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Preparation of ionic-crosslinked chitosan-based gel beads and effect of reaction conditions on drug release behaviors

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Abstract

Drug-loaded chitosan (CS) beads were prepared under simple and mild condition using trisodium citrate as ionic crosslinker. The beads were further coated with poly(methacrylic acid) (PMAA) by dipping the beads in PMAA aqueous solution. The surface and cross-section morphology of these beads were observed by scanning electron microscopy and the observation showed that the coating beads had core–shell structure. In vitro release of model drug from these beads obtained under different reaction conditions was investigated in buffer medium (pH 1.8). The results showed that the rapid drug release was restrained by PMAA coating and the optimum conditions for preparing CS-based drug-loaded beads were decided through the effect of reaction conditions on the drug release behaviors. In addition, the drug release mechanism of CS-based drug-loaded beads was analyzed by Peppa's potential equation. According to this study, the ionic-crosslinked CS beads coated by PMAA could serve as suitable candidate for drug site-specific carrier in stomach.

Keywords: Chitosan; Trisodium citrate; Ionic-crosslink; Poly(methacrylic acid); Polyelectrolyte complex; Drug release

1. Introduction

Chitosan (CS) and its derivatives have some favorable characters, such as antiulcer, preventing bacterium, biodegradability and biocompatibility. They have attracted much interesting in the field of pharmaceutical and biotechnology (Calvo et al., 1997; Bravo-Osuna et al., 2007; Peppas et al., 2006). It is reported that a hydrogel obtained from CS as oral carrier-drug systems can prevent or reduce the stimulation on stomach mucosa (Gupta and Ravi Kumar, 2000; He et al., 2004).

CS hydrogel can be formed with covalent crosslinking or ionic crosslinking. To date, the most common crosslinker used for covalent crosslinking of CS are dialdehydes such as glutaraldehyde and glyoxal (Berger et al., 2004). Usually, the toxic reagents would be introduced into hydrogel through covalent crosslinking (Barreiro-Zglesias et al., 2005). CS is a polycation, well known for it reacting with negatively charged components, either ions or molecules, lead to the formation of network structure through ionic bridges between polymer chains. In the past years, the use of low molecular weight ions to prepare ionic-crosslinking polymer matrix has been reported due to the simple, mild and fast way (Shu et al., 2001; Shu and Zhu, 2002; Ko et al., 2002; Wang et al., 2006). Reversible physical crosslinking by electrostatic interaction instead of chemical crosslinking is applied to avoid possible toxicity of reagents and other undesirable effects. In addition, the slow erosion of non-covalently crosslinked hydrogel in aqueous environments offers more biodegradable and more possibilities as drug delivery system compared to covalently crosslinked hydrogel (Berger et al., 2004).

Citrate is a multivalent low molecular weight ion in certain pH aqueous solution. It is known that contact between CS and citrate in aqueous solution immediately induces ionic crosslinking of CS, thus forming gel beads. Poly(methacrylic acid) is a biocompatible synthetic polyelectrolyte with polyanion character (Vasconcelos et al., 2006). In previous studies (Chen et al., 2005, 2007), the electrostatic interaction characteristic of CS with PMAA was studied and the polyelectrolyte complex can be formed between them. It is reported that the stability of complexes formed by electrostatic interaction is dependent on environmental pH (Philippova et al., 1996), which means that the complexes have pH stimuli-response. Particularly, polyelec-

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trolyte complexes are directly or indirectly related to the delivery information of genes and the interaction of antigen–antibody (Shu and Zhu, 1999). Thus, the complexes can be used for drug-carrier for their special properties and pH-response.

Many studies have been reported about the release of hydrophobic drug, which have slow drug release rate partly due to the hydrophobic property of drug (Prabaharan et al., 2007). The controlled release materials using macromolecules as model drug also show slow release rate mainly owing to the large size of model drug and entanglement of model drug and polymer matrix (Hari et al., 1996). In our work group (Wang et al., 2007), the drug molecule that was covalently bonded to polymer matrix has been reported and the drug release is significantly controlled because of the slow hydrolysis of covalent bond.

The aim of this study was to develop a special drug release matrix in stomach for hydrophilic small molecule drug. Considering the gastric pH (pH about 1.8) (Chen et al., 2005), we attempted to prepare ionic-crosslinked CS gel beads crosslinked by trisodium citrate showing minimal disintegration in simulation gastric fluid by exploiting the formation of polyelectrolyte complex film between CS and PMAA. Due to the ionic interaction nature, the charge density of CS and citrate under preparation conditions may affect the beads formation and drug release performance. Therefore, the influence of reaction conditions on the release behaviors of model drug (aspirin) incorporated with the beads was investigated.

