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Novel pH-sensitive citrate cross-linked chitosan film for drug controlled release

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Abstract

Turbidimetric titration revealed that there were electrostatic attractive interactions between citrate and chitosan in the pH region of 4.3–7.6, depending on their degree of ionization. Citrate cross-linked chitosan film was prepared simply by dipping chitosan film into sodium citrate solution. The swelling ratio of citrate/chitosan film was sensitive to pH, ionic strength etc. Under acidic conditions, citrate/chitosan film swelled and even dissociated in the pH less than 3.5, and the model drugs (brilliant blue and riboflavin) incorporated in the film were released quickly (usually within 2 h released completely in simulated gastric fluid at 37°C) while under neutral conditions the swelling ratio of citrate/chitosan film was less significant and the release rate of brilliant blue and riboflavin was low (less than 40% released in simulated intestinal fluid in 24 h). Sodium chloride weakened the electrostatic interaction between citrate and chitosan, and therefore facilitated the film swelling and accelerated drug release. The parameters of film preparation such as citrate concentration, solution pH etc. influencing the film swelling and drug release profiles were examined. The lower concentration and the higher pH of citrate solution resulted in a larger swelling ratio and quicker riboflavin release. To improve the drug controlled release properties of citrate/chitosan film, heparin, pectin and alginate were further coated on the film surface. Among them only the coating of alginate prolonged riboflavin release noticeably (for 80% of drug released the time was extended from 1.5 to 3.5 h with 0.5% w/v alginate used). The results indicated that the citrate/chitosan film was useful in drug delivery such as for the site-specific drug controlled release in stomach.

Keywords: Chitosan film; Sodium citrate; pH-sensitive; Drug controlled release

1. Introduction

Chitosan with excellent biodegradable and biocompatible characteristics is a naturally occurring polysaccharide. Due to its unique polymeric cationic character, its gel and film forming properties, chitosan has been extensively examined in the pharmaceutical industry for its potential in the development of drug delivery systems (Yao et al., 1995; Illum, 1998).

Chitosan films were usually prepared by chemical cross-linking with glutaraldehyde etc. (Nakatsuka and Andrady, 1992; Thacharodi and Rao,

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1993; Illum, 1998). These films swelled under acidic conditions due to the ionization of amino groups but remained in a shrunken state under neutral condition. Moreover, chitosan was reported to have intragastric-floating characteristics and prolonged retention of the dosage form in the stomach. By utilizing these advantages, chitosan films or other dosage forms have been exploited widely for oral sustained drug delivery in the stomach (Inouye et al., 1988; Chandy and Sharma, 1993; Patel and Amiji, 1996; Gupta and Ravi Kumar, 2000). To improve the pH-sensitive performance, blended chitosan films have usually been prepared. For example, polyether oxide/chitosan film was reported to have excellent pH-sensitivity (Yao et al., 1993; Angelova et al., 1995; Patel and Amiji, 1996).

However, the chemical cross-linking agents possibly induce toxicity and other undesirable effects. To overcome these disadvantages, recently reversible physical cross-linking by electrostatic interaction was applied in the preparation of chitosan film (Illum, 1998). Polyanions were usually used as a component to prepare these films. For example, Yao et al. (1996) reported the preparation of pectin/chitosan films by dissolving this polyelectrolyte complex in formic acid and then evaporating the solvent. Chu et al. (1995) also prepared xanthan/chitosan complex film by the solvent evaporation method in the existence of concentrated sodium chloride (ca. 0.5 M) and then treatment at a high temperature.

On the other hand, the use of low molecular weight ions to prepare an ionic cross-linking polymeric matrix was found to be very simple and mild, and the cross-linking process was accomplished just by dipping the polymer films into cross-linking ion solution (Al-Musa et al., 1999). For instance Remuñän-López and Bodmeier (1997) prepared tripolyphosphate cross-linked chitosan film by dipping chitosan film into tripolyphosphate aqueous solution.

However, up to now, no other anion cross-linked chitosan film is reported in the literature. In our previous experiments, we found that there was electrostatic interaction between sodium citrate and chitosan, and citrate cross-linked chitosan beads or microspheres were prepared using our recently developed method (Shu and Zhu, 2000a,b). In this paper, we aim to prepare citrate cross-linked chitosan film and investigate the pH-sensitive performances of citrate/chitosan film. The preliminary results of citrate/chitosan film as pH-dependent drug controlled release matrix are also reported.

