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Preparation and characterization of *N*-(2-carboxybenzyl)chitosan as a potential pH-sensitive hydrogel for drug delivery

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Abstract—A novel water-soluble chitosan derivative [*N*-(2-carboxybenzyl)chitosan, CBCS] was synthesized. The chemical structure of CBCS was characterized by FTIR, ^{1}H NMR and UV spectroscopies. The degree of substitution (DS) of *N*-2-carboxybenzyl was determined by colloid titration. In different pH buffer solutions, the swelling characteristics of hydrogels based on CBCS (CBCSG) prepared by crosslinking with glutaraldehyde have been studied. Results showed that the swelling ratio (SR) of CBCSG decreased with an increase of the amount of glutaraldehyde, and that CBCSG swelled more significantly in alkaline solution than in acidic medium, showing the lowest SR at pH 5.0. The SR of CBCSG increased with the raising of the DS of the *N*-2-carboxybenzyl group in alkaline solution, but no significant change was observed in an acidic environment. CBCSG showed swelling reversibility when alternately soaked in pH 1.0 and 7.4 buffer solutions. Release profiles of fluorouracil (5-FU), a poorly water-soluble drug, from CBCSG were studied under both simulated gastric and intestinal pH conditions. The release was much quicker in pH 7.4 buffer than in pH 1.0 solution. Results indicated that CBCS could be a potential pH-sensitive carrier for colon-specific drug delivery system.

Keywords: Chitosan derivative; pH-Sensitive hydrogel; Fluorouracil; Drug delivery system

1. Introduction

Hydrogels, which are three-dimensional networks composed of a polymer backbone, water and crosslinking agents, can swell considerably in aqueous medium without dissolution. Hydrogels are gaining special interest as substances that exhibit phase transition (i.e., volume change) in response to changes in external conditions such as pH,[1] ionic strength[2] and temperature,[3] all of which are widely encountered in drug delivery systems.[4–6] In the design of oral colon-specific drug delivery system, pH-sensitive hydrogels have attracted increasing attention recently because they are useful techniques for colon-specific diseases by pH control based on pH change in human gastrointestinal tract.[5] Such drug delivery system could allow local treatment of a variety of colonic diseases such as Crohn's disease or ulcerative colitis. It also means that peptides and certain other labile drugs might be orally administrable if they were not released in the upper regions of the gastrointestinal tract.[6,7]

A variety of synthetic or natural polymers containing the weakly acidic or weakly basic groups have been employed as the pH-sensitive controlled release systems for drug delivery.[8] Many polysaccharides have been tried as colon-specific delivery systems, such as alginates,[9] pectins,[10] amylose,[11] chitosan,[12,13] and their complexes.[14] Among them, chitosan is one of the most commonly used.

Chitosan (CS) [poly-β-(1→4)-D-glucosamine], a natural polymer obtained by alkaline deacetylation of chitin, is nontoxic and biocompatible and can be completely digested by the colonic bacteria. These properties make chitosan a good candidate for the development of novel gastrointestinal drug delivery systems. Chitosan dissolves in acidic solutions since it has a number of amino groups, but it is insoluble under higher pH conditions due to the deprotonation of amines.[15] Chitosan is also of limited solubility in organic solvents. In order to

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overcome the above problems, some novel polyampholyte derivatives based on chitosan were prepared by introducing various groups to study their pH-sensitivity, tried as pH-sensitive carrier for colonic drug delivery system, for example, carboxymethyl chitosan,[12] N-alkylated chitosan[16] and maleilated chitosan.[17]

In this paper, the water-soluble derivative of chitosan, *N*-(2-carboxybenzyl)chitosan (CBCS) is synthesized and evaluated. The chemical structure of CBCS was characterized by FTIR, ^{1}H NMR and UV spectra. The DS of *N*-2-carboxybenzyl was determined by colloid titration. When introducing 2-carboxybenzyl groups onto the $-NH_2$ groups of chitosan, an amphoteric polyelectrolyte containing both cationic and anionic fixed charges was prepared. By varying the DS of the 2-carboxybenzyl group, we can obtain CBCS with various charge densities on the molecular chain, which provide a convenient way to investigate the swelling behavior of these polyampholyte hydrogels dependent on pH. Thus the pH sensitivity of CBCSGs based on CBCS with various DS values crosslinked by glutaraldehyde has been studied in this work. Additionally, the release profiles of a model drug (5-FU) from test hydrogels were studied in simulated gastric and intestinal media, respectively.