2. Experimental

2.1. Materials

Chitosan was obtained from Zhejiang Biochemistry Ltd. (China), its deacetylation degree is 90.8% and kinetic viscosity is 142 mPa s. Aspirin was selected as model drug and purchased from the National Institute for the Control of Pharmaceutical and Biological Products (China) used without further purification. Methacrylic acid was distilled under vacuum prior to use. 2,2′-Azobisisobutyronitrile (AIBN) was purified by recrystallization with 95% ethanol. PMAA was synthesized by free radical polymerization with methacrylic acid under nitrogen using AIBN as an initiator in anhydrous methanol according to the references (Chen et al., 2005, 2007). Trisodium citrate and other chemicals are analytical grade and used as received.

2.2. Beads preparation

Drug-loaded beads were prepared by droplet extrusion/precipitation of CS solution containing aspirin, an anionic hydrophilic small molecule model drug, into trisodium citrate aqueous solution. The CS solution containing drug was prepared by a simple mixing step of CS, aspirin, and acetic acid aqueous solution (1%, w/v) with magnetic stirring, the bubble in the mixed system was eliminated by placed for 2 h. Then it was dropped through 0.9 mm diameter needle into a gently stirred trisodium citrate aqueous solution at a flow rate of 1 mL/min, and beads can be formed instantaneously due to the electrostatic attraction between NH_3^+ on CS and COO^- on citrate. At the same time, the pH of trisodium citrate aqueous solution with a range of pH from 4.8 to 7.0 was adjusted by HCl and/or NaOH, and measured by pHS-3B Model pH meter (Leici, China). Beads were separated by filtration and rinsed with distilled water to remove excess drug on the surface, and then these beads were immersed in PMAA aqueous solution (2%, w/v). The polyelectrolyte complex film can be formed between CS beads and PMAA owing to the electrostatic attraction between NH_3^+ on CS and COO^- on PMAA, which may be slow down the drug release of CS beads. The reason for having chosen PMAA from various biocompatible polyelectrolytes with polyanion character is that a few number of studies about the system of CS and PMAA have been done, especially, using them for drug-loaded beads with core–shell structure. The CS beads coated by PMAA (CSCP) were washed with distilled water and placed in atmosphere for 12 h and then dried under vacuum for 48 h at room temperature. Beads without incorporating drug were prepared according to the same process. The morphology of wet and dry CSCP beads was recorded using an optical microscope, respectively.

The concentration of Na^+ entrapped in CSCP beads prepared under different trisodium citrate concentration was measured on ICP emission spectrum analyzer (IRIS ER/S, TJA). The measurement process is that a known amount of CSCP beads was immersed in HCl aqueous solution (10 mL) to be completely disintegrated, and then the solutions were measured on ICP analyzer.

The loading capacity (microgram of drug per milligram of dried drug-loaded beads, μg/mg) of CS-based gel beads for model drug was determined by immersed a known amount of the drug-loaded beads in HCl aqueous solution to be completely disintegrated. The solution was detected by UV spectrometer at 297 nm (Perkin-Elmer Lambda 35, USA) and the amount of drug was calculated from calibration curve that was obtained by absorbance of different concentration drug solution at 297 nm. The loading capacity of CS-based gel beads was about 25 μg/mg known from the measurements.

2.3. Gel fraction

To find out the optimum crosslink time for CS, the gel fraction at predetermined time was measured. The test beads were obtained by dropping the CS solution into trisodium citrate aqueous solution and sustained for different time intervals. The wet beads were washed and excess water on their surface was absorbed with filter paper, then weighed and dried under vacuum. Gel fraction (G_f) was calculated through the following expression:

$$G_f(\%) = \frac{W_2}{W_1} \times 100$$

Here W_1 and W_2 are the weights of wet and dried gel beads, respectively.

2.4. Swelling characteristics of CSCP beads

Swelling experiments were performed by immersed a known amount of dried CSCP beads (about 50 mg) in specified pH

buffer solutions (50 mL) at 37 ± 0.5 °C with the same ionic strength (0.1 mol/L) adjusted by adding NaCl. The specified pH buffer solutions were prepared with HCl (pH from 1.0 to 1.8), $C_8H_5O_4K$ (potassium acid phthalate)–HCl (pH from 3.0 to 5.0), NaH_2PO_4 (sodium dihydrogen phosphate)–NaOH (pH from 6.0 to 7.5). The pH value of buffer solutions was measured on pHS-3B Model pH meter. The weight of swollen samples was measured after the surface solution was removed by filter paper. The swelling ratio (SR) was calculated by the following expression:

$$\mathrm{SR} = \frac{W'}{W}$$

Here W and W' are the weights of dried and swollen beads, respectively.

2.5. Morphology observation

The surface and cross-section morphology of CS and CSCP beads, respectively, were examined using scanning electron microscopy (JSM-5600LV SEM, Japan) at an accelerating voltage of 20 kV. The used beads were freeze-dried for 15 h on LABCONCO Freeze-dried system (England) and dried naturally in atmosphere, respectively.