2. Materials and methods

2.1. Materials

Chitosan was obtained from Tianbao Chitosan Co. Ltd (China), and refined twice by dissolving in dilute HAc solution and precipitating from dilute ammonia, the degree of deacetylation was 86%, Mv was 460 000. Pectin (USP XXII) and sodium alginate (low viscosity) were obtained from Sigma (USA). Heparin (Mw 11 000, from porcine intestinal mucosa) was a gift from Jiuyuan Gene Co. Ltd (China). Riboflavin (Mw 376.37), theophylline (Mw 180.17) and 5-fluorouracil (5-FU, Mw 130.08) were all purchased from Aldrich (USA). Coomassie brilliant blue R250 (Mw 825) was purchased from Fluka A.G. (Switzerland) and used after sieving (less than 50 μm). Sodium citrate (analytical grade) and other reagents were all commercially available and used as received.

2.2. Turbidimetric titration

The interactions of sodium citrate and chitosan were investigated by turbidimetric titration according to the reported method (Park et al., 1992; Mattison et al., 1995). A solution of 0.2 g/l sodium citrate and 0.2 g/l chitosan was prepared at pH 1.0. Titrant (0.01–0.2 M NaOH) was delivered with a microburette into the solution with gentle stirring at 20 ± 0.2°C, and the pH was monitored by a digital pH meter with a precision of ± 0.01. Changes in turbidity were monitored at 420 nm with an UV–vis spectrophotometer and reported as $100 - \%T$ which is linearly proportional to the true turbidity for $T > 0.9$. The time interval between turbidity measurements was ca. 4 min.

2.3. Potentiometric titration

Potentiometric titration was performed according to the method reported by Ikeda et al. (1995) to evaluate the pH-dependent ionization degree of chitosan and citrate, respectively. Sodium citrate solution (100 ml; 10 mM) or 0.1% (w/v) chitosan solution were neutralized by adding 0.1 M HCl or NaOH, respectively, at 20 ± 0.2°C with a microburette in a nitrogen atmosphere, and the solution pH was monitored by a digital pH meter with a precision of ± 0.01.

2.4. Preparation of cross-linked chitosan film

Chitosan films were produced by a casting/solvent evaporation technique. Chitosan solutions (4.0%, w/v) containing model drug (brilliant blue, riboflavin, theophylline or 5-FU, 1.0% w/v) were prepared by dissolving chitosan and the model drug (or dispersing) in 4.0% (w/v) acetic acid. The above solutions (40 ml) were sonicated, left to stand until trapped air bubbles were removed, and poured on a glass plate (casting area, 10×10 cm^2). The films were dried for 48 h in an oven at 37°C, then further dried under vacuum at room temperature until constant weight. The dried films were cut into 2×2 cm^2 test sections. The thickness of the dried films were determined to be ca. 100 μm.

Citrate cross-linked chitosan films were prepared by soaking the chitosan films (ca. 50 mg) in an aqueous solution of sodium citrate (100 ml) at 4°C. The cross-linking conditions were 1.0–10.0% (w/v) sodium citrate; solution pH, 5.0–7.0; cross-linking time, 0.5–4 h. The citrate/chitosan films formed were then washed with distilled water, put on a glass plate and oven-dried at 37°C for 48 h, and then dried under vacuum at room temperature until reaching a constant weight.

In some cases, wet citrate/chitosan films were further coated with polyanions (pectin, alginate or heparin) by dipping the films into 100-ml polyanion aqueous solution (concentration 0.25 or 0.5% w/v) at pH 5.5 for 15 min.

The model drug loss during cross-linking process was determined by measuring the UV–vis absorption, 590 nm for brilliant blue, 444 nm for riboflavin, 272 nm for theophylline and 265 nm for 5-FU. Model drug loading percent = (1 − the drug loss/the drug given) × 100%.

2.5. Morphology observation

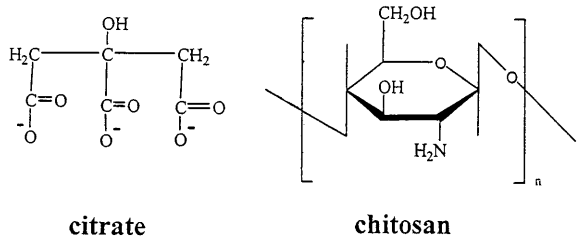
The surface and cross-sectional morphologies of citrate/chitosan films were examined using scanning electron microscopy (SEM, S-590, Hitachi). Cross-sectional samples were prepared by fracturing films in liquid nitrogen. Prior to observation, samples were mounted on metal grids, using double-sided adhesive tape, and coated with gold under vacuum before observation.