2. Experimental

2.1. Materials

Chitosan with a degree of deacetylation of 92.8% was supplied by Dalian Xindie Chitin Co., Ltd (China). 2-Carboxybenzaldehyde was purchased from Tokyo Kasei Kogyo Co., Ltd (Japan). Glutaraldehyde (25% aq solution) and sodium borohydride were from Shanghai Chemical Company, China. Potassium polyvinyl sulfate (PVSK), poly(diallyldimethylammonium) chloride (PDADMAC) and Toluidine Blue were of analytical grade for colloidal titration obtained from Wako Pure Chemical Industries, Ltd (Japan). 5-Fluorouracil (5-FU) was purchased from Sinopharm Chemical Reagent Co., Ltd (China). All other chemicals and reagents used were of analytical grade, and were used without further purification.

2.2. Synthesis of CBCS

Synthesis of CBCS was carried out as shown in Figure 1. Table 1 lists the ratios of reactants and conditions used for preparing each of the CBCS sample. The method given below is for CBCS5. Chitosan powder (2.0 g) was dissolved in 0.7% (w/v) aq HOAc (250 mL), to which a solution of 2-carboxybenzaldehyde (3.6 g) in abs EtOH (20 mL) was added dropwise over a 30-min period. After stirring at 50 °C in a water bath for 5 h, the mixture was cooled down to room temperature, and then an aq solution of $NaBH_4$ (1.2 g, 15 mL) was added dropwise to bring about reduction of the Schiff base. Stirring was continued at room temperature for 2 h. An adequate amount of MeOH was added into the reaction mixture, and the precipitate thus produced was filtered and washed with acetone. The solid obtained was soaked in acetone (100 mL) for 24 h, then filtered to obtain a pale-yellow product.

The partially derivatized product was dialyzed against deionized water for 3 days and precipitated by adding an adequate amount of acetone to obtain the purified CBCS, which was then dried under vacuum to constant weight for structure characterization.

2.3. Degree of substitution of *N*-2-carboxybenzyl groups

The DS of *N*-2-carboxybenzyl group was determined by colloid titration according to the method reported.[18]

A 0.02% (w/v) CBCS solution was prepared by dissolving appropriate amount of CBCS in 100 mL of distilled water. The CBCS solution (10 mL) was transferred into a conical flask, and 1 mL of 0.1 M NaOH was added to make the medium alkaline. PDADMAC standard solution (0.5 mM, 10 mL) was then added into the flask. To determine the titer V_1 (mL) of PVSK, the mixture was shaken for 2 min with one drop of 0.1% Toluidine Blue as an indicator, and 0.5 mM PVSK standard solution was added titrimetrically from a burette until the blue color of the indicator changed into reddish purple. At the same time flocculation or precipitation of the reacting complexes appeared abruptly. As a blank titration, 10 mL of distilled water was used in place of the CBCS solution. The other procedures were the same as the above, and the titer V_2 (mL) of PVSK was recorded. All the titration experiments were performed three times to calculate average values. The DS was expressed by the following equation: DS (mmol/g) $= c \cdot (V_2 - V_1)/100g$, where c is the concentration of the PVSK standard solution (mmol/L), and g is the quantity of CBCS sample (g).

2.4. Preparation of CBCSG and chitosan hydrogels (CSG)

CBCS solution (1.2%, w/v) was prepared in distilled water (15 mL). In the presence of different volume of crosslinking agent 1% (v/v) glutaraldehyde, the bubble-free solutions were poured into shallow dishes (with a diameter of 7.5 cm) with stirring for 2 min at room temperature and let to stand overnight for gel formation. The hydrogels (CBCSG) were rapidly frozen at −18 °C and then dried in a freeze-dryer (FD-1 freeze mobile, Boyikang Tech. Co., Beijing, China) to yield the xerogels.

Chitosan solution (1.2%, w/v) was prepared in 0.7% (w/v) aq HOAc (15 mL). Freeze-dried CSG were pre-

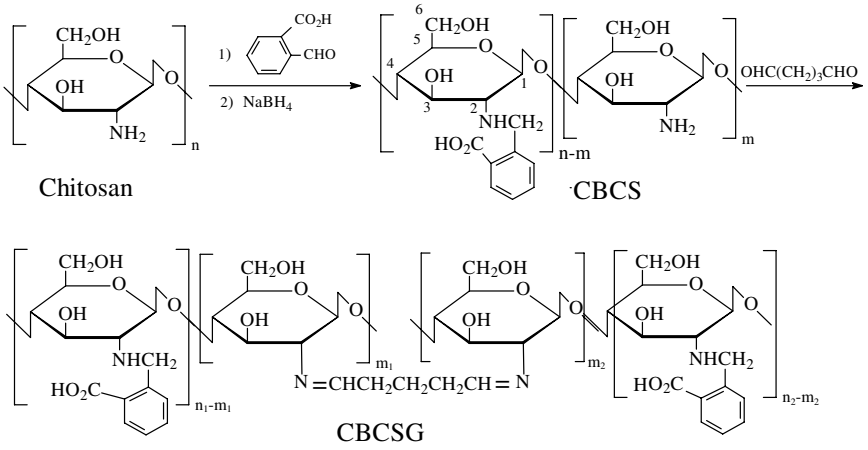

Figure 1. Synthetic scheme for CBCS and CBCSG.