2.6. In vitro drug release

Release tests of model drug were carried out according to the following step. The in vitro release medium was HCl aqueous solution (pH 1.8, simulation gastric pH). About 50 mg beads were added to the buffer (50 mL) and the system was maintained at 37 ± 0.5 °C throughout the study. A certain amount of the release medium was collected at appropriate intervals and the amount of drug was detected using UV spectrometer at 297 nm. The percentage of drug release was calculated by the following expression:

$$\text{Drug released}\,(\%) = \frac{A_t}{A_\infty} \times 100$$

Here A_t and A_∞ are the absorbance of releasing drug at time t and the absorbance of complete releasing drug, respectively.

3. Results and discussion

3.1. Preparation of chitosan beads

The gel fraction of CS beads crosslinked with trisodium citrate for distinct durations is shown in Fig. 1. For trisodium citrate aqueous solution, CS solution dropped in it was shaped immediately owing to crosslinking, and then the ionic-crosslinker, citrate, diffusing from outside into core of the gelled bead gradually, that is, the bead was crosslinked from the surface to the center step by step. The gel fraction increases with an increase in crosslinking time before 30 min. After crosslinking for 30 min or for more long time, there is no obvious difference in the gel fraction. This indicates that crosslinking of CS beads with trisodium citrate can be completed within 30 min. Therefore, 30 min duration is used to crosslink CS for the rest of the study.

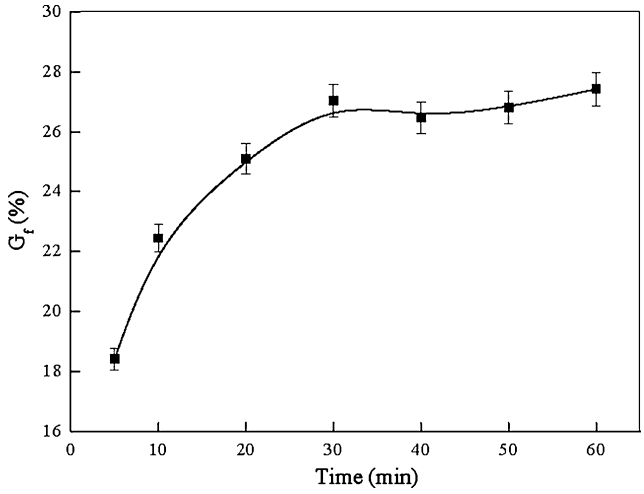

Fig. 1. Gel fraction of ionic-crosslinked CS gel beads as a function of time.

3.2. Morphology of CS beads and CSCP beads

Macroscopic observation shows that CSCP beads had a spherical shape and smooth surface (Fig. 2). Generally, the diameter of wet CS beads was about 3.1–3.4 mm. Meanwhile, the diameter of wet beads was reduced from 3.1–3.4 to 2.8–3.0 mm after coating with PMAA observed during experiment. This is because more compact structure resulting from complex makes some water molecules within the gel network remove. After drying of CSCP beads, the beads had a firm texture and its diameter was reduced to 1.0–1.2 mm.

Fig. 3 shows the SEM photos of typical surface and cross-section morphology of CS-based beads. It can be seen from the surface morphology observations that the pore of CSCP bead is smaller (Fig. 3b and c) than that of CS bead (Fig. 3a) and an unobvious pore for CSCP bead prepared with higher CS concentration (Fig. 3c). Cross-section observations of CSCP beads (Fig. 3e and f) reveal that there is a distinctive boundary between the film layer and the core, that is, a very loose core, crosslinked CS network, and a compact shell, polyelectrolyte complex film formed by crosslinked CS and PMAA. Obviously, both compactness and thickness of shell of CSCP beads are higher than that of CS bead (Fig. 3d). This complex phenomenon occurring between positively and negatively charged polymers, known as complex coacervation, has also been studied in relation to utilization for drug delivery systems (Ahn et al., 2002; Torre et al., 2003). Fig. 3f shows that there is high crosslinking density for both core and shell of CSCP bead obtained with high CS concentration. The nature-dried CSCP bead has very compact core–shell structure seen from Fig. 3g, which would limit the release of drug molecule before swelling of drug-loaded beads.