2.6. Swelling ratio measurement

Blank citrate/chitosan films (ca. 50 mg) were suspended in glass bottles containing 250 ml of media, and incubated on a shaking water-bath at 37°C, 50 rpm. At an appropriate time interval, the films were taken out, and the excess water was removed carefully with filter paper from the film surface, and then weighed immediately. The swelling ratio $= W_t/W_0$, where W_t was the film weight at time t and W_0 was the initial film weight, was calculated. The media for the swelling studies were either 0.1 N HCl (pH 1.0), 10 mM acetic acid–sodium acetate (pH 3.5, 4.5 and 5.5), or 10 mM phosphate-buffered solution (pH 6.5, 7.4, 8.5 and 9.5). The ionic strength of above buffered solutions was carefully adjusted to 0.145 M by adding an appropriate amount of sodium chloride. Different concentrations of sodium chloride solution (0, 0.45, 0.9, and 1.8% w/v), and enzyme-free simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) (USP XXII) were also used for test.

2.7. Release studies

The model drug release from citrate/chitosan film was performed under the same conditions described in the swelling studies. At appropriate time intervals, the solutions were withdrawn and the content of the model drugs were determined by measuring UV–vis absorption at the wavelengths described in Section 2.4. An equal volume



Scheme 1.

of the same dissolution medium was added back to maintain a constant volume. In some cases, chitosan leaching from the films was also monitored by the phenol–sulfuric acid color reaction (Dubois et al., 1956; Thu et al., 1997).

3. Results and discussion

3.1. The interaction between citrate and chitosan

Citrate is an anion with three carboxylic groups and chitosan is a polybase (Scheme 1), the charge densities of citrate and chitosan are mainly controlled by solution pH (Fig. 1). Due to the weak acid characteristic of citric acid, under neutral and weakly acidic conditions the decrease of the solution pH resulted in a significant decrease of the degree of ionization of citrate. At low pH (less than ca. 4.1), the ionization of carboxyl groups was normally depressed (the degree of ionization

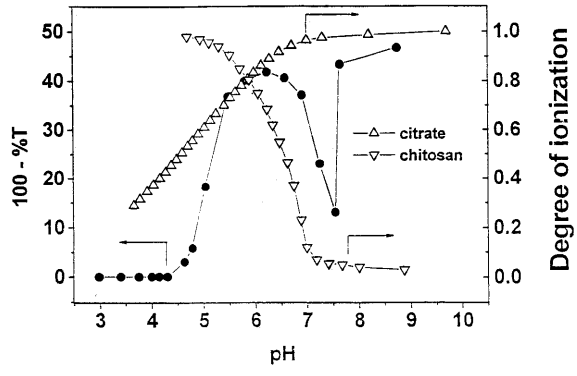


Fig. 1. The turbidity titration curves of citrate/chitosan solution at 420 nm (0.2 g/l citrate and chitosan, respectively), and the degree of ionization curves of citrate and chitosan.

was usually less than 0.3), i.e. less than one negative charge was carried by one citrate. For chitosan (a weak polybase), the opposite was the case as the ionization of amine groups decreased greatly when the solution pH increased above 6.0 (around the pK_a of chitosan 6.3) (Yalpani and Hall, 1984), and at pH higher than 7.5 usually less than 10% of amine groups were ionized.

The turbidimetric titration curve of sodium citrate/chitosan is also shown in Fig. 1, which is in accordance with the pH-dependent charge density of citrate and chitosan. At low pH (1.0–4.0), the solution was optically clear due to the low charge density of the citrate. The turbidity increased greatly and the solution began to separate into two phases when pH increased over 4.3. This could be attributed to the significant charge densities of citrate and chitosan in this pH region. Further increase of solution pH over ca. 6.3 led to the decrease of the charge density of chitosan greatly, and hence the decrease of turbidity significantly. The lowest value of turbidity was observed at pH ca. 7.6, and then turbidity increased at pH values over 7.6, which was attributed to the poor solubility of chitosan in this pH region (Shu and Zhu, 2000b).

3.2. Morphology of citrate/chitosan films

The surface morphologies of citrate/chitosan films are shown in Fig. 2. The bottom surface of citrate/chitosan films was very smooth (Fig. 2a) while the upper surface was relatively rough (Fig. 2b), which was in accordance with the morphology of chitosan films before cross-linking (pictures not shown). Sodium citrate concentration, pH and cross-linking time had little effect on the surface morphology of citrate/chitosan films. The cross-section of the citrate/chitosan films was very integral and dense (pictures not shown).

The surface and cross-section morphologies changed significantly due to the incorporation of model drugs into the citrate/chitosan film. For example, large pores were observed on both the bottom and upper surface of riboflavin loaded citrate/chitosan films (Fig. 3a), and the cross-section was very rough and many deficiencies were observed (Fig. 3b).

