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Preparation of dual crosslinked alginate–chitosan blend gel beads and in vitro controlled release in oral site-specific drug delivery system

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Abstract

Alginate–chitosan (ALG–CS) blend gel beads were prepared based on Ca^{2+} or dual crosslinking with various proportions of alginate and chitosan. The homogeneous solution of alginate and chitosan was dripped into the solution of calcium chloride; the resultant Ca^{2+} single crosslinked beads were dipped in the solution of sodium sulfate sequentially to prepare dual crosslinked beads. The dual crosslinkage effectively promoted the stability of beads under gastrointestinal tract conditions. The sustained release profiles of single and dual crosslinked gel beads loaded bovine serum albumin (BSA), a model protein drug, were investigated in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid (SCF). In SGF, compared to Ca^{2+} single crosslinked beads, from which BSA released fast and the cumulative drug release percentages were about 80% of all formations in 4 h, the BSA total release from dual crosslinked gel beads was no more than 3% in 8 h. In SIF and SCF, Ca^{2+} single crosslinked beads were disrupted soon associating with the fast drug release. As to the dual crosslinked beads, the BSA total release from the ALG–CS mass ratio 9:1 (81.24%) was higher than that of 7:3 and 5:5 (less than 60%) in 8 h in SIF; the BSA release from all beads was much faster in SCF than in SIF. The dual crosslinked beads incubated in gastrointestinal tract conditions, the BSA cumulative release of ALG–CS mass ratios 9:1, 7:3 and 5:5 were respectively 2.35, 1.96, 1.76% (in SGF 4 h), 82.86, 78.83, 52.91% (in SIF 3 h) and 97.84, 96.81, 87.26% (in SCF 3 h), which suggested that the dual crosslinked beads have potential small intestine or colon site-specific drug delivery property.

Keywords: Alginate; Chitosan; Beads; Controlled release; Site-specific drug delivery system

1. Introduction

Naturally occurring polysaccharides sodium alginate and chitosan have received much attention in drug delivery system for their excellent biocompatibility. Chitosan is a weak cationic polysaccharide, composed mainly of (1, 4) linked 2-amino-2-deoxy-β-D-glucan. Alginic acid is a linear copolymer of (1, 4) linked-D-mannuronic and -l-guluronic acid residues arranged in a non-regular block wise pattern. Thanks to amino groups in the chitosan molecule and carboxyl groups in the alginate molecule, they are pH-sensitive materials as drug carriers. The interaction between alginate and chitosan had been systematically investigated (Becherán-Marón et al., 2004). Their polyelectrolyte complex has been widely used to obtain devices for the controlled release of drugs (Miyazaki et al., 1995; Murata et al., 1996; Zhou et al., 2001; Mi et al., 2002; Ribeiro et al., 2005). The sponges or scaffolds prepared of chitosan and alginate together were easily to manipulate both mechanical properties and drug release properties (Lai et al., 2003; Li et al., 2005). The alginate-based chitosan hybrid polymer fibers promoted favorable biological responses of seeded chondrocytes including enhancing cell attachment and proliferation (Iwasaki et al., 2004). The research of Wong et al. (2002) indicated that the release-retarding property of chitosan-coating alginate calcium beads was mainly induced via alginate–chitosan complexation, as well as alginate crosslinkage.

Preparation methods of chitosan–alginate beads were mainly focused on single calcium crosslinking, such as chitosan-coating alginate calcium beads (Murata et al., 1996; Gåsevød et al., 1998; Zhou et al., 2001; Shu and Zhu, 2002; Ribeiro et al., 2005), which were endowed with bioadhesion. On the other hand, alginate calcium beads contained chitosan powder were also widely researched (Murata et al., 1999; Tomoaki et al., 2000; González-Rodríguez et al., 2002; Murata et al., 2002), but the controlled

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properties of pH sensitivity, stability and site specific release under the gastrointestinal condition have not been sufficiently investigated. The alginate–chitosan blend gel beads have been prepared based on dual crosslinking with $CuCl_2$ and glutaraldehyde by Gotoh et al. (2004) and showed rapid adsorption of heavy metal ions in wastewater stream.

It is significant to study on preparation of stable ALG–CS beads by easy method, which are endowed with controlled release properties in oral such as stomach, small intestine or colon site-specific delivery. Our present work was to prepare the stable alginate–chitosan blend gel beads based on calcium chloride and sodium sulfate dual ionic crosslinking and study their release behaviors of protein model drug BSA in oral site-specific delivery system, which was different from traditional single crosslinked beads. We also investigated the influence of mass proportion of alginate and chitosan and the comparison with single crosslinked gel beads on delivery property.

2. Materials and methods

2.1. Materials

Chitosan was purchased from Zhejiang Yuhuan Ocean Biochemistry Co. Ltd. (China), and degree of deacetylation and molecular weight (M_w) were 90.2% and 210,000. BSA with M_w 68,000 was purchased from Sigma Chemical Co. (USA). Sodium alginate was purchased from Fuchen Tianjing Chemical Co. Ltd. (China). All other chemicals were of reagent grade.