3.3. Swelling characteristic

The swelling ability of ionic-crosslinked gel is strongly dependent on the pH value of swelling medium. The swelling

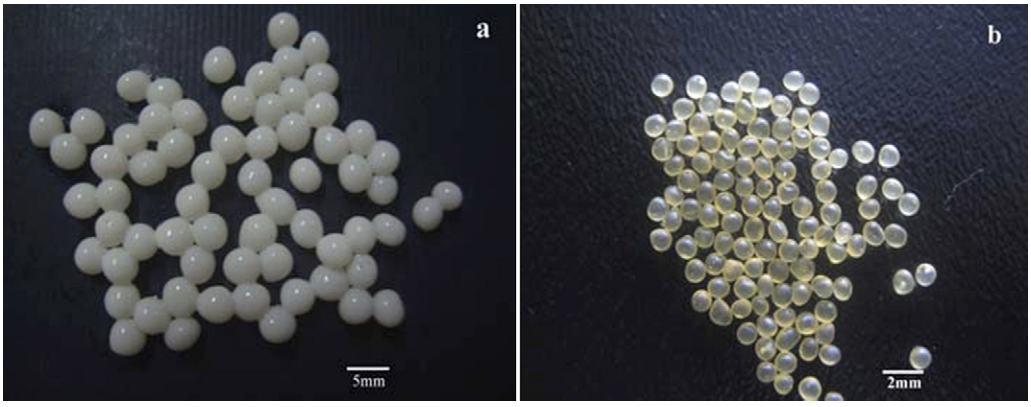

Fig. 2. Macroscopic photos of CSCP beads: (a) before drying and (b) after drying.

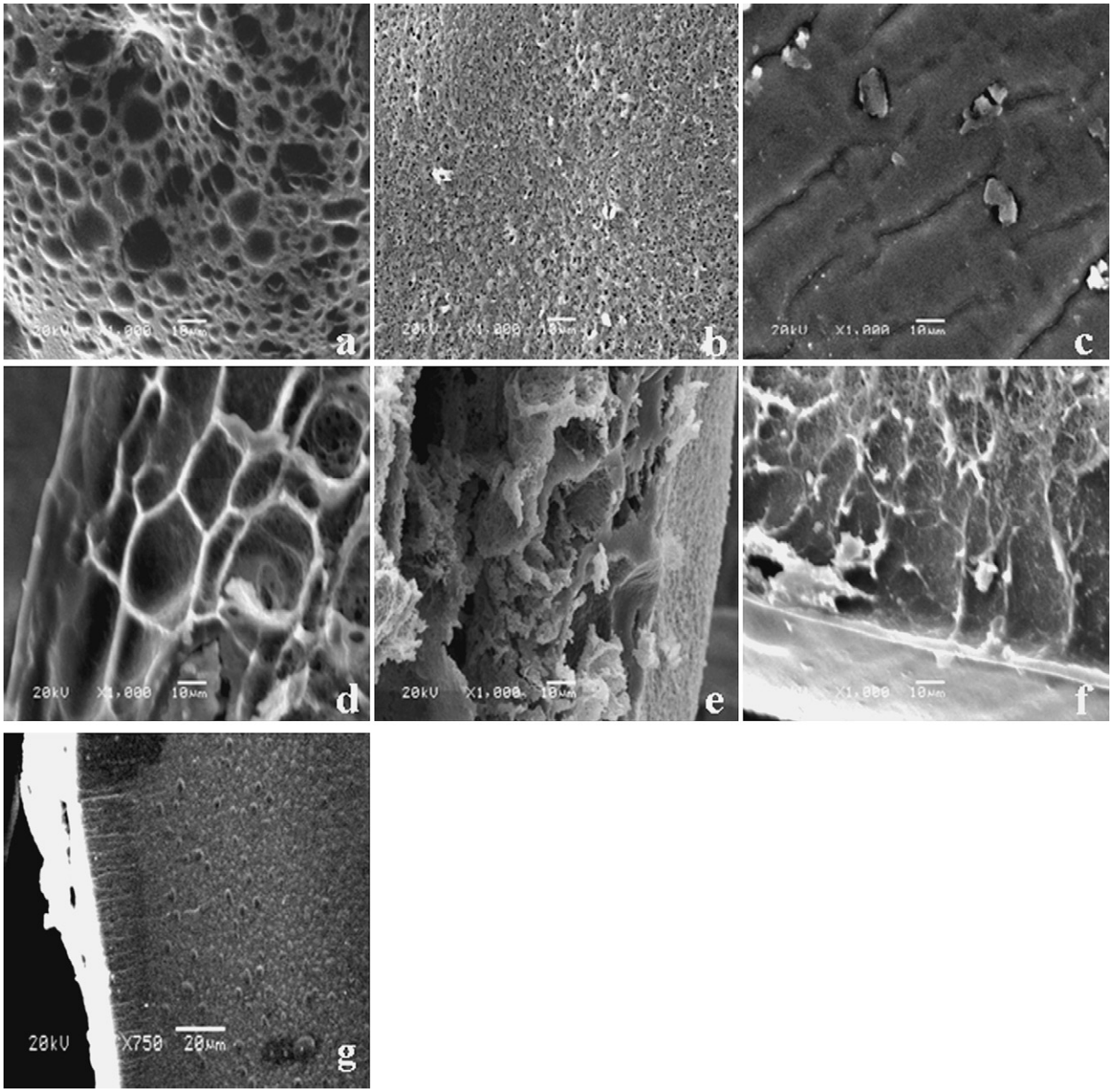

Fig. 3. SEM photos: surface morphology of CS bead (3%, w/v, CS concentration) (a), CSCP bead (3%, w/v, CS concentration) (b) and (4%, w/v, CS concentration) (c); cross-section morphology of CS bead (3%, w/v, CS concentration) (d), CSCP bead (3%, w/v, CS concentration) (e) and (4%, w/v, CS concentration) (f); cross-section morphology of nature-dried CSCP bead (3%, w/v, CS concentration) (g).