Table 1. Conditions and results of the reaction for preparing CBCS[a]

Sample	CS (g)	CBBA (g)[b]	CHO/NH_2 (mol/mol)	Temperature (°C)	Time (h)	DS[c] (mmol/g)
CBCS1	2.0	1.8	1:1	25	3	1.58
CBCS2	2.0	2.7	1.5:1	25	3	1.64
CBCS3	2.0	3.6	2:1	25	3	1.73
CBCS4	2.0	3.6	2:1	50	3	2.10
CBCS5	2.0	3.6	2:1	50	5	2.62

[a] Followed reduction by 1.2 g $NaBH_4$ for 2 h at 25 °C.
[b] 2-Carboxybenzaldehyde.
[c] DS of *N*-2-carboxybenzyl was measured by colloid titration.

pared according to the method mentioned above. The hydrogels (about 0.15 mm in thickness) were cut into small disks ($1 \times 1\ cm^2$) for the following studies. Table 2 lists the feed composition of a series of hydrogel samples.

2.5. Characterization

The Fourier-transform infrared (FTIR) transmission spectra of samples were measured with a KBr disk on a Nicolet Magna 750 FTIR spectrometer (USA). The samples were scanned from 400 to 4000 cm^{-1}. ^1H NMR spectra were determined on a Varian Unity 500 NMR Spectrometer (USA) with an internal standard of 2,2-dimethylil-2-silapentane-5-sulfonate sodium (DSS) using deuterium oxide as a solvent.

Table 2. Feed composition of a series of hydrogels

Sample	1.2% Solution of sample[a]	DS (mmol/g)	1% Glutaraldehyde (mL)
CBCSG1	CBCS	2.62	0.4
CBCSG2	CBCS	2.62	0.6
CBCSG3	CBCS	2.62	0.8
CBCSG4	CBCS	2.10	0.6
CBCSG5	CBCS	1.64	0.6
CSG	CS	0	0.6

[a] CBCS was dissolved in aqueous solution, CS was dissolved in 0.7% (w/v) HOAc solution.

Ultraviolet spectra were measured on a 752PC Spectrum UV–vis spectrophotometer (Shanghai spectrum instrument Co., China). Chitosan (0.2%, w/v) and CBCS (0.2%, w/v) were dissolved in 0.1 M HCl and water, respectively. The samples were scanned from 200 to 400 nm.

2.6. Swelling of the hydrogels

The swelling ratio (SR) was determined by immersing the xerogel in aqueous solutions with different pH in sealed containers at room temperature. At appropriate time intervals, the hydrogels were taken out. After the excess water was removed carefully and rapidly with filter paper from the hydrogels surface, the hydrogels were weighed on a sensitive balance immediately (AL104 electronics balance, Shanghai Mettler–Toledo Co., Ltd, China, 0.1 mg). The SR was expressed by the following formula, $SR = (W_t - W_0)/W_0$, where W_t was the weight of hydrogel at time t and W_0 was the initial xerogel weight. The media for the swelling studies were 0.1 M HCl (pH 1.0), phosphate-buffered solutions (pH 3.0, 5.0, 7.4), or pH 9.0 buffer solution prepared by aminoacetic acid and NaOH. The ionic strength of the above buffer solutions was carefully adjusted to 0.15 M by adding an appropriate amount of sodium chloride. The swelling reversibility of the CBCSG was

measured in the pH 1.0 and 7.4 buffers by soaking CBCSG in two buffer solutions for 3-h intervals in turn. Experiments were performed three times to calculate average value.

2.7. Release profiles of 5-fluorouracil (5-FU) from CBCSG

In the preparation of the drug-loaded CBCSG, 5-FU with a final concentration of 0.5% (w/v) was added to the dissolved CBCS (with a DS of 2.62 mmol/g) solution with continuous stirring. After dissolution of the drug, the blend was crosslinked by adding 0.4 mL 1% (v/v) of glutaraldehyde. The rest of the procedures used were similar to those in the preparation of CBCSG2 without drug loading. The content of the loaded drug as determined by the literature method[19] was 147 mg per gram of xerogel.

