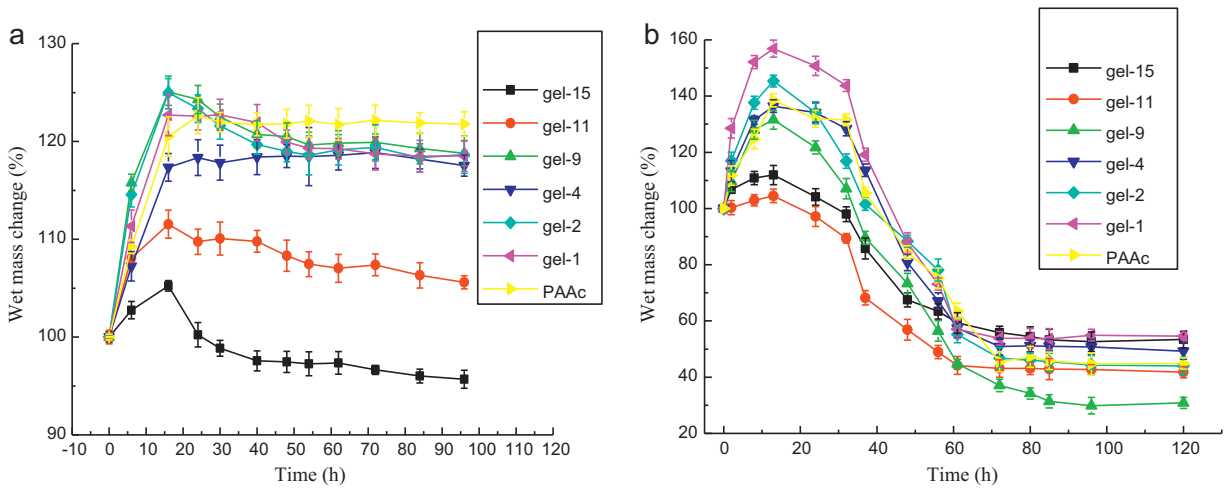


Fig. 4. The wet mass changes of hydrogels: (a) in the simulated gastric fluid at pH 1.5 and (b) in the simulated intestinal fluid at pH 7.4.

water uptake is controlled collaboratively by hydrogel relaxation and water diffusion (non-Fickian diffusion). For $n > 1$, the controlled relaxation of the polymer chain dominates the water transport (anomalous diffusion). The plots of $\mathrm{Ln}(W_t/W_\infty)$ *versus* $\ln t$ gave a line with a good linear correlation coefficient. The values of n and the coefficients (r) that were determined from the slopes and correlations of the fit lines, respectively, are summarised in Table 2. Notably, the n value was $n < 0.5$ at pH 1.5, which indicated that the water transport followed Fickian swelling process dominated by free diffusion of water. The n values increased in both neutral and basic solutions, which was mainly ascribable to the increasing ionisation of COOH groups, which generated strong electrostatic repulsion forces. These strong forces led to easier polymer relaxation for the accommodation of more water (Kim & Peppas, 2002), which resulted in deviation from Fickian diffusion and a tendency towards anomalous diffusion. The anomalous diffusion-controlled water transport has been demonstrated to provide an essential condition to realise zero-order drug release from a hydrogel (Rao & Devi, 1988).

The n values of the hydrogels that were prepared with various AAc/HC ratios decreased in the order gel-2 > gel-3 > gel-1. HC was the rigid backbone in the hydrogel network, so the polymer chain relaxation became easy when the HC content in the hydrogels decreased. However, electrostatic repulsion forces increased with increasing AAc/HC ratio, which also led to easier polymer chain relaxation. Therefore, the n values increased with the increase in the AAc/HC ratio. The amount of initiator has little influence on the water absorption mechanism compared with other factors, as indicated in Table 2. A decrease in the crosslinking density resulted in an increase in the n values, and water transport became more dependent on the polymer relaxation. The AAc neutralisation degree strongly influenced not only the equilibrium swelling but also the water absorption mechanism, as shown in Table 2. The n values increased with an increase in the number of fixed ionised groups, which resulted in a major polymer relaxation. The n values of gel-12 and gel-14 at pH 7.4 and 10.0 were greater than 1, which demonstrated that the water transport was dominated by the controlled-relaxation of the polymer chain.