2.2. Preparation of Ca^{2+} crosslinked blend gel beads

The blend solution contained 2% (w/v) sodium alginate and chitosan was prepared with mass proportions of 5:5, 6:4, 7:3, 8:2, 9:1 and 10:0. Firstly the certain amount of sodium alginate was dissolved in 30 ml distilled water at 40 °C under mechanical stirring for 5 min; the certain chitosan powder was added into the solution and mixed homogeneously. Then chitosan was dissolved by adding 0.3 ml acetic acid into the mixture; pH was adjusted to 5.0 by NaOH (0.1 mol/l) solution; homogeneous blend solution of two polymers was formed under stirring at 40 °C for 20 min. Lastly the blend solution was dripped through a 16# (the Chinese Pharmacopoeia 2005) injection needle into the 100 ml solution of 2% (w/v) calcium chloride; smooth and spheric beads were formed under mechanical stirring for 15 min; washed with distilled water three times and dried under vacuum at 40 °C.

2.3. Preparation of SO_4^{2-} crosslinked gel beads

Thirty milliliter of 2% (w/v) chitosan solution was obtained by addition of 0.3 ml acetic acid. pH was adjusted to 5.0 by 0.1 M NaOH solution. The solution was dripped through a 16# (CP2005) injection needle into the 100 ml solution of 2% (w/v) sodium sulfate to form SO_4^{2-} crosslinked gel beads under mechanical stirring for 15 min. The resultant weak gel beads were washed with distilled water three times and dried under vacuum at 40 °C.

2.4. Preparation of dual crosslinked blend gel beads

The above Section 2.2 prepared Ca^{2+} crosslinked beads without vacuum desiccation, were directly dipped into 50 ml solution of 2% (w/v) sodium sulfate for 15 min and then the Ca^{2+} and SO_4^{2-} dual crosslinked blend gel beads were obtained, washed by distilled water three times and then dried under vacuum at 40 °C.

2.5. Preparation of the BSA loaded blend gel beads

BSA, as a model protein drug, was dissolved with 20% (w/w, to the total weight of alginate and chitosan) after the formation of homogeneous blend solution. Then the other processes were the same as Section 2.2 or Section 2.4 preparation of Ca^{2+} or dual crosslinked blend gel bead.

2.6. Swelling analysis

2.6.1. Swelling degree determination

The dried blend gel beads were dipped in the buffer saline with the pH range from 1.0 to 9.0 at 37 °C for 24 h, the swelling degree of equilibrium (SDs) of beads was calculated from $SDs = (W_e - W_o)/W_o$; where W_e is equilibrium weight of beads in buffer saline and W_o is the absolutely dried weight of beads. Each W_o determination contained no less than 0.1 g beads, the average value of three samples was reported. Buffer salines, which readily provides different pH values required were prepared freshly from solutions of citric acid, dipotassium hydrogen phosphate, boracic acid, barbitone and NaOH, the strength of ion was adjusted by NaCl. The solution media of pH 1.0 was simulated gastric fluid, consisting of 0.1 mol/l hydrochloric acid.

2.6.2. Swelling kinetics

The dried blend gel beads were dipped in SGF, SIF or SCF at 37 °C. The swollen beads were periodically removed and weighed. The wet weight of the swollen beads was determined by blotting them with filter paper to remove moisture adhering to the surface, immediately followed by weighing on an electronic balance. All experiments were done in triplicate. The percentage of swelling of the beads was calculated from the formula: $SW = (W_t - W_o)/W_o$; where W_t is the weight of beads at appropriate intervals in buffer saline and W_o is the absolutely dried weight of beads. Each W_o determination contained no less than 0.1 g beads.

2.7. Morphology characterization

The particle size of the single and dual crosslinked dried beads were measured with a micrometer (Mittotuyo Micrometer, NSK Co., Japan) and calculated as the average value of the size of 100 beads.

The prepared wet beads without vacuum desiccation were dried by a freeze dryer; a gold layer was coated on the surface, morphologies of specimens were then examined by using an EDAX (S-570, Hitachi, Japan) scanning electron microscope (SEM).

2.8. Release of the BSA in vitro

The in vitro BSA release profiles of beads were determined as follows: the BSA loaded beads were placed into conical flask with 50 ml of release medium and incubated at 37 °C under shaking 100 strokes/min. The release media were SGF (pH 1.0), SIF (pH 6.8) and SCF (pH 7.4), prepared according to the Chinese Pharmacopoeia 2005, respectively. At appropriate intervals, 5 ml of the solutions were replaced by fresh medium. The amount of BSA released from the beads was evaluated at 280 nm using a UV–vis spectrophotometer. The sample absorption degree was detected by using non-loaded BSA beads as correction. All samples were analyzed in triplicate.

3. Results and discussion

3.1. The swelling behaviors of beads

The swelling degree of equilibrium in different buffer saline with pH 1.0, 3.0, 5.0, 7.0, 9.0 was shown in Figs. 1 and 2. Fig. 1 showed swelling behaviors of Ca^{2+} single crosslinked beads, which indicated that the Ca^{2+} single crosslinked beads that contained chitosan were sensitive at low pH; increasing the mass ratio of chitosan promoted the SDs of beads. Carboxyl of alginate was ion-crosslinked by Ca^{2+}; the beads contained chitosan swelled rapidly, which resulted from protonation of the amino of chitosan at lower pH. Ca^{2+} single crosslinked beads were not stable at higher pH of 7.0, Dainty et al. (1986) reported that the disruption of calcium–alginate gel matrix occurred fast in phosphate buffer solution with pH above 5.5 due to the chelating action of phosphate ions. The affinity of phosphate for calcium is higher than that of alginate (Liu et al., 1997).