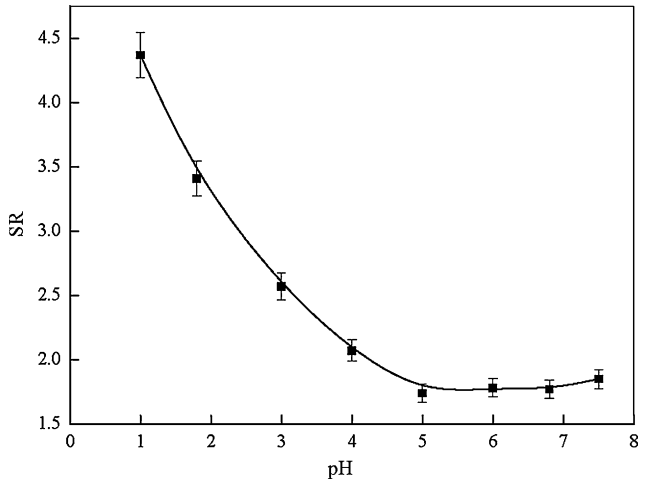

Fig. 4. The swelling characteristic of CSCP beads as a function of pH.

characteristic of blank CSCP beads at different pH value is shown in Fig. 4. The beads show high swelling degree at low pH, however, low swelling degree when pH higher than 5.0. The higher swelling degree is attributed to the strong protonize of amino groups on CS, which bring strong electrostatic repulsion among intrachain and interchain of CS, resulting in the relaxation of polymer network. Meanwhile, protonize of carboxylate on citrate and PMAA should break the ionic bond formed by CS with citrate and PMAA and reduce the crosslinking density of gel. At higher pH, the acidity of swelling medium would not obviously destroy the complex of CS with citrate and PMAA because both of these components had higher ionization degree when the CSCP beads were prepared. The matrix that swells at gastric acidity can be used for site-specific drug delivery system in stomach.

3.4. Effect of reaction conditions on drug release behaviors

3.4.1. Effect of coating on drug release behaviors

CS gels without coating disintegrated gradually in buffer medium (pH 1.8) during the test, on the other hand, CSCP gels disintegrated slowly. In Fig. 5, the drug release behaviors of these gels are displayed. It can be found that an initial drug burst effect is more obvious and the drug release rate is faster for CS beads than these of CSCP beads. The initial drug burst effect of CS gel beads may be attributed to the rapid swelling of CS gel and the release of drug adsorbed towards the surface of gel matrix. However, the release pattern of drug incorporated with CSCP gel is significantly different. The reason is that CS gel beads can be reinforced by PMAA, which suppress the rapid swelling and disintegration of CS gel beads resulting from the formation of complex film between CS and PMAA through electrostatic attraction. The complex film formed on the surface of crosslinked CS beads not only limits the erosion of CS matrix but also retards initial release. The result shows that a coating to CS beads effectively prolong drug delivery in gastric pH, which would decrease physiological toxicity resulting from fast release of drug. The drug release behaviors of CS and CSCP beads also

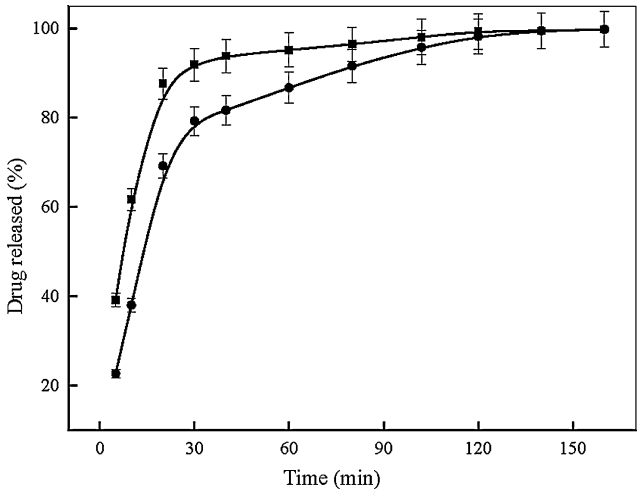

Fig. 5. In vitro release profiles of model drug in buffer medium (pH 1.8) from CS beads (■) and CSCP beads (●). Beads preparation: CS solution (3%, w/v) was crosslinked by 1.0 mol/L trisodium citrate aqueous solution (pH 7.0) for 30 min (CS beads), and then the CS beads were immersed in PMAA aqueous solution for 30 min (CSCP beads).

confirm the formation of physical barrier associated with CS and PMAA.