To study the release profiles for the drug-loaded CBCSG, dried test samples were immersed in 200 mL of phosphate buffer (pH 7.4) or 0.1 M HCl (pH 1.0) solution and were left in a shaking water bath at 37 ± 0.1 °C. At predetermined time points, 3 mL of the release solution was taken out, and the release of 5-FU was determined by measuring the optical density at 265 nm. The percentage of cumulative release of 5-FU was obtained from standard calibration curves. After each sampling, 3 mL of fresh medium was supplemented to maintain a constant volume. All experiments were repeated in quadruple. Data represented in the graph show the mean ± standard deviation of four experiments.

3. Results and discussion

3.1. Synthesis of CBCS and DS of *N*-2-carboxybenzyl group

By varying the reaction time and molar ratio of 2-carboxybenzaldehyde to chitosan (shown as mole ratio CHO/NH_2 in Table 1), CBCS samples with different DS values were prepared as shown in Table 1. As shown, the DS values of the product increased insignificantly with an increase in the molar ratio of CHO/NH_2 when reacted at 25 °C for 3 h. This might mainly be attributed to a relational twisting of polymer chain caused by intrachain hydrogen bonds in gelatinous solution, which brought about stereospecific blockage, resulting in incomplete reaction between the aldehydo groups and amino groups.[20] With the same molar ratio of CHO/NH_2 (2:1) for 3 h, the DS values of the product obviously increased by raising the reaction temperature to 50 °C. The products with higher DS value (2.62 mmol/g) were obtained by prolonging the reaction time for another 2 h. As we know, with the raising of reaction temperature, interchain interactions and intermolecular hydrogen bonds of CS decrease significantly. Chitosan molecules possess better chain flexibility and less stereochemical blockage,[21] which is of advantage in the condensation reaction between $–NH_2$ and –CHO. While our experiment indicated that the DS value of CBCS was insignificantly increased with further prolongation of the reaction time at 50 °C (mole ratio $CHO/NH_2 = 2{:}1$) when the reaction time exceeded 7 h. In addition, the introduction of hydrophilic groups such as $–CO_2H$ along the side chain of chitosan molecules can efficiently destroy the regular packing of the original polymer chains, and weaken the intermolecular hydrogen bonds of $–NH_2$ in chitosan molecules.[1,16] Therefore, to improve the solubility of CBCS in aqueous solution, a water-soluble amphoteric polyelectrolyte derivative of chitosan was synthesized.

By changing the DS value of the 2-carboxybenzyl groups on the $–NH_2$ groups of chitosan, we can obtain CBCS with various charge densities along the molecular chain, which provide a convenient way to investigate the swelling behavior of natural polyampholyte hydrogels in response to pH. The different DSs of CBCSs result in various intermolecular interactions, for example, dipole electrostatic interaction, hydrogen bonding and hydrophobic interactions. These intermolecular forces existing ubiquitously in polymers are believed to play important roles in the pH response swelling behavior of CBCSG.

As an amphoteric polyelectrolyte, the DS (i.e., the content of $–CO_2H$) of CBCS is difficult to measure by acid–base titration, conductance titration, infrared spectral analysis, among other techniques. Colloidal titration, also called polyelectrolyte titration,[18,22] is a micrometric volumetric analysis method based on the rapid stoichiometric reaction between polyanions and polycations in very dilute solution. The strongly basic medium (pH 12) in this test made the acidic benzoyloxy groups of CBCS ionize and become negatively charged. The ionized CBCS could then react with the added overdose polycation PDADMAC. Then the rest of the polycations were titrated with the standard solution of polyanion PVSK, so the $–CO_2H$ content can be expediently and quantitatively assayed.

3.2. Structure characterization of CBCS

The FTIR spectra of chitosan and CBCS are shown in Figure 2. Comparing the FTIR spectra of CS with its derivative, it was found that new peaks appeared at 755 cm^{-1} and 718 cm^{-1}, which could be assigned to the C–H bending vibration that is a characteristic peak of an aromatic ring.[23] The peaks observed at 1609 cm^{-1} are for the asymmetrical $–CO_2^-$ stretching vibrations,[24] and the peaks observed at 1589, 1454 cm^{-1} are from the C–C bonded framework vibrations of an aromatic ring, indicating the existence of a benzene ring. The strong