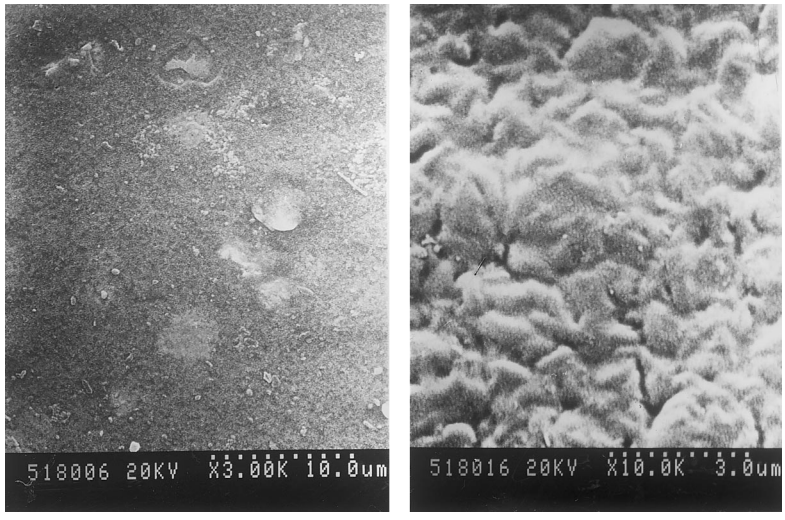


Fig. 2. The surface morphology of blank citrate/chitosan film: bottom surface (a) and upper surface (b). The film was prepared with 5.0% w/v sodium citrate (pH 7.0) and a cross-linking time of 1 h.

3.3. Factors influencing citrate/chitosan film swelling and drug controlled release properties

3.3.1. Media pH

From Fig. 1, it could be seen that the degree of ionization of citrate and chitosan was mainly controlled by the solution pH; hence citrate/chitosan films exhibited pH-dependent swelling, which is shown in Fig. 4. At pH 5.5 and 6.5, the swelling ratio was the lowest (2.45–2.50) due to significant electrostatic attraction between citrate and chitosan. The decrease of pH weakened salt-bonds and therefore facilitated the film swelling (swelling ratio 2.83 at pH 4.5). Moreover, when pH was less than 4.5, citrate/chitosan film swelled more significantly and dissociated within 24 h because no ionic cross-linking was observed in this pH region as revealed by turbidimetric titration (Fig. 1). On the other hand, the increase of pH over 6.5 should also weaken salt-bonds, and result in a larger swelling ratio (swelling ratio 2.95 at pH 7.4). However, the further increase of pH to 8.5 and 9.5 led to the decrease of swelling ratio greatly (2.58 and 2.46 for pH 8.5 and 9.5, respectively). It was usually reported that the swelling of polyelectrolyte complex films (such as pectin/chitosan film) under weak basic conditions (pH 8–10) was very significant (Yao et al., 1996), mainly resulting from the dissociation of ionic cross-linking and the repelling interaction between negatively charged carboxylic groups. But in our experiments, the dissociated citrate at pH 8.5–9.5 may diffuse out from the films freely and no repelling interaction between carboxylic groups existed inside the films, which as well as other factors such as the hydrogen-bonding between amine of chitosan, attributed to the shrinkage of the film in this pH region. Similar results were also observed in the case of tripolyphosphate cross-linked chitosan film (unpublished results).

Fig. 5 shows the chitosan leaching from the citrate/chitosan film in a buffered solution with different pHs at the same ionic strength (0.145 M). At pH 1.0 and 3.5, the film dissociated quickly (within 5.0 h), while at pH 4.5, the leaching percent of chitosan was less than 20% in 24 h due to the relatively weak electrostatic attractive force between citrate and chitosan (Fig. 1), and at pH 5.5, 6.5 and 7.4 no leaching of chitosan occurred.

The release of brilliant blue with poor water solubility from citrate/chitosan films also possessed pH-sensitivity (Fig. 6), which was in accordance with the pH-dependent chitosan leaching (Fig. 5) except at pH 4.5 where brilliant blue release was faster than chitosan leaching (ca. 67%