3.6. Degradation test

The biodegradability of hydrogels strongly influences their biomedical applications, especially with respect to controlled drug delivery. The degradation of the HC-based hydrogels was studied under simulated physiological conditions. The wet mass changes in the selected hydrogels in simulated gastric fluid and in simulated intestinal fluid are shown in Fig. 4a and b, respectively. Fig. 5a and b demonstrates the dry mass losses of the hydrogels after degradation in buffer solutions without enzymes and in simulated gastric/intestinal fluid for 96 h, respectively. According to the report by Metters (Metters, Bowman, & Anseth, 2000), two types of degradation processes occur in hydrogel networks: surface erosion and

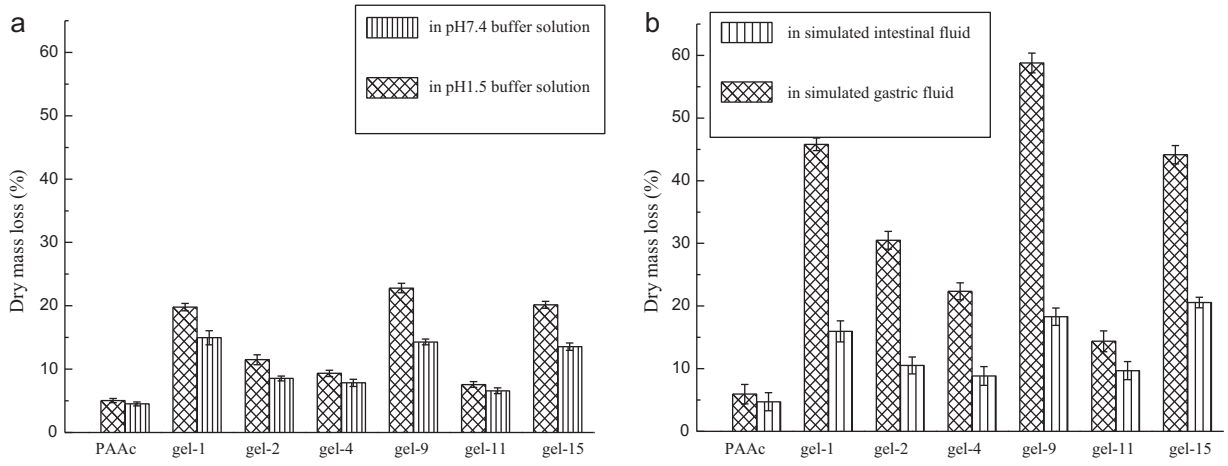


Fig. 5. The dry mass loss of hydrogels after 96 h of degradation: (a) in pH 1.5 and 7.4 buffer solutions and (b) in the simulated intestinal fluid and gastric fluid.

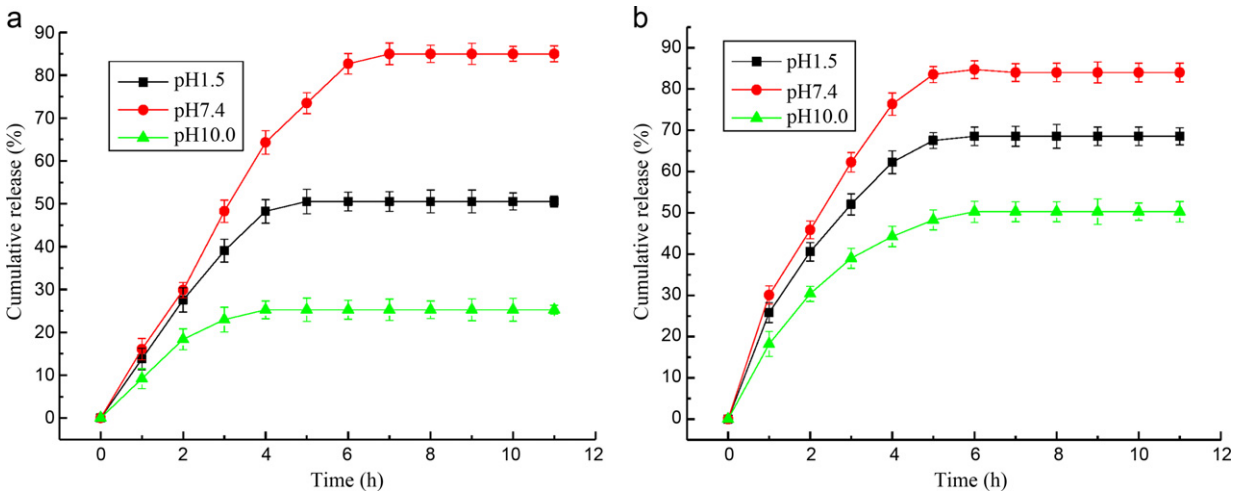


Fig. 6. *In vitro* cumulative drug release from the drug-loaded hydrogels in various pH buffer solutions at 37 °C: (a) acetylsalicylic acid and (b) theophylline.

bulk erosion. In the process of surface erosion, the rate of water diffusion into the network is slower than the rate of the hydrolysis reaction, and the water will be adsorbed on the surface before it diffuses into the bulk. In contrast, when the rate of water diffusion into the sample is faster than the rate of the hydrolysis reaction, bulk erosion occurs. The times required to achieve equilibrium swellings during the study of the water absorption mechanism were all less than 20 h. A comparison of the swelling rate and the degradation rate of the hydrogel samples indicated that the degradation of the HC-based hydrogels is a bulk-erosion process.