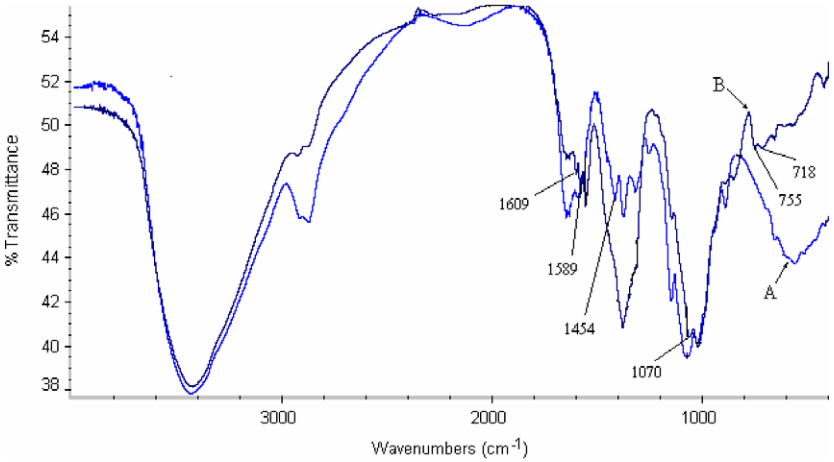

Figure 2. IR spectra of CS (A) and CBCS (B).

absorption peak of 1070 cm^{-1} is a C–O stretch. The results support the fact that a 2-carboxybenzyl group is bonded to the amino group of CS.

Compared with CS, the ultraviolet spectra of CBCS shown in Figure 3 show an absorption band for a benzene ring. A red shift is obviously observed because of the conjugated effect between the benzene ring and carboxyl group that contains a π bond. The λ_{max} values are at 208 and 225 nm for the absorption of the E1 and E2 bonds arising from the π–π* transition of the benzene ring. The λ_{max} at 268 nm is for the characteristic peak of the B bond of the benzene system, which is present in CBCS.

The ^{1}H NMR spectra of CBCS and CS are presented in Figure 4. As shown in the spectrum of chitosan (Fig. 4a), the chemical shift at 2.222 ppm is for the methyl protons in the residual *N*-acetyl group,[25] and the signal at 5.035 ppm is for the protons of pyranose ring.[26] The peak at 2.058 ppm due to the acetyl protons for CBCS also appeared. In the spectrum of CBCS (Fig. 4b), the emergence of a ^{1}H peak at 7.396–7.502 ppm is for the protons of the benzene ring. The chemical shifts at 4.093–4.791 ppm are the ^{1}H peaks of C-3–C-6 on the pyranose ring, and the resonance at

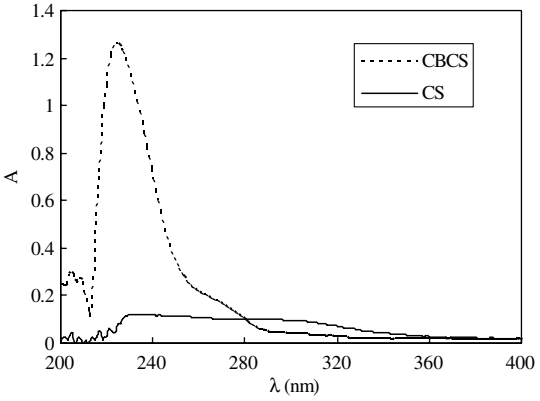

Figure 3. UV spectra of CBCS and CS.

3.697 ppm is for the proton of C-2.[24] The signals at 2.576 and 2.691 ppm are for the protons of methylene in the benzyl group.

3.3. Swelling characteristics of hydrogels

The pH-dependent swelling behavior and kinetics of hydrogels based on chitosan and its derivatives have been reported recently.[12–16] In this study, a series of hydrogels with different degrees of crosslinking based on CBCS of various DS values were prepared. The feed compositions of those hydrogels are listed in Table 2.

The swelling behavior of the CBCSG in solution depends mainly on the osmotic pressure difference between the inside of the gel and the surroundings caused by the redistribution of mobile ions, which is described in the Donnan membrane equilibrium.[27] As shown in Figure 5, the swelling behavior of the CBCSGs with various degrees of crosslinking in different pH buffers (ionic strength was 0.15 M) obviously showed pH sensitivity. CBCS is a polyampholyte containing both $–NH_2$ and $–CO_2H$ groups. The hydrogels based upon CBCS can form a network with oppositely charged structures which could change the charge state of the ionic groups by varying the pH. In the case of high pH (7.4–9.0), the dominant charges in the CBCSGs are the dissociated carboxylate group ($–CO_2^-$). In this pH region, the stronger the alkalinity of the solution, the larger the concentration of $–CO_2^-$ inside the hydrogels, which results in an osmotic pressure and makes the CBCSGs swell. Along with decreasing pH, the amount of $–CO_2^-$ is gradually reduced inside the hydrogels, which leads to a decrease in osmotic pressure and makes the SR of the hydrogels smaller. Therefore the SR of CBCSGs gradually decreased. As shown in Figure 5a–c, the SR was significantly increased with the raise of pH in the range of pH 5.0–9.0. This could be attributed to increasing of the mobile ions $–CO_2^-$ inside the