However, the dual crosslinked gel beads showed completely different properties, Fig. 2 showed the swelling behaviors of Ca^{2+} and SO_4^{2-} dual crosslinked blend gel beads. The

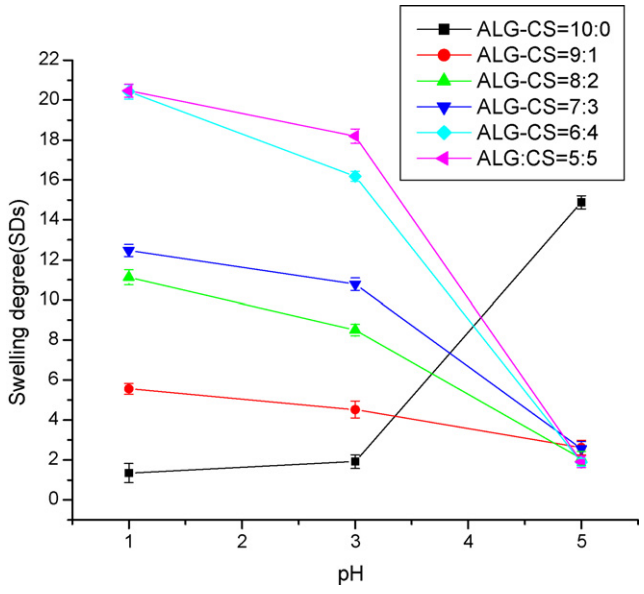

Fig. 1. Swelling behavior of different formation of ALG–CS Ca^{2+} crosslinked blend gel beads, $n = 3$.

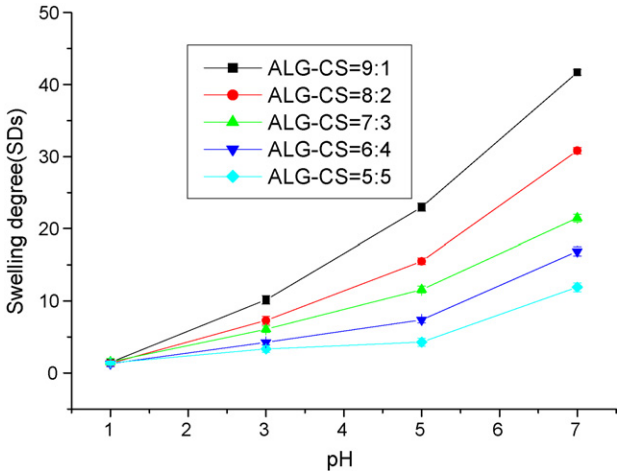

Fig. 2. Swelling behavior of different formation of ALG–CS Ca^{2+} and SO_4^{2-} dual crosslinked blend gel beads, $n = 3$.

higher the pH value and the alginate mass ratio, the higher the SDs. The amino groups of chitosan were crosslinked by SO_4^{2-}, which restrained the swelling of beads at lower pH, and endowed the beads with higher mechanical strength. In SGF (pH 1.0), there was no obvious difference of SDs among all formations of gel beads. It could be explained that stable ion crosslinking reactions under the condition resulted in low swelling degree. With the increase of pH, carboxyl groups of alginate that were not crosslinked by Ca^{2+} or disrupted from calcium–alginate crosslinking network were ionized and absorbed water, which resulted in higher SDs. Ca^{2+} single crosslinked beads were rapidly disintegrated in higher pH (>7.0), while the dual crosslinked beads were disintegrated after dipped in pH 9.0 buffer saline for 4–7 h. The dual crosslinked network structure was much stronger than the single one. The SO_4^{2-} single crosslinked blend gel beads were also prepared, but their mechanical strength was too weak to be tested SDs.

The swelling kinetics was also studied. Fig. 3 showed the Ca^{2+} single crosslinked beads swelling kinetics in SGF. The result indicated that the swelling equilibrium time was increased with the increase of mass ratio of ALG due to the ion permeation protection effect of alginate (Anal and Stevens, 2005; Tang et al., 2005). The swelling kinetics of Ca^{2+} single crosslinked beads in SIF and SCF were not investigated due to their burst disintegration. Fig. 4 showed dual crosslinked beads swelling kinetics in SIF and SCF. In SIF, the increase of ALG promoted SDs; swelling equilibrium time of all formations were about 5 h. In SCF, all the beads swelled associating with slight erosion. We studied the swelling kinetics during a shorter time. The result indicated that the dual crosslinked beads swelled faster and got higher SDs in SCF than in SIF.