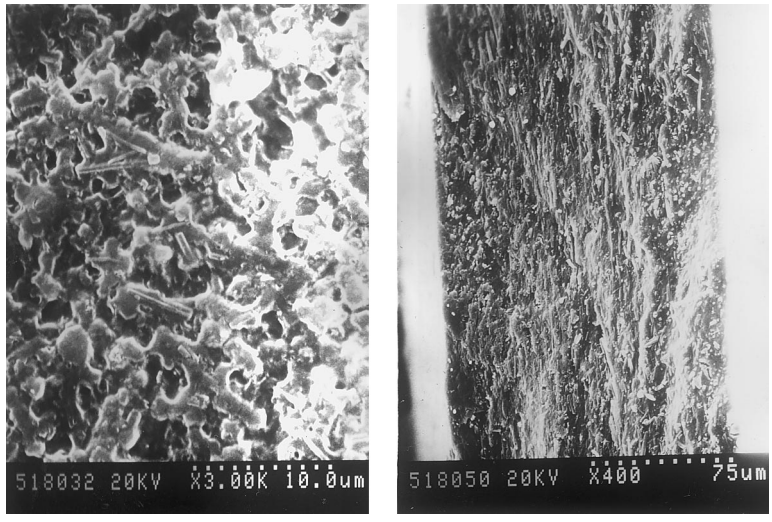


Fig. 3. The morphologies of bottom surface (a) and cross-section (b) of riboflavin (ca. 20% w/w) loaded citrate/chitosan film. The film was prepared with 5.0% w/v sodium citrate (pH 7.0) and a cross-linking time of 1 h.

released for brilliant blue and less than 20% for chitosan in 24 h). The results indicated brilliant blue release from citrate/chitosan films was mainly controlled by the chitosan leaching, i.e. the film dissociation.

3.3.2. The salt concentration in media

Salt usually had a shielding effect on the electrostatic force, and hence weakened the salt-bond between citrate and chitosan. Fig. 7 shows the influence of sodium chloride concentration on the swelling of citrate/chitosan film and the release of riboflavin from the film. More significant swelling occurred in higher concentrations of sodium chloride solution, and hence resulted in a quicker riboflavin release. In 24 h, with sodium chloride concentrations of 0, 0.45, 0.90 and 1.80% (w/v), the swelling ratio was 1.67, 2.07, 2.49 and 2.96, respectively (Fig. 7a), and the drug release was 20.2, 25.8, 27.5 and 39.9%, respectively (Fig. 7b).

3.3.3. Parameters in film preparation

In our experiments, a cross-linking time of more than 0.5 h only slightly limited the swelling of citrate/chitosan film and prolonged riboflavin release. For example, with 5.0% (w/v) sodium citrate (pH 7.0), the equilibrium swelling ratio was found to be ca. 1.65 in distilled water and ca. 2.0 in SIF with the cross-linking time extending from 0.5 to 4.0 h.

On the other hand, under the same conditions, the increase of citrate concentration resulted in a decrease of swelling ratio in distilled water (Fig. 8a) and in SIF (Fig. 8b) significantly, which indicated that more cross-linking structure formed in the case of high concentration of citrate (Remuñán-López and Bodmeier, 1997). In Fig. 8b, it

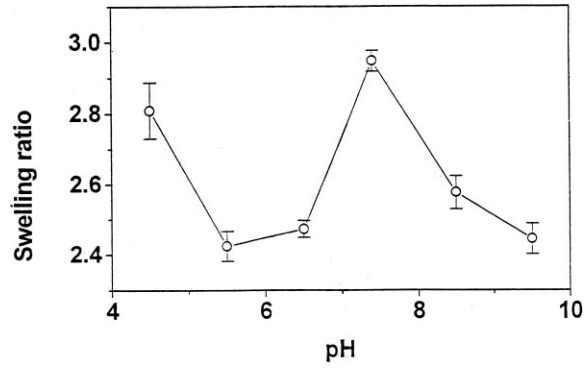


Fig. 4. The equilibrium swelling ratio of blank citrate/chitosan film in buffered solution with the same ionic strength (0.145 M). The film was prepared with 1.0% (w/v) sodium citrate (pH 7.0) and a cross-linking time of 1.0 h. pH 1.0 (0.1 M HCl); pH 3.5, 4.5 and 5.5 (10 mM acetic acid–sodium acetate buffer); pH 6.5, 7.4, 8.5 and 9.5 (10 mM phosphate-buffered solution).

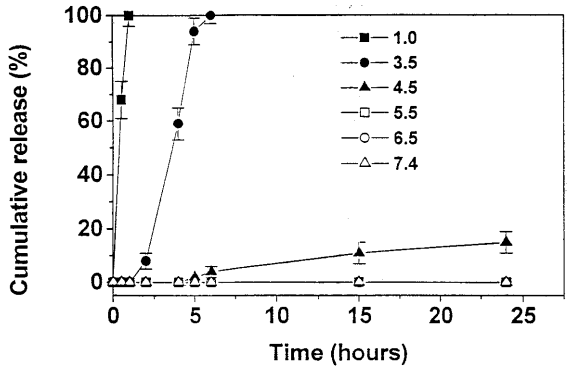


Fig. 5. The leaching of chitosan from blank citrate/chitosan film in buffered solution with the same ionic strength (0.145 M). The film was prepared with 1.0% (w/v) sodium citrate (pH 7.0) and a cross-linking time of 1.0 h. pH 1.0 (0.1 M HCl); pH 3.5, 4.5 and 5.5 (10 mM acetic acid–sodium acetate buffer); pH 6.5, 7.4, 8.5 and 9.5 (10 mM phosphate-buffered solution).

could be seen that in SIF the film swelled to the greatest extent at first 2 h, then the swelling ratio decreased gradually to a constant value. It was probably caused by some further interpolyelectrolyte bonds being formed as suggested by Arguelles-Monal et al. (1990), Macleod et al. (1999).