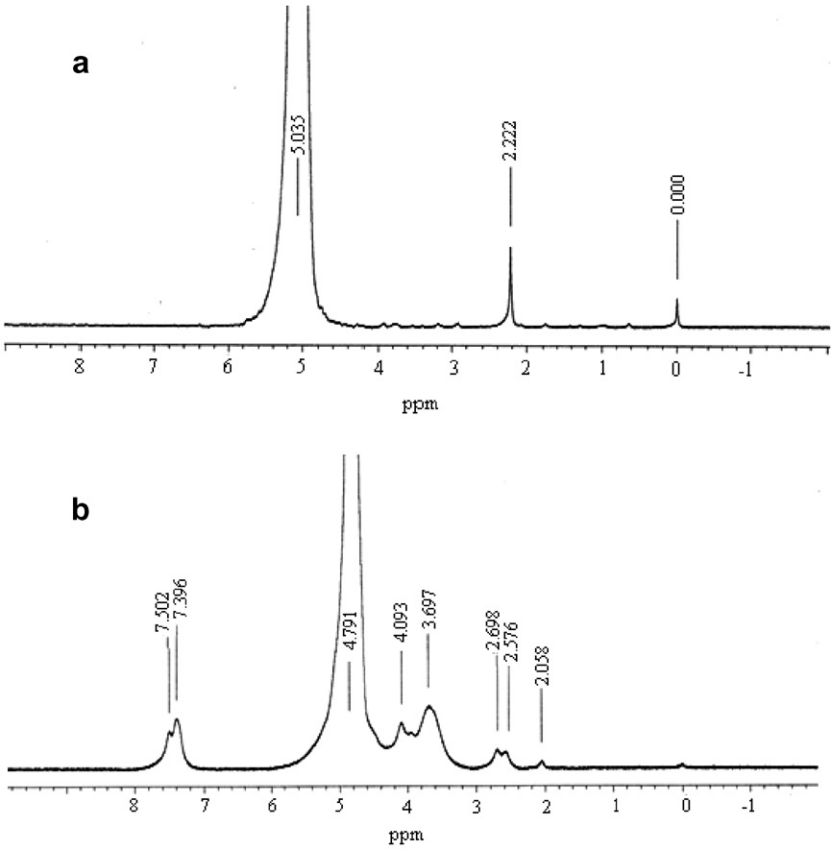

Figure 4. ^{1}H NMR spectra of CS (a) and CBCS (b).

hydrogel and osmotic pressure driving the gel in the swelling state.

When pH < 7.0, the dissociation of the carboxyl group being hindered resulted in a decrease of $–CO_2^-$ in CBCSG. On the other hand, the number of $–NH_3^+$ groups was increased with the decreasing of pH, while at pH 5.0, the isoelectric point of CBCS, the numbers of $–NH_3^+$ and $–CO_2^-$ in amphoteric hydrogels were equal, and ionic interaction between opposite charges resulted in the lowest SR. As shown in Figure 5, the lowest swelling occurred almost always at pH 5.0 among CBCSGs with various degrees of crosslinking. With the further diminishing of pH to 1.0, the dissociation of carboxyl groups was completely inhibited, and the dominant ionic groups were $–NH_3^+$. However, the majority of the $–NH_2$ groups were linked, and there was only a small residual part of $–NH_2$ groups in the CBCS. Thus, the CBCSGs swelled torpidity as pH diminished in the range of pH 1.0–5.0. Furthermore, the SR of the CBCSG in acidic medium was obviously always smaller than that in alkaline medium. This property is of considerable interest in using as drug vehicle to pass through the low pH environment of the stomach and release in the intestine.[5] Additionally, the hydrophobic interaction of benzene ring and hydrogen bonding among molecular chains should be considered at this time, because they will hinder the permeation of solvent, which could also result in a decrease of SR.[16]

It was noted that SR decreased with an increase in crosslinkers at the same pH medium. The higher degree of crosslinking, which enhances the compactness of the hydrogel network, would hinder the permeation of solvent and result in the lower SR. The swell equilibrium of CBCSGs was almost reached after 24 h of the test. The equilibrium times were shorter than the 2–5 days reported,[12,17] for the xerogel used in our experiments that were made by cryodesiccation. The xerogels were of porous structure, which would be advantageous to micromolecules to diffuse into interior of the hydrogels, which caused the swell to reach equilibrium.

