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Preparation and Properties Evaluation of Chitosan/Alginate Hydrogels in Drug Controlled Release

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pH-sensitive hydrogels based on chitosan-sodium alginate was synthesized by using glutaradehyde as cross-link agent. The effects of the degree of the dosage of crosslinking and pH on the swelling behaviours of the hydrogel have been studied and the swelling ratio of this hydrogel in acide solution is much larger than that in alkaline solution. The release behaviour of bovine serum albumin entrapped in the hydrogels was of distinctly difference with the changes of pH value of loading medium. The release of bovine serum albumin in those two kinds of hydrogels in the medium of pH=1 was much quicker in pH=7.4 and 9.18. The amount of bovine serum albumin released from the films at different time intervals was estimated by UV spectrophotomertic method at 279 nm. The dissolution profile and *in vitro* release kinetics showed that chitosan-sodium alginate hydrogels were promising for controlled delivery of the drug. Formulation containing chitosan and sodium alginate may be suitable as a coating formulation for colon targeted drug delivery.

Keywords: Chitosan, Sodium alginate, Bovine serum albumin, Controlled release.

INTRODUCTION

Chitosan is the deacetylated derivative of chitin[1-5], the most abundant natural polymer on earth after cellulose[6-8], obtained from crustaceans[9-12], such as shrimps, squids and crabs. Chitosan is the only basic polysaccharide in nature. It is greatly dominant to be used as a drug carrier due to the non-toxicity[13]. Chitosan with good biocompatibility and biodegradation has widely application in many fields, such as wastewater treatment[14-16], medicine, food, drug, environmental protection, light industry and agriculture[16-22].

Sodium alginate widely exists in all kinds of natural polymer in the brown seaweed, can form simple gel with multivalent cations under mild conditions and the gel is non-toxic and suitable for embedding materials as a drug.

This research selects chitosan and sodium alginate as the research object and the effect of crosslinking agent, pH value on swelling rate are studied and the effects of the performance of drug release are also investigated.

EXPERIMENTAL

Chitosan and sodium alginate (Deacelation degree 80 %) were purchased from Fuda Chemical Co. in China. Glutaraldehyde (GA, 50 wt % in water) and glacial acetic acid were purchased from Across, Morris Plane, NJ; Bovine serum albumin; buffer solution (pH=1.70, 4, 7.4, 9.18). All commercially solvents and reagents were used without further purification. All other chemicals were of analytical grade.

Preparation of hydrogels: A series of hydrogels with 3.2 wt. % total solid but different composition were generated mixing sodium alginate and chitosan in different amount. Chitosan-sodium alginate hydrogels were prepared in hot water (50 ± 0.5 °C containing 1 wt % acetic acid) with vigorous stirring (1000 rpm) 1.5 h. After complete interdispersion of the solution, glutaraldehyde (2 wt %) was added to the chitosan, sodium alginate solution, to get a series of different glutaraldehyde concentration solutions, under thorough and continuous mixing (550 rpm) 1 h to crosslink the gelatin and form the hydrogels.

Once formed, all hydrogels were degassed and spread over the bottom of petri dishes (100 mm diameter) or polycarbonate rectangular templates (300 mm length × 150 mm width) depending on the specific successive analysis. Final hydrogels were obtained after evaporation of water in a vacuum oven at 40 ± 0.5 °C for 24 h. Crosslinked hydrogels were additionally washed several times with Milli-Q water and then air-dried room temperature for 24 h.

FT-IR analysis: FT-IR spectra were recorded using a Spectrum One spectrophotometer (NICOLET 200SXV FT-IR, Perkin Elmer, USA) equipped with an Universal Attenuated Total Reflectance (UATR) device for tablet analysis in the spectral region (4500-500 cm^{-1}).

Swelling behaviour: To evaluate the water sorption resistance of the CS-GA films, square piece of dry samples were weighed (W_i) and then immersed in distilled water at 30 °C

with shaking (100 rpm) for up to 24 h. Swollen hydrogels were removed from water periodically, blotted dry and weighed (W_f) to track sportion kinetics. The swelling rate (SR) was determined expression by the folloiwng:

$$SR\ (\%) = \frac{(W_f - W_i)}{W_i} \times 100$$

Dissolution tests *in vitro*: Hydrogels samples (0.5 ± 0.001 g) were accurately weighed and immersed in bovine serum albumin solution (bovine serum albumin, 0.5 wt %) at 0 °C for 25 h. The swollen hydrogels loaded with drug were placed in a vacuum oven and dried under vacuum at 37 °C. The loading amount of drug in the hydrogels was calculated from the decrease in the concentration for the bovine serum albumin solution (279 nm) which was determined using a UV spectrophotometer (UV-2401-PC, Shimadzu, Kyoto, Japan).