An initial increase in the wet mass of the hydrogels appeared in both the simulated gastric fluid and the simulated intestinal fluid, which may result from the reduced crosslinking density. After the initial increase, the wet weights of the hydrogels exhibited no significant changes in the simulated gastric fluid. In contrast, an apparent decrease in the wet weight was observed for the hydrogel in the simulated intestinal fluid. Although the change in the wet mass of the PAAc hydrogel in the intestinal fluid was obvious when the degradation time was extended, its dry mass changed little, which indicated that, although the PAAc hydrogel exhibited apparent swelling behaviour, trace degradation occurred in the intestinal fluid. Degradation of the hydrogel samples was also conducted in a buffer solution without enzymes, and the trend with respect to the dry mass loss was almost the same as that in the simulated gastric/intestinal fluid. All of the dry mass losses of hydrogels in the simulated gastric fluid were less than 20%; however, the dry mass losses of hydrogels in the simulated intestinal fluid changed significantly. The effect of the protease on the degradation of the hydrogels was not clear, whereas the phenomenon was very clear. With increasing HC content, the loss of dry mass increased in the order gel-1 > gel-2 > gel-4, which indicated that the introduction of biodegradable materials accelerated the degradation in the simulated intestinal fluid. The crosslinking density is known to exert a profound effect on the degradation of hydrogels (Metters, Anseth, & Bowman, 2001), and our results are consistent with this conclusion. The dry mass loss of gel-9, which exhibited low crosslinking density, was significantly greater than that of gel-11, which exhibited high crosslinking density.

3.7. Drug release

Drug release from the HC-based hydrogel was examined using acetylsalicylic acid and theophylline as model drugs. Acetylsalicylic acid is an important anti-platelet drug for the prevention of cardiovascular events, such as myocardial infarction and vascular occlusion in the cerebral and peripheral circulation (Tang & Singh, 2008). Fig. 6a shows the *in vitro* cumulative release of acetylsalicylic acid at 37 °C in pH 1.5, 7.4 and 10.0 solutions. The cumulative drug release in pH 7.4 solution was approximately 85%, which was significantly greater than that achieved in pH 1.5 solution. Because the swelling ratio was higher, the polymeric matrix size became larger, which resulted in a higher degree of drug release (Zhang, Zhang, Niu, Zhang, & Tian, 2008). At pH 1.5, which is the pH value of gastric juice, the low swelling ratio restricted the release of acetylsalicylic acid from the hydrogel. When the drug granules were placed in a slightly alkaline environment, which mimics the conditions of the intestinal tract, the water absorption of the drug-loaded hydrogel obviously increased, and the model drug was released uniformly for 6 h. The release dynamics closed to zero-order drug release kinetics, and no initial burst release that appeared with other hydrogels was observed (Zhang et al., 2011). However, the COOH group in acetylsalicylic acid, whose dissociation was affected by the pH value of the solution, could affect the drug release of the hydrogel. Consequently, theophylline was also used as a model drug to examine the controlled release of the prepared hydrogel. Theophylline is a xanthine derivative, which is mainly used in the chronic treatment of bronchial asthma and bronchospastic diseases (Ceballos, Cirri, Maestrelli, Corti, & Mura, 2005). As evident in Fig. 6b, the difference between the cumulative release amount of theophylline in pH 1.5 and 7.4 solutions was less obvious than that of acetylsalicylic acid. Furthermore, the release amount within the first hour was greater, which indicated that the molecular structure of acetylsalicylic acid plays an important role in the controlled release. Although the controlling action of the hydrogel could not be ignored, the total cumulative release amount of theophylline in pH 7.4 solution was greater than that in pH 1.5 and 10.0 solutions, and the sustained release in pH 7.4 solution was maintained for 5–6 h. The *in vitro* release profile of the model drugs implied that the HC-based hydrogel has controlled release properties and can be used as potential carriers for intestine-specific drug delivery.

4. Conclusions

A novel pH-sensitive and biodegradable HC-based hydrogel was prepared by grafting AAc into HC. The swelling ratio showed apparent transitions at physiological pH. A porous honeycomb-like structure was clearly shown in the SEM images of the resulting hydrogels. The swelling kinetic experiments revealed that a Fickian diffusion process dominated the swelling of the hydrogels in media of pH 1.5 and that water uptake was controlled

collaboratively by hydrogel relaxation and water diffusion in media of pH 7.4 and 10.0. Degradation tests were conducted under simulated physiological conditions, and the HC content and crosslinking density were the major factors that influenced the biodegradability. With acetylsalicylic acid as a model drug, the release dynamics of the drug-loaded hydrogels closed to zero-order drug release kinetics for 6 h, and the cumulative release rate of 85% was achieved. As a comparative test, the release of theophylline from the hydrogels verified the controlling effect of the HC-based hydrogels.

Because of the excellent pH-sensitivity and biodegradability, the HC-based hydrogels can be used as a carrier for oral drugs. The HC-based drug-loaded hydrogels can be prepared and processed as tablets according to the procedure described in this paper. Because the swelling ratio of the drug-loaded hydrogels differs under the various pH values in the human digestive tract, the hydrogel can prevent the drug from releasing in the stomach (where pH values are low), whereas the drug can be selectively released in the small intestine or colon (where pH values are high).

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