In the preparation process, sodium citrate solution was much in excess and they mainly determined the preparation pH value in 5.0–7.0. Fig. 9 shows the swelling of chitosan film in sodium

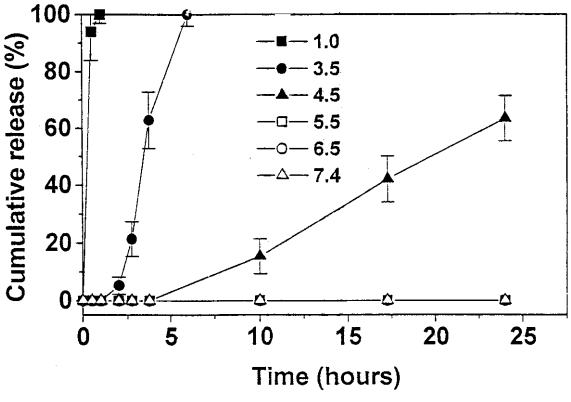


Fig. 6. The release of brilliant blue from citrate/chitosan film in buffered solution with the same ionic strength (0.145 M). The film was prepared with 1.0% (w/v) sodium citrate (pH 7.0) and a cross-linking time of 1.0 h. pH 1.0 (0.1 M HCl); pH 3.5, 4.5 and 5.5 (10 mM acetic acid–sodium acetate buffer); pH 6.5, 7.4, 8.5 and 9.5 (10 mM phosphate-buffered solution).

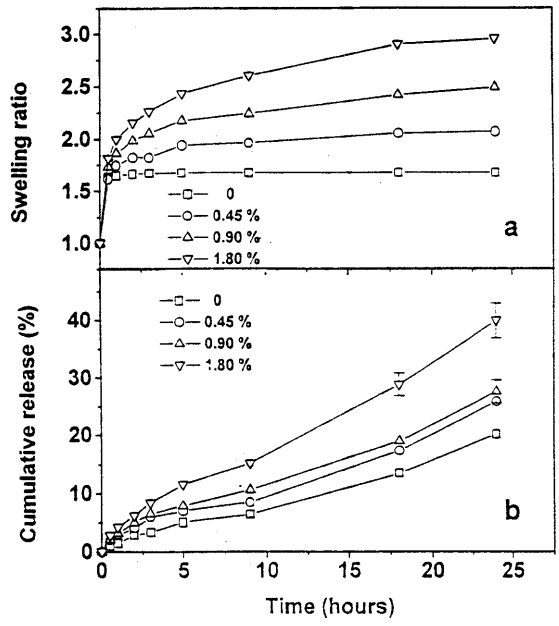


Fig. 7. The swelling of blank citrate/chitosan film (a) and the release of riboflavin from citrate/chitosan film (b) in different concentration NaCl solution (w/v). The film was prepared with 5.0% (w/v) sodium citrate, pH 7.0 and a cross-linking time of 1.0 h.

citrate solution (5.0% w/v) with different pHs during cross-linking process. More significant swelling occurred in higher pH citrate solution. The swelling ratio was 2.51, 2.28 and 2.19 in 4 h for pH 7.0, 6.0 and 5.0, respectively. At pH 5.0, most of the amine groups of chitosan (more than 95%) ionized (Fig. 1), so more cross-linking structure should be formed, which resulted in the lowest swelling ratio. However, at pH 6.0 and 7.0, only part of amines was ionized (ca.78% for pH 6.0 and ca.12% for pH 7.0) and hence less cross-linking sites formed.

Fig. 10 shows the swelling and riboflavin release from citrate/chitosan film prepared at pH 5.0, 6.0 and 7.0, respectively, in SIF. In accordance with the above discussion, the increase of preparation pH resulted in the increase of swelling ratio and drug release slightly (Fig. 10a and b). In 24 h, with preparation pH 5.0, 6.0 and 7.0, the swelling ratio was 1.85, 1.99 and 2.03, respectively, and the riboflavin release was 31.1, 34.2 and 39.7%, respectively.