Figure 6 shows the swelling curves of CBCSGs with various DS in different pH buffers for 24 h. The higher DS value that CBCSG possessed, the bigger SR it exhibited in the range of pH 7.4–9.0. While in the range of pH 1.0–5.0, the result was contrary to the above-mentioned results. In the case of chitosan gel (CSG), the side-chain groups relating to pH sensitivity were the amino groups. The swelling behavior of CSG observed was similar to the results described in the literature.[15] In the acidic pH regions, the SR of CSG decreased with a decrease of $–NH_3^+$ when raising the pH from 1.0 to 7.0 (see Fig. 6). In an alkaline environment, the amino

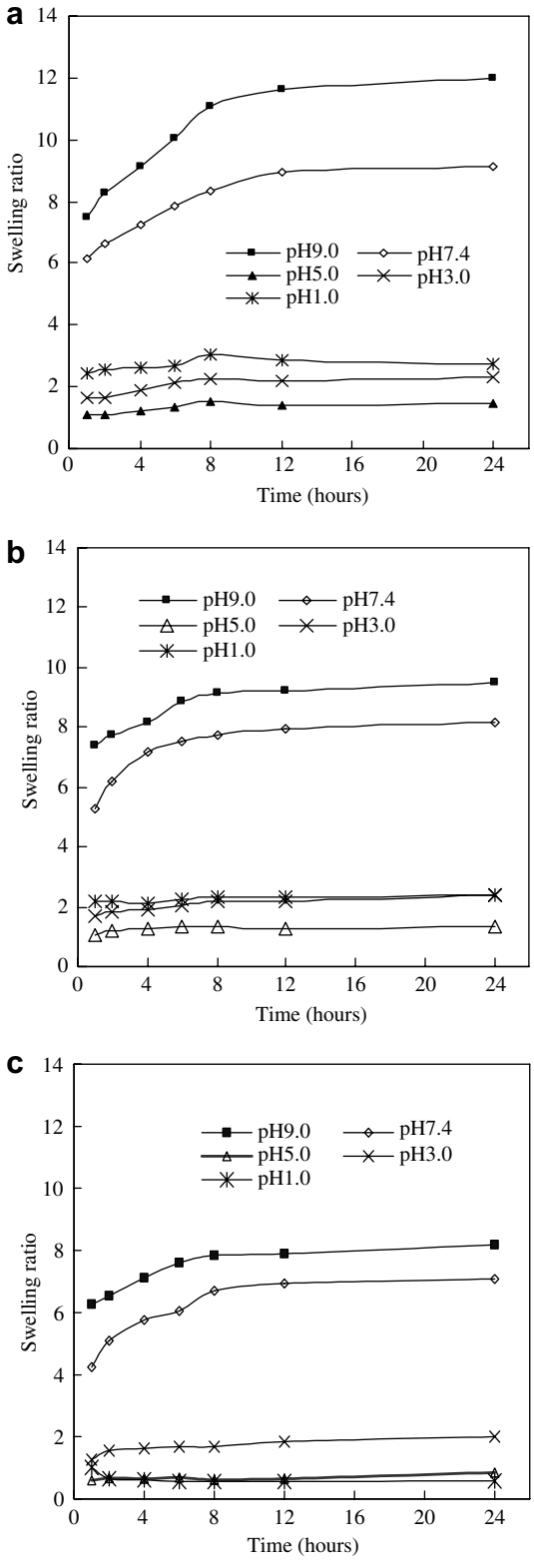

Figure 5. Swelling behavior of CBCSG in different buffer solutions: (a) CBCSG1, (b) CBCSG2, and (c) CBCSG3.

groups were completely deprotonated. That CSG swelled hardly when pH > 7.0 could be due to the loss

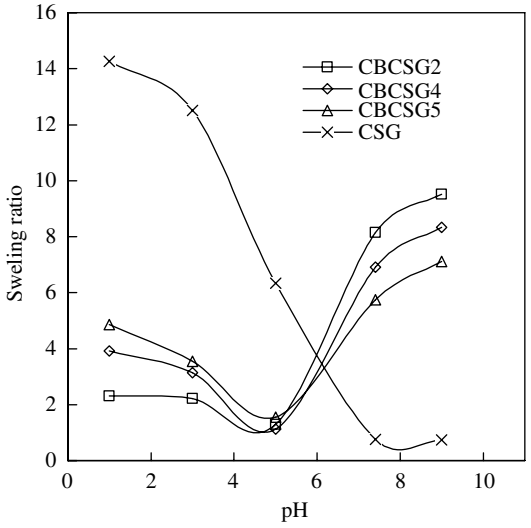

Figure 6. Swelling characteristics of the CBCSG with different DS and CSG in different buffer solutions for 24 h.