According to Donnan equilibrium, SDs depends on concentration difference of outer and inter ion of beads, when anion and cation of amphoteric polyelectrolyte is far from equilibrium, the osmotic pressure of free ion increased in the beads. At the isoelectric point, the amount of $-NH_3^+$ and $-COO^-$ is equal, the concentration of free ion in the beads is the lowest, the beads will shrink by outer osmotic pressure. The pKa of alginate is

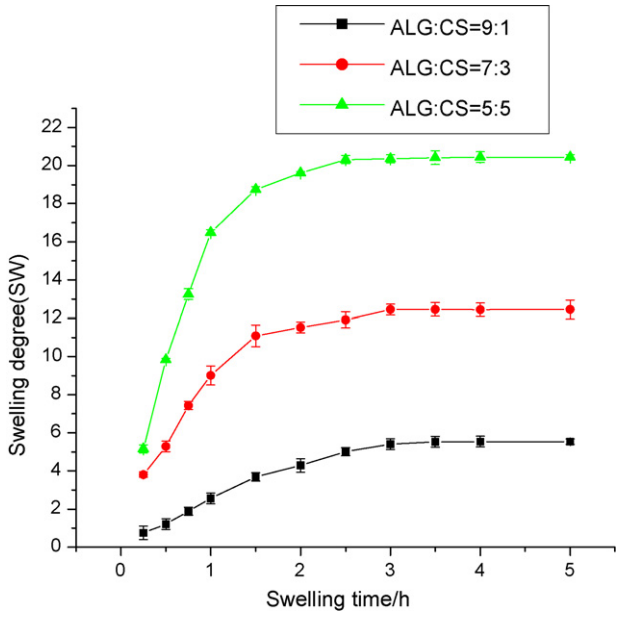

Fig. 3. Swelling kinetics of different formation of ALG–CS Ca^{2+} crosslinked blend gel beads in SGF, $n = 3$.

from 3.38 to 3.65 (Simsek-Ege et al., 2003); the pK_a of chitosan is around 6.3 (Claesson and Ninham, 1992); the lowest SDs of the beads should be at pH 4–6, which is not correlated well with what was shown in Figs. 1 and 2; this could be explained by integrative effect of hydrogen bond, van der waals' force, hydrophobic interaction between alginate and chitosan and the crosslinked network (Chen et al., 2004). At lower pH (1–3), as to the single crosslinked beads, difference of SDs is mainly controlled by the formation of $-NH_3^+$ of chitosan, but that of dual crosslinked beads is controlled by the structure of crosslinked chitosan network. At higher pH (5.0–7.0), dual crosslinked network promotes greatly the mechanic strength of beads and the SDs of dual crosslinked beads (pH 5.0) is much higher than that of the single crosslinked beads, which could result from Ca^{2+} partly disrupting from crosslinked alginate network when crosslinking occurs between chitosan and SO_4^{2-}.

3.2. Morphological characterizations

3.2.1. Beads size dispersal

The shape of the Ca^{2+} crosslinked beads was spherical. Increasing the mass ratio of alginate, the shape of the beads was more regular. The shape of Ca^{2+} and SO_4^{2-} dual crosslinked

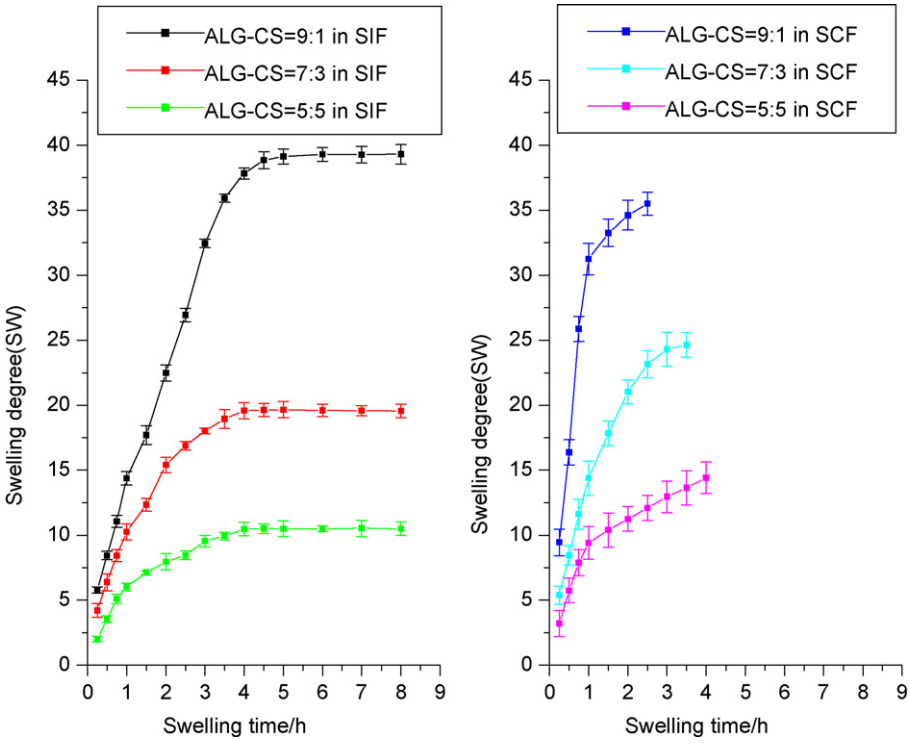

Fig. 4. Swelling kinetics of different formation of ALG–CS Ca^{2+} and SO_4^{2-} dual crosslinked blend gel beads in SIF and SCF, $n = 3$.