The kinetics of drug release were recorded using a Distek TM dissolution 2100 A paddle system (500 rpm, 37 ± 0.5 °C) coupled with an UV Hewlett Packard spectrophotometer for detection of bovine serum albumin and presented using the diffusion equation as the ratio of the amount of drug released at the time t(M_t)/the total amount (M_{inf}) of the drug release from the hydrogels. The concenteation of bovine serum albumin in the samples was calculated based on average calibration curves (n = 6). All dissolution studies were performed in triplicate.

RESULTS AND DISCUSSION

Best proportion of chitosan and sodium alginate: Five batches of hydrogels (CA-1, CA-2, CA-3, CA-4, CA-5) were prepared with increasing concentration of polymer sodium alginate of 25, 37.5, 50, 62.5 and 75 % relative to total solid weight in Table-1.

TABLE-1
CHOICE OF BEST RATIO TO
CHITOSAN AND SODIUM ALGINATE

Samples	Sodium alginate (g)	Chitosan (g)	Glutaraldehyde (mL)	Glacial acetic acid (mL)	Swelling rate
CA-1	0.2	0.6	1.28	5	5.9052
CA-2	0.3	0.5	1.28	5	3.2505
CA-3	0.4	0.4	1.28	5	2.4666
CA-4	0.5	0.3	1.28	5	1.7676
CA-5	0.6	0.2	1.28	5	1.8920

Table-1 was used to ensure that the CA-4 hydrogels of swelling rate was the smallest because the charge between $-COO^-$ and $-NH_3^+$ was equal, just as isoelectric point. Therefore, the swelling rate is smaller at the point. The best ratio of chitosan and sodium alginate was 3:5.

According to the best ratio of chitosan and sodium alginate, five batches of hydrogels (A, B, C, D, E) were prepared with increasing concentration of glutaraldehyde (GA, 2.5 %) of 1.28, 3.84, 5.12, 6.4 and 8.48 % relative to total solution weight.

FT-IR analysis: FT-IR spectroscopy was used to ensure that the crosslinking reaction between the chitosan and sodium alginate had occurred. From the FT-IR spectral interpretation the following result were obtained. The FTIR of chitosan show intense band at 1600 cm^{-1} correspongding to the functional group $-NH_2$ bending. And the FT-IR of sodium alginate show the band at 1732 cm^{-1} belongs to the -COOH stretching vibration peak.

The absorption peaks at 1531 cm^{-1} can be assigned to the $-NH_2$ bending vibration of gelatine. In contrast, after crosslinking, the vibrational band corresponding to primary amino groups at 1600 cm^{-1} weaken and the vibrational band at 1662 cm^{-1} disappeared (Fig. 1), which prominent bands at 1428 cm^{-1} was ascribed to $-COO-NH_2$. These results clearly confirmed that the crosslinking reaction had occured between the polymers.

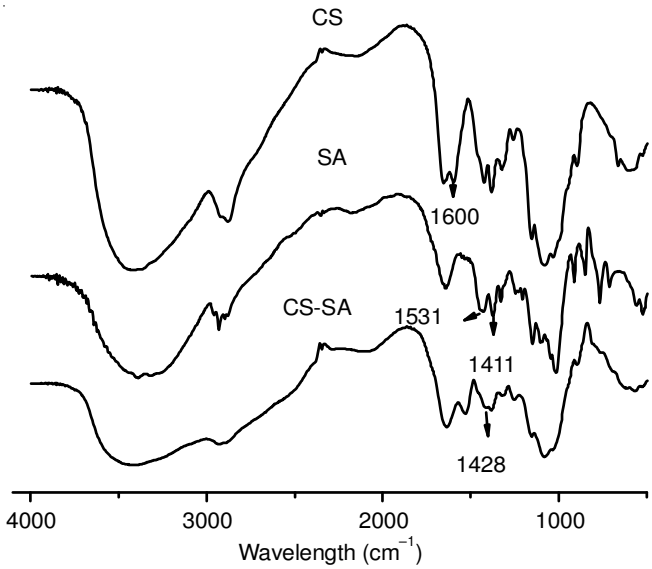

Fig. 1. IR spectrum of chitosan (CS), sodium alginate (SA) and chitosan-sodium alginate hydrogel