3.4.2. Effect of CS concentration on drug release behaviors

Usually, drug release behavior for CS matrix can be modulated by swelling–erosion rate. In ionic-crosslinked hydrogels, swelling of gel and erosion of network structure are prevented by inter-ionic interaction, which is related to CS concentration used for preparing the drug-loaded beads. The drug release behavior of CSCP beads prepared with different CS concentrations is shown in Fig. 6. With CS concentration increase, the crosslinking density increases due to electrostatic attraction of a larger amount of CS with citrate and PMAA, and physical entanglement among CS chains, which lead to com-

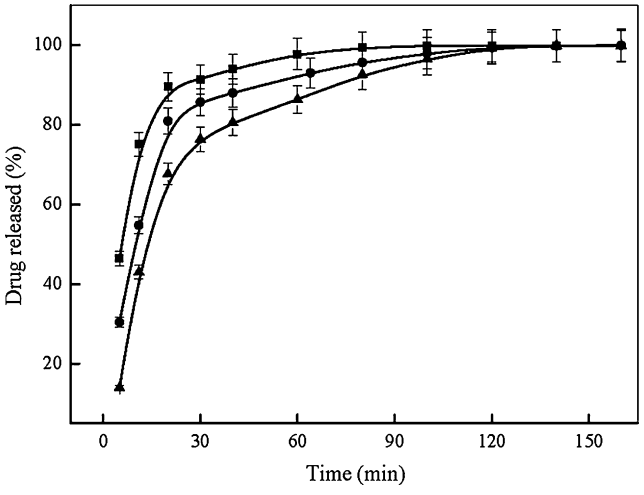

Fig. 6. Effect of CS concentration on drug release behavior of CSCP beads in buffer medium (pH 1.8). Beads preparation: CS solution was crosslinked by 1.0 mol/L trisodium citrate aqueous solution (pH 7.0) for 30 min, and then the beads were immersed in PMAA aqueous solution for 30 min (CS concentration (w/v): 2% (■); 3%(●); 4% (▲)).

pact core and compact polyelectrolyte complex film seen from the cross-section morphology of CSCP bead (Fig. 3f). These factors would be expected to slow swelling–erosion process. Meanwhile, the diameter of CS beads may be increased slightly because the viscosity of CS solution increases with an increase in CS concentration, which may delay the drug diffuse. Therefore, the slower release rate for CSCP beads obtained at higher CS concentration known from Fig. 6 can be easily understood.

3.4.3. Effect of trisodium citrate concentration on drug release behaviors

Fig. 7 depicts the release profiles of model drug from CSCP beads prepared with various trisodium citrate concentrations. The result shows that the drug release rate is fast with an increase in trisodium citrate concentration. The concentration of Na^+ (microgram of Na^+ per milligram of dried drug-loaded beads, μg/mg) entrapped in CSCP beads is 72.5, 53.9, 29.3, and 10.1 μg/mg, respectively, for CSCP beads prepared with trisodium citrate of 1.0, 0.6, 0.3, and 0.1 mol/L. For the drug-loaded bead prepared with higher trisodium citrate concentration, the inner of bead contains a larger amount of Na^+ resulting from ionizing of trisodium citrate, which leads to higher osmotic pressure within the inner of bead and faster swelling. In addition, the stability of polyelectrolyte complex depends on the amount of free ions because the electrostatic interaction between polyanions and polycations can be destroyed by salt ions owing to electrostatic screen (Schatz et al., 2004). Thus, the formation of crosslink is inhibited with an increase in trisodium citrate concentration because of electrostatic screen, leading to low corsslinking density. The Na^+ in the inner of beads would also screen the carboxylate on citrate and PMAA when the beads swell, which bring on the dissociation of ionic bond formed by CS with citrate (or with PMAA) and larger swelling degree. The screen action is stronger when