Table 1
The mean size of all formations of single and dual crosslinked beads

	Formations (mass ratio ALG:CS)					
	10:0	9:1	8:2	7:3	6:4	5:5
Ca^{2+} crosslinked (mm)	1.003 ± 0.1768	1.534 ± 0.3224	1.568 ± 0.0794	1.684 ± 0.0958	1.748 ± 0.1170	1.924 ± 0.2369
Dual crosslinked (mm)	–	1.466 ± 0.1328	1.506 ± 0.0392	1.532 ± 0.2242	1.69 ± 0.1458	1.876 ± 0.1652

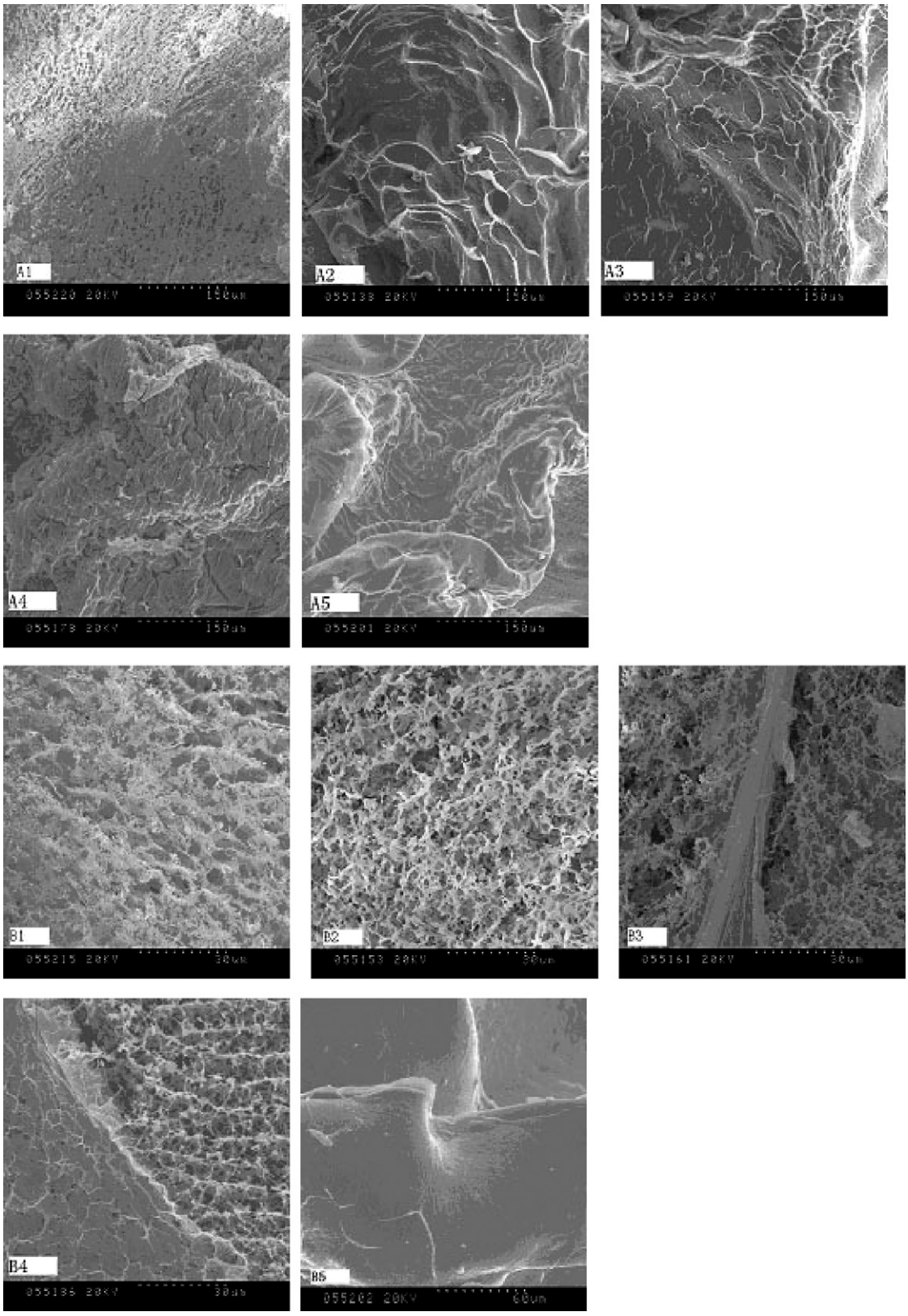

Fig. 5. SEM micrographs of dual crosslinked beads. Group A: the surface of beads, group B: the section of beads, 1–5: ALG–CS mass ratios 0:10, 5:5, 7:3, 9:1 and 10:0.

beads were not as regular as the former. The mean size of all formations of blend gel beads was shown in Table 1. The diameter of dual crosslinked beads was less than that of single crosslinked beads, which suggested the shrinkage of beads occurs during the second step crosslinking. Increasing the mass ratio of alginate, the diameter was also decreased, which indicated that the crosslinked network of alginate is more compact than that of chitosan.