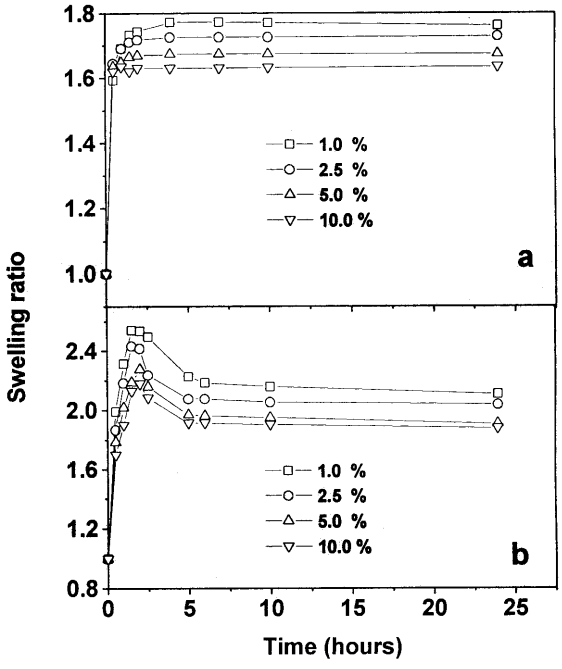


Fig. 8. The influence of sodium citrate concentration on the swelling of blank citrate/chitosan film in distilled water (a) and SIF (b) (cross-linking time 1.0 h, pH 7.0).

3.3.4. Polyanion coating

In low pH (1.0–3.5), citrate/chitosan film usually dissociated and the model drug released quickly (Figs. 5 and 6). For example, in SGF the release of riboflavin was usually completed within 2 h. To prolong the drug release from citrate/chitosan film in SGF, polyanions were further coated on the surface of citrate/chitosan film. However, the coating of pectin and heparin only slightly retarded riboflavin release in SGF (Fig. 11a and b). On the other hand, the coating of alginate greatly prolonged riboflavin release; the time period for 80% riboflavin released was extended from 1.5 to 2.4 and 3.5 h after being coated with 0.25 and 0.50% alginate (w/v), respectively.

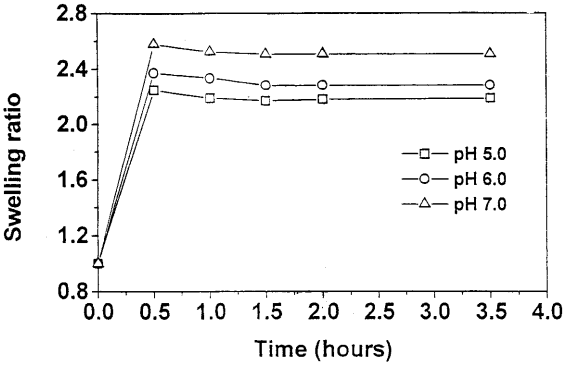


Fig. 9. The swelling curves of blank chitosan film in sodium citrate solution (5.0% w/v) with different solution pHs during cross-linking process.

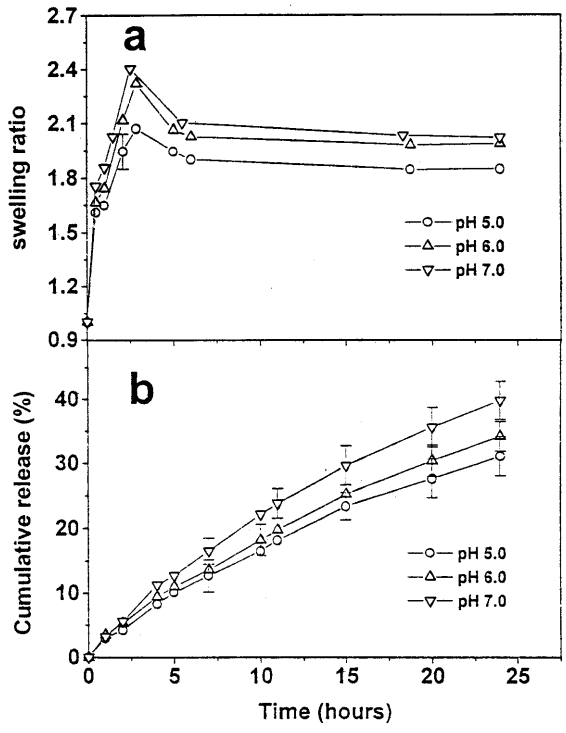


Fig. 10. The swelling of blank citrate/chitosan film (a) and the release of riboflavin from citrate/chitosan film (b) in SIF. The film was prepared with sodium citrate 5.0% w/v (pH 5.0, 6.0 or 7.0) and a cross-linking time of 1.0 h.

From the point of polyelectrolyte interaction, the coating of heparin should retard drug release in SGF most effectively, because the interaction between heparin and chitosan was the strongest due to the highest charge density of heparin (carboxylic and sulfonic groups) (Kihuchi and Noda, 1976). As for pectin and alginate, the weakly acidic carboxyl groups protonated in SGF (pH 1.0–1.1), and the electrostatic attractive force between pectin (or alginate) and chitosan disappeared (Macleod et al., 1999; Yao et al., 1996).