Effect of crosslinking agent on the swelling of hydrogel: Hydrogel swelling ratio reduced with increasing the amount of crosslinking agent in Fig. 2, this is because that the amount of crosslinking agent decreased, not only the molecular chain crosslinking density among chitosan and sodium alginate is low, but also the chain network structure of hydrogel molecular is loose and free space. Furthermore, there are strong hydrophilic interaction between -OH, -COOH and $-NH_2$ groups, so the hydrogel interior can hold a lot of water and keep the larger degree of equilibrium swelling. However, when the amount of crosslinking agent increased, the crosslinking density of the hydrogel increases and the network structure and grid are reduced, therefore, water molecular inward permeability effective channel pore contract, so the equilibrium swelling degree reduced.

Effection of pH on chitosan-sodium alginate hydrogel swelling properties: The pH is a pivotal factor that can strongly influence on the swelling capacity of a film. At first, in order to survey the pH sensitivity of the hydrogel, swelling behaviour of the chitosan-sodium alginate hydrogel at 25 °C in water with the pH ranging from 1 to 9.18 was investigated. The swelling rate of the film decreased in the pH rang between 1 to 4 and from 7.4 to 9.18, but it is increased with increasing pH from 4 to 7.4. The minimum swelling rate of the film was achieved at pH 9.18 (Fig. 3).

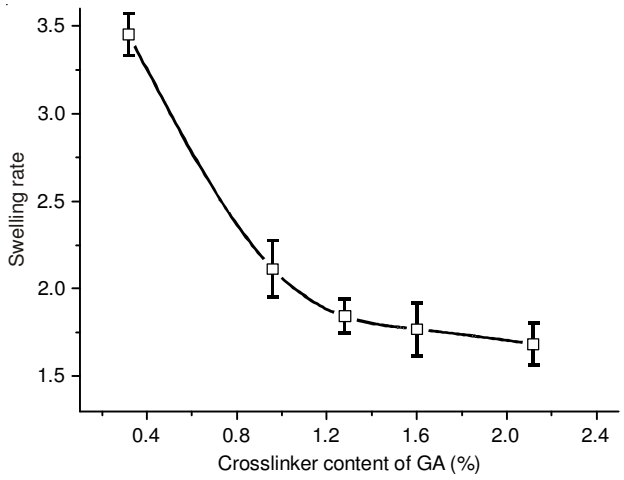

Fig. 2. Effect of crosslinking agent on the swelling degree of hydrogels

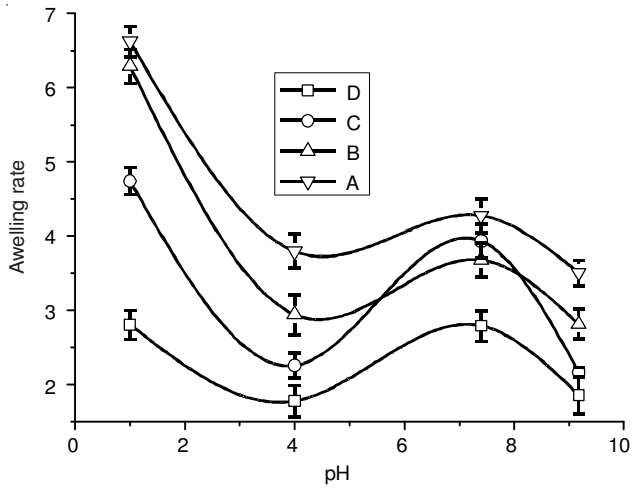

Fig. 3. Room temperature the affection of pH value on the swelling ratio of chitosan-sodium alginate hydrogels

Swelling rate in different buffer solution with pH sensitivity is different, this is because of the polar groups such as -COOH, $-NH_2$, -OH and other else in the hydrogels and the difference of the degree of ionization. In the solution of pH 1, $-NH_2$ in chitosan-sodium alginate composite hydrogel is protonated into $-NH_3^+$, increased the electrostatic repulsion and hydrophilicity, leading to swelling degree greater. In pH 4, the swelling rate is lower, because that protonation degree and mutual electrostatic repulsion effect were weakened. In pH 9.18 solution, composite membrane was in isoelectric point, thus swelling degree was minimum.