3.2.2. Morphology of dual crosslinked blend gel beads

The SEM of various mass ratios dual crosslinked beads by freezing dryer was shown in Fig. 5. The surface and section morphology of the ALG–CS formations with 10:0, 9:1, 7:3, 5:5 and 0:10 were observed. Group A (A1–A5) indicated that the surface of the beads was smoother with the increase of alginate. The SEM A1 was the single chitosan SO_4^{2-} crosslinked gel beads. There was much wrinkle resulting from the interaction between ALG and CS in A2 and A3 (mass ratio of ALG–CS 5:5 and 7:3); A4 and A5 (mass ratio of ALG–CS 9:1 and 10:0) were much smoother. Lai et al. (2003) explained that the blend system could have formed a random fibrillar network. Group B was the section of beads with different formations. As to the single formation of alginate or chitosan crosslinked beads, the former were much more compact than the latter; many pores were shown in the latter. Increasing the mass ratio of alginate, the degree of compaction was increased, which is in accordance with the results of size determination of blend gel beads.

3.3. The BSA release in vitro

Based on the above swelling and morphological characterizations, the sustained release behavior of representative beads with the mass ratios of ALG–CS 5:5, 7:3, 9:1 and 10:0 was investigated in small intestine or colon site specific environment. The BSA encapsulation efficiency of all beads was high (>97%), the detail data were not shown here.

3.3.1. BSA release profiles of Ca^{2+} single crosslinked beads

Figs. 6–8 showed the BSA release profiles in SGF, SIF and SCF, respectively. Fig. 6 indicated that BSA was released continuously from the beads in SGF in 8 h. As to all formations, BSA cumulative release percentages of all beads were higher than 80% in 5 h. The higher the mass ratio of chitosan, the faster the BSA release. It was coincident with the swelling trend in SGF. Fast swelling and high SDs behaviors of higher mass ratio of chitosan promoted BSA release. As shown in Figs. 7 and 8, due to rapid disintegration in higher pH (about 7), the Ca^{2+} single crosslinked beads were soon disintegrated in SIF and SCF associated with burst release of BSA.

3.3.2. BSA release profiles of dual crosslinked beads

The BSA release behaviors of dual crosslinked beads were studied in SGF, SIF and SCF. There was less than 3% BSA released from all dual crosslinked beads in SGF in 4 h. After dipped in SGF 10 days, the total release was less than 50%, and all dual crosslinked beads were still stable.

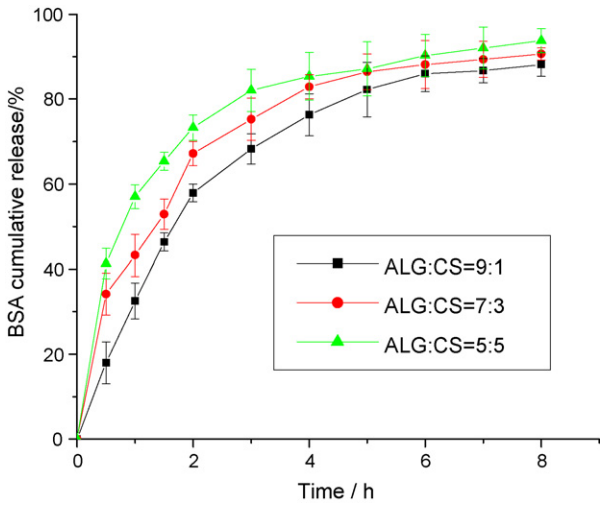

Fig. 6. The BSA release data of the Ca^{2+} crosslinked blend gel beads of the different formations in SGF, $n = 3$.

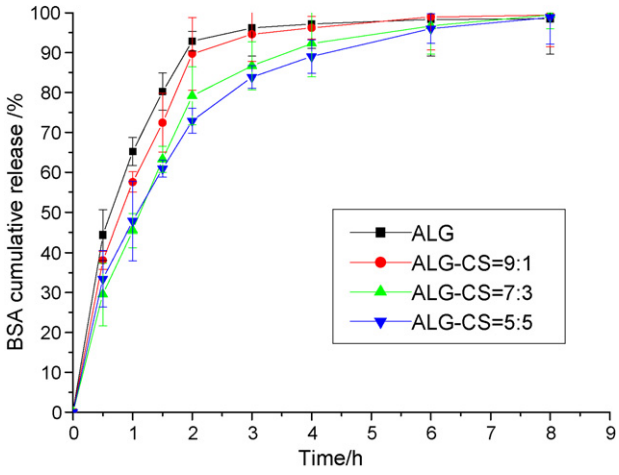

Fig. 7. The BSA release data of the Ca^{2+} crosslinked blend gel beads of the different formations in SIF, $n = 3$.

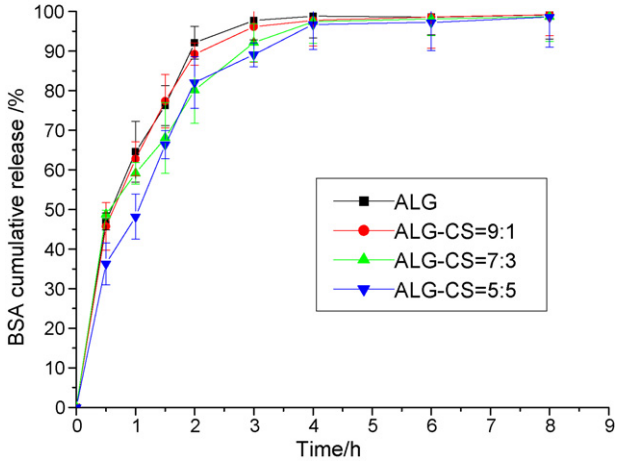

Fig. 8. The BSA release data of the Ca^{2+} crosslinked blend gel beads of the different formations in SCF, $n = 3$.