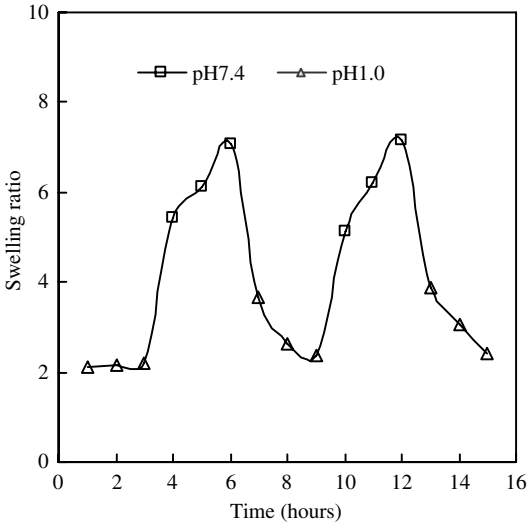

Figure 7. Swelling reversibility of the CBCSG2 in pH 1.0 and 7.4 buffer solutions.

of solubility of the chain segments and also due to the formation of new crosslinks by hydrogen bonding.[28]

3.4. Swelling reversibility of CBCSG

The swelling reversibility of the CBCSG2 was alternately performed in the pH 1.0 and pH 7.4 buffers. After the samples were immersed in pH 1.0 buffer for 3 h, no obvious swell phenomenon had been observed. These were then transferred to a solution at pH 7.4 for another 3 h, and the obvious swell was measured. A shrinking was observed for next 3 h in pH 1.0 buffer. The reversible swelling was repeated when the samples were placed back into the pH 7.4 buffer (see Fig. 7). When being used

as drug carrier, this reversible swell–shrink phenomenon would be a desirable characteristic for a pH-sensitive controlled-release system with controllable swelling ability.

3.5. Drug release

The studies on the release of 5-FU from CBCSG2 were carried out by immersing the 5-FU-incorporated gels in pH 1.0 or 7.4 buffers. As shown in Figure 8, an initial burst was observed with both the buffers within the first 15 min. This might be due to crystallization of a small portion of 5-FU on the surface of xerogel, the rapid dissolution of this portion 5-FU resulted in a burst release for about 25%. About 20 min later, the hydrogels serve as diffusion barriers and the drug was released mainly by diffusion mechanism.

As expected, the amount of 5-FU released under acidic conditions (pH 1.0) was relatively low. Only about 40% of the loaded drug was released after 12 h of the test. It was reasonable to relate to the comparatively low SR of the hydrogel at pH 1.0 (Fig. 5b). At pH 7.4, the release of 5-FU increased significantly along with the swelling of the hydrogel network. Approximately 90% of the loaded drug was released after 10 h in pH 7.4 buffer. 5-FU is used clinically as a chemotherapeutic agent for treatment of colorectal carcinoma, and there is a need for a colon-specific controlled-release delivery system to ensure direct treatment at the disease site in the colon.[29] The results of the release experiment of 5-FU from gel indicated that CBCS could be a potential pH-sensitive carrier for a colon-specific drug delivery system.

For designing peroral dosage forms, the formulator must consider that the natural pH environment of gastrointestinal tract varies from acidic in the stomach to slightly alkaline in intestine. The pH of the gastrointestinal tract gradually rises from the stomach (pH 1.5–3) to the terminal ileum (pH 7.5 ± 0.5). The pH drops to 6.4 ± 0.6 upon entry into the colon. The pH is 6.6 ± 0.8 in the mid-colon and 7.0 ± 0.7 in the left-colon.[30] The pH-dependent release of 5-FU from the CBCSG could indicate that this polymer has the desired protective effect for the oral delivery route of some drugs, such as peptides, which are easily destroyed by gastric acid. The loaded drug can be released in lesser amounts from the gel as it passes through the stomach. Upon reaching the colon, a significant fraction of drug retained in the polymer can be released from the gels. The good pH sensitivity of CBCSG and the pH-dependent release of a drug from the CBCSG make it a potential carrier for an oral colon-specific drug delivery system.

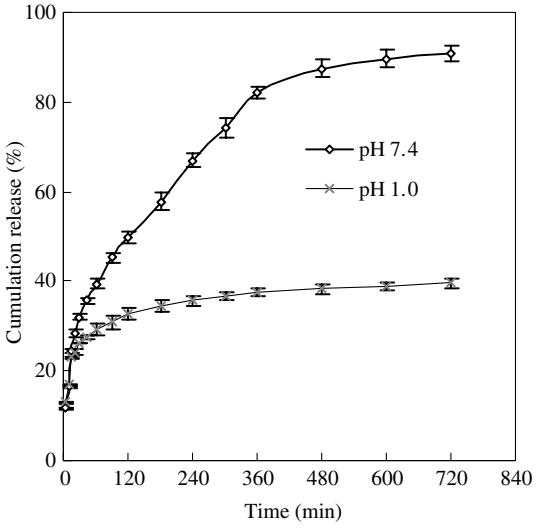

Figure 8. 5-FU release from CBCSG2 in pH 1.0 and 7.4 buffers.

Acknowledgements

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