Drug release kinetics from chitosan-sodium alginate hydrogel in different pH buffer solution: A as drug-loaded hydrogel carrier, was accurately weighed into three part composite membrane of A. The drug loading rate were 7.037×10^{-5}, 6.385×10^{-5}, 6.196×10^{-5} g/g, after immersing in 0.5 % (w %) bovine serum albumin solution for 34 h in room temperature. The release kinetics of bovine serum albumin from composite membrane in pH 1, 4, 7.4 and 9.18 buffer solutions are presented in Fig. 4. The sample of A in pH 1 solution rapidly disintegrated ($t_{90\%}$, 6 h), whereas those in other pH solution remained intact in aqueous medium. In pH 4-7.4 solutions, show relatively short release times ($t_{90\%}$, 12-16 h).

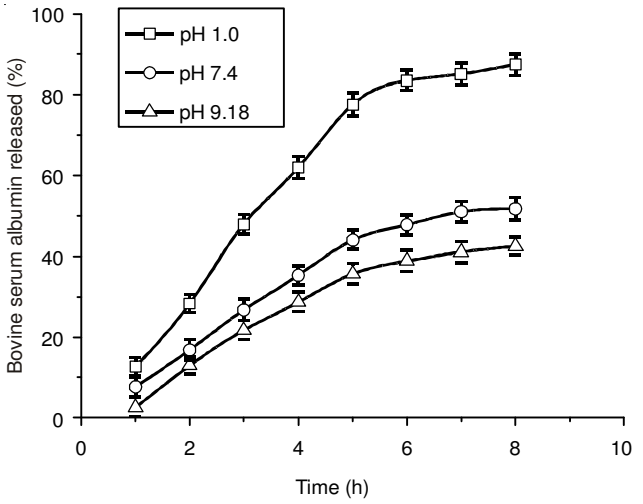

Fig. 4. Release curve of bovine serum albumin in different pH value solution

A longer release (36 h) was recorded for the pH 9.18 buffer solution. This is attributed to a hydrophobic barrier limiting access of water and dissolution of the drug. According to Peppas[23,24], there are three primary mechanisms by which the release of active agents can be controlled: erosion, diffusion and swelling followed by diffusion. Erosion may take palce *via* hydration or hydrolysis of the bulk, the polymer being slowly degraded starting at the periphery of the film. Diffusion can occur through the unhydrated polymer matrix but will generally be facilitated as the polymer gradually swells, in contact with the body fluids. Therefore, composite membrane as a carrier for colonic drug delivery has been demonstrated and was useful to achieve the best pH-dependent colonic drug delivery.

Effect of crosslinker content on the release of bovine serum albumin: The maximum drug release rate was sample A (crosslinking agent amount less), which also was the longest drug release (Fig. 5). Crosslinking agent concentration was higher (B and C), the release speed was slower, mainly because that crosslinking agent made the aperture of the hydrogel lesser,

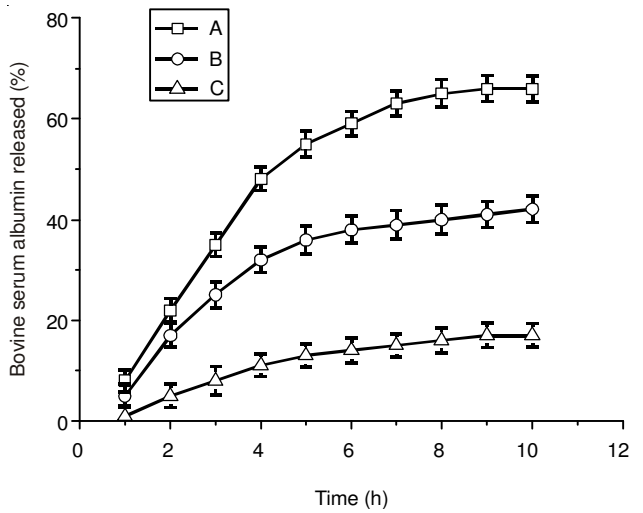

Fig. 5. Effect of different crosslinker content on the release of bovine serum albumin, at room temperature in pH 7.4 buffer solution

bovine serum albumin was not easy to release from it. The cumulative drug release rate were 40 and 16 %, respectively.

Conclusion

Chitosan-sodium alginate hydrogels are of interest for use as excipients in controlled drug delivery systems. Hydrophobic interactions are belived to enhance the stability of interactions of chitosan and sodium alginate. It suggested that the release of drug is controlled by diffusion, or by swelling followed by diffusion, depending on both the degree of crosslinking.

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