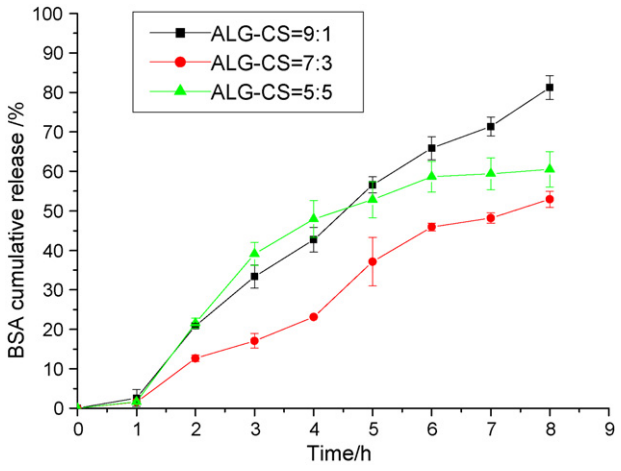

Fig. 9. The BSA release data of the dual crosslinked blend gel beads of the different formations in SIF, $n = 3$.

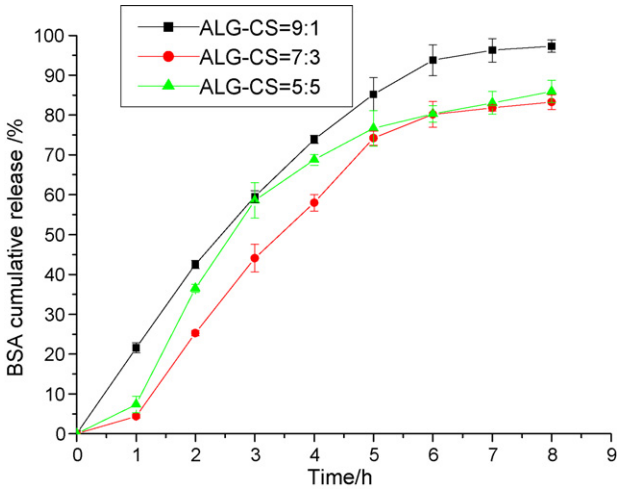

Fig. 10. The BSA release data of the dual crosslinked blend gel beads of the different formations in SCF, $n = 3$.

3.3.2.1. BSA release behavior in SIF. Fig. 9 showed the release profiles of BSA from different formations of dual crosslinked beads in SIF. BSA total release from formation ALG–CS 5:5, 7:3, 9:1 was respectively 33.38, 17.09, 39.09% in 4 h, which was much lower than that from the single crosslinked beads. BSA release speed of beads with mass ratio ALG–CS 7:3 was much slower than that of 9:1 and 5:5. The BSA total amount (81.24%) released from ALG–CS 9:1 was much higher than those of other two formations (less than 60%) in 8 h. As shown in SEM and size of beads analysis, with the increase of chitosan, the dual crosslinked beads showed looser structure, and many micropores which made for drug release were formed in the beads during subsequently SO_4^{2-} crosslinking. As shown in swelling studies, with the increase of chitosan, the dual crosslinked network was more stable and the swelling degree was decreased obviously. Chitosan molecule has both amino and hydroxyl groups that can couple with proteins under mild conditions (Yang et al., 2001). Hydrophobic interactions between chitosan and BSA inside the network were favored. Strong charge to charge interactions have been demonstrated between protein and chitosan with a less cumulative release amount of protein even upon dissolution of the chitosan matrix (Ma et al., 2002). BSA release speed could be influenced concurringly by these factors.

3.3.2.2. BSA release behavior in SCF. Fig. 10 showed the release behavior of BSA from dual crosslinked blend beads in SCF. Compared with in SIF, the release trend of all formations was the same, but the BSA release percentages were dramatically increased at the same interval. The BSA release from the formation ALG–CS 9:1 was much faster than that from the others and BSA total release was up to 97.31% in 8 h, which is consistent with the swelling kinetics studies: the ion-crosslinking between calcium and alginate was less stable at higher pH value (>7), and the swelling degree of dual crosslinked beads was enhanced with the increase of alginate.

3.3.2.3. The BSA release behavior in gastrointestinal tract conditions. Dual crosslinked blend gel beads were incubated in SGF for 4 h firstly, then in SIF for 3 h, lastly in SCF for 3 h, their release behaviors were shown in Fig. 11. The cumulative release of BSA of ALG–CS 9:1, 7:3 and 5:5 was respectively 2.35, 1.96, 1.76% (in SGF 4 h), 82.86, 78.83, 52.91% (in SIF 3 h) and 97.84, 96.81, 87.26% (in SCF 3 h). Compared with the release behavior only in SGF or SIF, there were some differences under the simulated gastrointestinal tract condition. BSA release from the three formations was no more than 3% in SGF for 4 h. Transferring into the SIF, the BSA release rate was higher than only in SIF, and BSA release was accelerated with the increase of alginate. Being displaced into SCF, the surplus BSA was almost completely released in 3 h. With the increase of chitosan mass ratio in the dual crosslinked gel beads, the sustained effect was more obvious, which was resulted from the stability and lower swelling property of the beads under small intestinal and colonic conditions as shown in swelling studies. The beads with mass ratio ALG–CS 5:5 showed the slowest release in SGF