However, only the coating of alginate prolonged riboflavin release significantly, which indicated that there were possibly other reasons but not electrostatic interaction resulting in the above result. It was reported that the aqueous solubility of alginate under acidic conditions was very poor (Yoshihisa et al., 1991), though in SGF the salt-bonds between alginate and chitosan dissociated, the precipitated alginate layer was still kept on the surface of citrate/chitosan film, which may limit film swelling and prolong drug release.

3.3.5. Model drug nature

The model drug properties, especially solubility, affected their release behavior from citrate/chitosan film seriously. Fig. 12 shows the loading percent and loss percent of brilliant blue, riboflavin, theophylline and 5-FU during cross-linking process. No obvious loss of brilliant blue and riboflavin occurred because they slightly dissolved in water, and even taking 4 h for cross-linking the loading percents were both larger than 97. But for more water-soluble and also smaller molecular weight theophylline and 5-FU, the loading efficiency decreased greatly with cross-linking time, and the loading efficiencies were both less than 20% in 2.5 h.

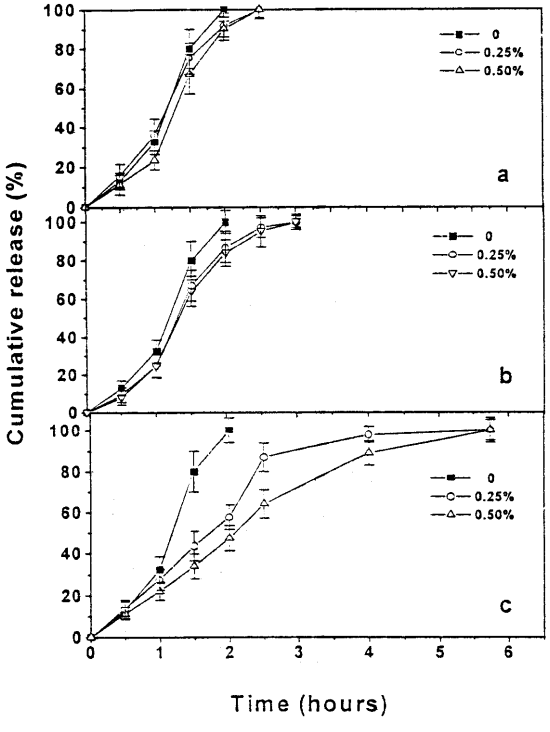


Fig. 11. The release of riboflavin from polyanion coating citrate/chitosan film. The films were prepared with 5.0% w/v sodium citrate (pH 7.0) and a cross-linking time of 1 h, and then dipped into polyanion solutions (pH 5.5) with different concentrations (w/v) for 15 min, (a) pectin, (b) heparin, and (c) sodium alginate.

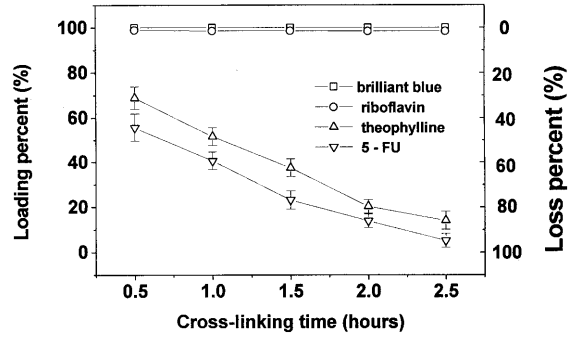


Fig. 12. The loading percent and loss percent of model drugs during cross-linking process, 5.0% w/v sodium citrate, pH 7.0.

The release of theophylline and 5-FU from citrate/chitosan film in SIF was very quick, in most cases more than 90% drug released in 2 h, while under the same condition the release percents of brilliant blue and riboflavin were both less than 5%.

4. Conclusions

Novel citrate cross-linked chitosan film was prepared by dipping chitosan film into citrate solution. Citrate/chitosan film possessed pH-sensitive swelling and drug controlled release properties. Sodium chloride weakened ionic cross-linking and facilitated film swelling and model drug release. Sodium citrate solution concentration and pH during cross-linking process affected film swelling and drug controlled release profiles, and using higher concentration and lower pH of sodium citrate resulted in less swelling and slower drug release. The further coating of alginate on the surface of citrate/chitosan prolonged riboflavin release in SGF significantly, while the

coating of heparin and pectin only retarded drug release slightly. The significant difference of citrate/chitosan film swelling and model drug release profiles in SIF and SGF indicates that these films may be useful for site-specific drug delivery in the stomach.

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