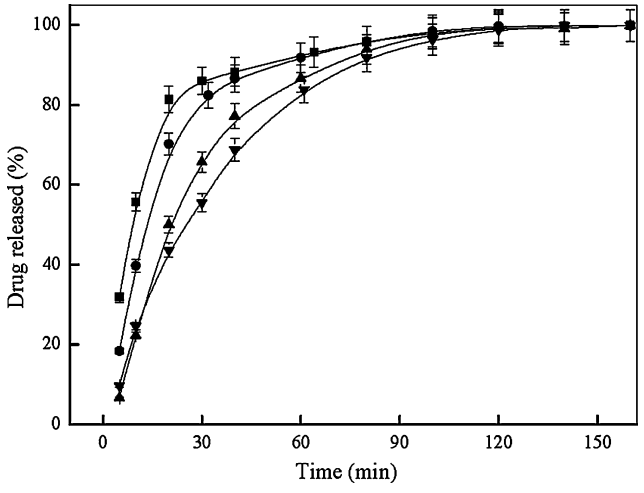

Fig. 7. Effect of trisodium citrate concentration on drug release behavior of CSCP beads in buffer medium (pH 1.8). Beads preparation: CS solution (3%, w/v) was crosslinked by trisodium citrate aqueous solution (pH 7.0) for 30 min, and then the beads were immersed in PMAA aqueous solution for 30 min (trisodium citrate concentration: 1.0 mol/L (■); 0.6 mol/L (●); 0.3 mol/L (▲); 0.1 mol/L (▼)).

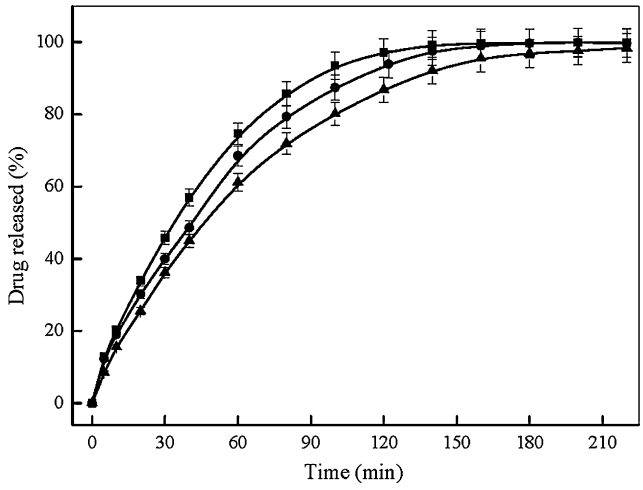

Fig. 8. Effect of pH value of trisodium citrate aqueous solution on drug release behavior of CSCP beads in buffer medium (pH 1.8). Beads preparation: CS solution (4%, w/v) was crosslinked by 0.1 mol/L trisodium citrate aqueous solution for 30 min, and then the beads were immersed in PMAA aqueous solution for 30 min (pH value of trisodium citrate aqueous solution: 4.82 (■); 6.05 (▲); 6.92 (●)).

the amount of Na^+ is higher. Based on these considerations, the rate of drug release from drug-loaded beads to swelling medium is fast for the beads corsslinked by high trisodium citrate concentration. Better release effect can be obtained when trisodium citrate concentration is 0.1 mol/L. For trisodium citrate concentration lower than 0.1 mol/L, the fast drug release rate is owing to low crosslinking density of CS gel (data not shown).

3.4.4. Effect of the pH value of trisodium citrate solution on drug release behaviors

It could be speculated that the ionic bond between polyanions and polycations depends on pH value of reaction medium due to change of charge density on polyions, causing difference in crosslinking density. Fig. 8 displays the drug release behavior of CSCP beads prepared at different pH values for crosslinker solution. When the pH value of crosslinker solution is 6.05, the

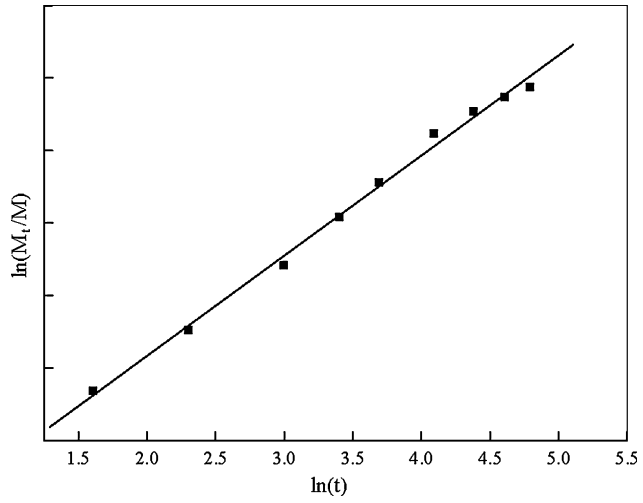

Fig. 9. The fitted curve of drug release behavior against time for CSCP beads with optimum drug release effect.