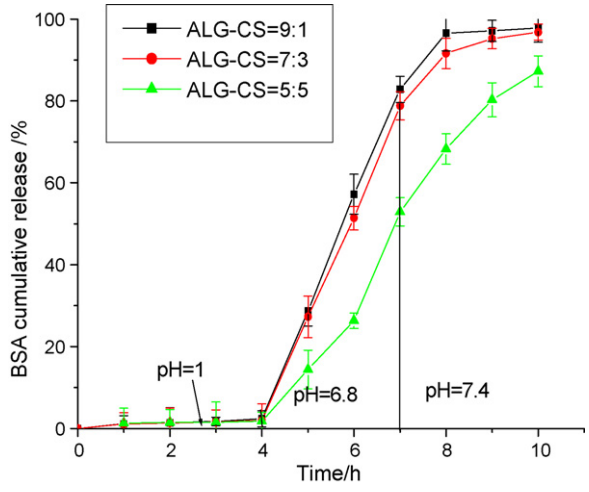

Fig. 11. The BSA release data of the dual crosslinked blend gel beads of the different formations in different pH conditions, in SGF, SIF and SCF for 4, 3 and 3 h, respectively, $n = 3$.

and SIF. As shown in SEM studies, the beads with the mass ratio ALG–CS 5:5 was more porous than that of ALG–CS 7:3 for the ion permeation protection effect of alginate (Anal and Stevens, 2005; Tang et al., 2005); BSA release seemed to occur both by diffusion and erosion of the dual crosslinked blend gel beads in SIF and SCF. The disintegration of the beads was pH-dependent. The micropores contained in beads absorbed some SGF during dipping for 4 h and then transferred into SIF, the pH value of inner beads of ALG–CS 5:5 was lower than that of ALG–CS 7:3, 9:1, which maybe result in the lowest BSA release.

Compared with Ca^{2+} single crosslinked gel beads, from which BSA released fast in SGF (BSA cumulative release of all formations were about 80% in 4 h) and soon disintegrated in SIF and SCF, dual crosslinked beads had the potential for intestine or colon site-specific drug delivery.

As for pellets of chitosan and alginate prepared by extrusion/spheronisation without crosslinking, there was no significant advantage by using a mixture of the two polymers in terms of retarding drug release (Onal and Zihnioglu, 2002). As for Calcium crosslinked alginate gel beads containing chitosan salt powder, taurocholic acid rapidly released from in SGF (Murata et al., 1999). Chitosan coated alginate microspheres loading insulin (Chatchawalsaisin et al., 2004), albumin (Anal et al., 2003), and hirudin (Chandy et al., 2002), alginate at the surface has a very low content of negative charges and cannot interact strongly either with calcium or positively charged chitosan (Huguet et al., 1994). The stability of chitosan coated alginate capsules was shown to depend strongly on the amount of chitosan bound to the microspheres, the multi chitosan-coating alginate calcium beads decreased the burst release under SGF, but after a 4 h incubation of coated microspheres in SIF, dark-pointed sponge-like precipitates was shown (Ribeiro et al., 2005). Chitosan–alginate multilayer beads offer an opportunity for controlled gastrointestinal passage (Anal and Stevens, 2005), which was prepared by multi-processing based on combinations of chitosan and Ca^{2+} as cationic components and alginate and polyphosphate as anion. We prepared the novel alginate–chitosan blend gel beads based on simple dual crosslinking, which are very stable in SGF, SIF and SCF, and have the controlled release properties in SIF or SCF by adjusting the formation of ALG–CS mass ratio. The short release time from formation ALG–CS 9:1 is due to the low stability of the chelating junction of alginate in phosphate buffer above pH 5 (Liu et al., 1997). The longer release time from formation ALG–CS 5:5 and 7:3 due to sulfate ion stabilizing the chitosan salt, amino groups in chitosan coupling with BSA (Yang et al., 2001). The BSA release may be controlled by diffusion and erosion of the dual crosslinked blend gel beads in SIF and SCF. The disintegration of the beads is obviously pH-dependent. The dual crosslinking effectively promotes the stability of beads and prolongs the sustained release time of BSA, illustrating that the chitosan may play a key role in dual crosslinked blend gel beads. The dual crosslinked blend gel beads, especially with the formation contained relatively more chitosan, are stable and suitable for the small intestine or colon specific drug delivery.

4. Conclusion

Experiments were done to prepare alginate–chitosan blend gel beads suitable for oral site-specific drug specific drug sustained release. The beads were prepared by dripping an ALG–CS blend solution into calcium, transferring the calcium crosslinked gel beads into sodium sulfate. In vitro release studies showed little BSA is released from all blend beads in SGF; the BSA total release from the beads of ALG–CS mass ratio 9:1 is higher than that of 7:3 and 5:5 in SIF; the BSA release from all blend beads is much faster in SCF than in SIF. The beads were incubated in gastricintestinal tract conditions, which indicated dual crosslinked ALG–CS blend gel beads are potential drug carriers for small intestinal or colon specific drug delivery system.

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