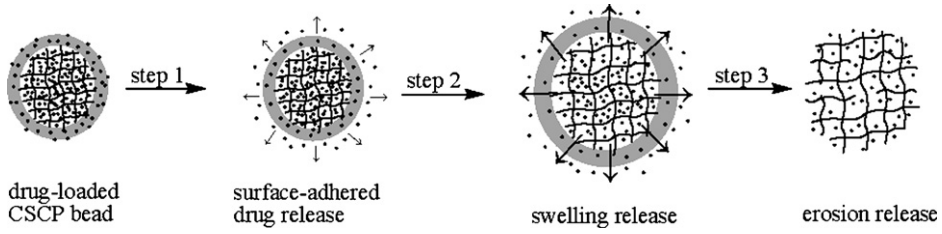

Fig. 10. Schematic of the drug release process for CSCP bead.

drug release rate of obtained CSCP beads is slower than that prepared in the medium of pH 4.82 and 6.92. It is known that pK_a of CS is about 6.3; pK_{a_2} and pK_{a_3} of citric are 4.76 and 6.4 (Li et al., 2004), respectively. At pH 4.82 of trisodium citrate aqueous solution, ionization degree of citrate is low leading to weak electrostatic interaction between citrate and CS although CS can be protonized strongly. At pH 6.92 of trisodium citrate aqueous solution that higher than pK_a of CS, protonization degree of CS is weak resulting in weak inter-ionic interaction between CS and citrate (and PMAA) although a large number of carboxylate exists. Meanwhile, it should be noted, if the pH value is too high, the positive charges of CS are neutralized and the system is not only ionic crosslinking but also undergoes coacervation-phase inversion, since CS precipitates, which may bring on low crosslinking density. However, both CS and citrate have high ionization degree at pH 6.05 known from reference (Shu et al., 2001). This means that the charge density of CS and crosslinker must be sufficiently high at this pH value, which allow optimum interaction and ensure a high crosslinking density. Thus, a slower drug release rate for CSCP beads prepared at pH 6.05 than that prepared at pH 4.82 and 6.92. In addition, better complex of CS with PMAA reported previously is pH from 4.0 to 6.2 with study of solution properties of them (Chen et al., 2007). So the coating reaction is performed in PMAA solution with pH value corresponding to the pH value of trisodium citrate aqueous solution.

3.5. Drug release mechanism of CSCP beads prepared under optimum reaction conditions

To investigate more precisely the release of model drug from CSCP beads obtained under optimum conditions (major conditions: CS concentration is 4% (w/v); trisodium citrate concentration is 0.1 mol/L; pH 6.05), the result is analyzed according to Peppa's potential equation (Tapia et al., 2005): $M_t/M = kt^n$, where M_t/M is the amount of drug released at time t, n is a diffusion exponent and k is the apparent release rate. From the fitted plot of $\ln(M_t/M)$ versus $\ln(t)$ (Fig. 9) shown good fit ($r^2 = 0.9950$; r, correlation coefficient), kinetic parameters, n and k, can be calculated. Using the Peppa's model the release order for CSCP beads is $n = 0.69$, which shows that the drug release of CSCP bead is a mechanism of combined process of drug diffusion and relaxation of polymer matrix (Tapia et al., 2005). Namely, the drug release kinetics of the controlled release matrix can be determined by diffusion process of drug partially through the swollen polymer network and partially through the water-filled pores and channels in the network structure, and the erosion of polymer matrix.

The results of in vitro drug release indicate that the release of model drug from CSCP beads takes place through three steps as depicted in Fig. 10. The surface-adhered drug is released firstly (Fig. 10, step 1), then the inner drug is released from swollen CSCP beads and the release rate is sustained, which is mainly governed by the diffusion ability (Fig. 10, step 2). After drug release from swollen CSCP beads, swollen CSCP beads begin to erode from outside to inner and the drug molecule is released through erosion of polymer matrix (Fig. 10, step 3).

In controlled release, major problems related with carriers are prominent initial burst release (Ferreira-Almeida and Almeida, 2004) and incomplete unloading of encapsulated drug (Zhang et al., 2004; Desai and Park, 2005). In present study, the initial burst release can be improved by coating and ionic-crosslinked polymer matrix can ensure the drug release completely to enhance the using efficiency of drug owing to its particular swelling–erosion properties. The drug release behavior demonstrated by CSCP may be beneficial for site-specific drug delivery in stomach, because of the limitations of gastric emptying time (He et al., 2004).

4. Conclusions

Gel beads composed of negatively and positively charged polymers can be prepared without a tedious process. The ionic-crosslinked CS-based beads exhibit a particular swelling characteristic that will be useful for specific delivery system. The drug release rate of CS beads can be substantially slowed by coating with PMAA to CS beads because of the formation of polyelectrolyte complex film between CS and PMAA. Increasing the CS content (up to 4%, w/v), decreasing trisodium citrate content (down to 0.1 mol/L), and selecting pH value of trisodium citrate aqueous solution (at 6.05) results in improvement concerning the retarding of drug release. Major problems about carriers, which are initial burst release and incomplete unloading of encapsulated drug, are resolved in present study. The analysis about the drug release indicates that drug release mechanism is a combined process of drug diffusion and erosion of the drug-loaded matrix. According to the results, the obtained CSCP matrix may be beneficial for site-specific drug delivery in stomach. In future, it should be possible to control the release of various drugs by a proper selection of drug, by modification of gel matrix and by improvement of gel preparation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2007.08.029.

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