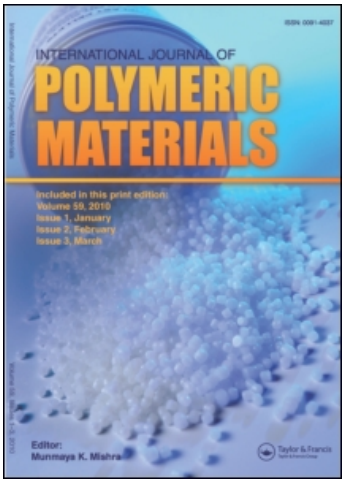

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Preparation and Properties of Drug-Loaded Chitosan-Sodium Alginate Complex Membrane

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Chitosan, sodium alginate and berberine complex membranes were prepared. The structure and properties of the drug-loaded membrane were studied using scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR) and thermal gravimetric and differential thermal analysis (DTA). The drug-release property of membranes with different ratios of chitosan and sodium alginate was also investigated. The results show that when chitosan and sodium alginate were mixed in weight ratio of 5:1, a polyelectrolyte complex film was formed and exhibited better thermal stability and stronger control ability over drug release.

Keywords berberine, chitosan, complex membrane, sodium alginate

INTRODUCTION

Chitosan is a natural carbohydrate biopolymer derived by deacetylation of chitin, a major component of the shells of crustacea such as crab, shrimp, and crawfish. Chitosan is very abundant in nature and has biodegradable and biocompatible properties. Chitosan also is a positively charged polymer, which gives it the ability to chemically bind with negatively charged materials [1]. Alginate is a linear negatively charged copolymer of β-D-mannuronate and α-L-guluronate and belongs to one of the polysaccharides extracted from seaweeds. Sodium alginate also has good biocompatibility and biodegradability [2]. Both natural polymers show excellent performance as membrane

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material, and good polyionic interaction between them. Hence, they are applied broadly in the pharmaceutical, biomedical, vaccinal and cell carrier fields [3–5]. Berberine, a yellow benzylisoquinoline alkaloid, is conventionally used as an antidiarrhetic, bitter stomachic, and antimalaria drug both in modern and traditional medicine in many countries. Berberine has a broad spectrum of antibacterial actions and shows strong antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as other micro-organisms [6,7]. The purpose of this study is to fabricate a drug-loaded membrane of chitosan in a mixture of different ratios with anionic polymer (sodium alginate), combining the good characteristics of both homopolymers and use the polyelectrolyte as drug carrier to control the release speed.

EXPERIMENTAL

Materials

Chitosan (90% degree of deacetylation) was purchased from Bangcheng Chemical Company of Shanghai. Sodium alginate was purchased locally. Berberine (purity $\geq$95%) was provided by Cayman Chemical Company. Acetic acid, sodium hydroxide and glycerin were all analytical grade.

Preparation of Complex Membrane Loaded with Berberine

Chitosan/sodium alginate/berberine membranes were produced by solution casting and solvent evaporation technique. 2 wt% solution of chitosan was prepared with 1 wt% acetic acid solution and distilled water. 2 wt% solution of sodium alginate was prepared with distilled water. Under mechanical stirring, the chitosan solution was dripped through a 8# injection needle into the sodium alginate solution. After that, berberine (0.8 mg) and glycerin (0.5%wt) were added and dissolved in the blended solution (60 ml), respectively. Then the mixed solution was stirred at room temperature for about 2 h to make a homogeneous blend. After the trapped air bubbles were removed by applying vacuum, the blended solution free of bubbles, was poured on a Teflon plate of 14.5 cm $\times$ 12.5 cm and then dried in an oven at 37°C. The complex membranes thus formed were immersed in 1 wt% solution of sodium hydroxide for a few minutes. After being taken out, the films were washed with distilled water and dried in atmosphere at room temperature. According to mass proportions of chitosan and sodium alginate, the complex membrane-loaded berberine was marked as CAB1 (5:1) and CAB2 (2:1), respectively. Pure chitosan film and sodium alginate film-loaded with drug was marked as CB and AB, respectively.

Morphology Observation

The surface morphology of membrane was observed using scanning electron microscope (SEM), Hitachi S-450 (Japan). Before observation, the samples were coated with a gold layer under vacuum.

FTIR Analysis

The FTIR spectra of pure and complex membrane loaded with drug were scanned using a NETZSCH FTIR spectrometer with ATR. The spectra were recorded between 600 cm^{-1} and 4000 cm^{-1} by 32 scans for each at a resolution of 4 cm^{-1}.

TG/DTA Analysis

Thermal scans of samples were obtained on a TG 209 F1 (NETZSCH). The testing was carried out from 20°C to 600°C in flowing nitrogen atmosphere (10 ml/min) at a heating rate of 20°C/min.

Release of Berberine in vitro

The membranes loaded with berberine were placed in beakers containing 50 ml of 0.9% sodium chloride solution, and incubated at 37°C to examine static release. At appropriate time intervals, 2 mL solution was withdrawn and the absorbency (A) was evaluated by UV spectrophotometry (Shimadzu UV 2550) at λ_{max} of 345 nm. An equal volume of fresh release medium was added back to maintain a constant volume. The amount of drug in release solution (C) was calculated using the standard equation ($A = 61.432C$, $R^2 = 0.9969$) established before. The accumulated amount of the released drug was calculated with the following equation:

$$cumulative\ release(\%) = \frac{amount\ of\ drug\ released\ from\ membrane}{total\ drug\ amount\ in\ membrane} \times 100(\%) \quad (1)$$

RESULTS AND DISCUSSION

Surface Morphology of Complex Membranes

The SEM micrographs of drug-loaded membrane are shown in Figure 1. The surface morphology of the chitosan/sodium alginate blends with 6:0, 5:1, 2:1 and 0:6 were observed. It indicated that the surfaces of all membranes were compact but the surfaces of CB and AB were smoother. There were many wrinkles resulting from the interaction between chitosan and sodium alginate

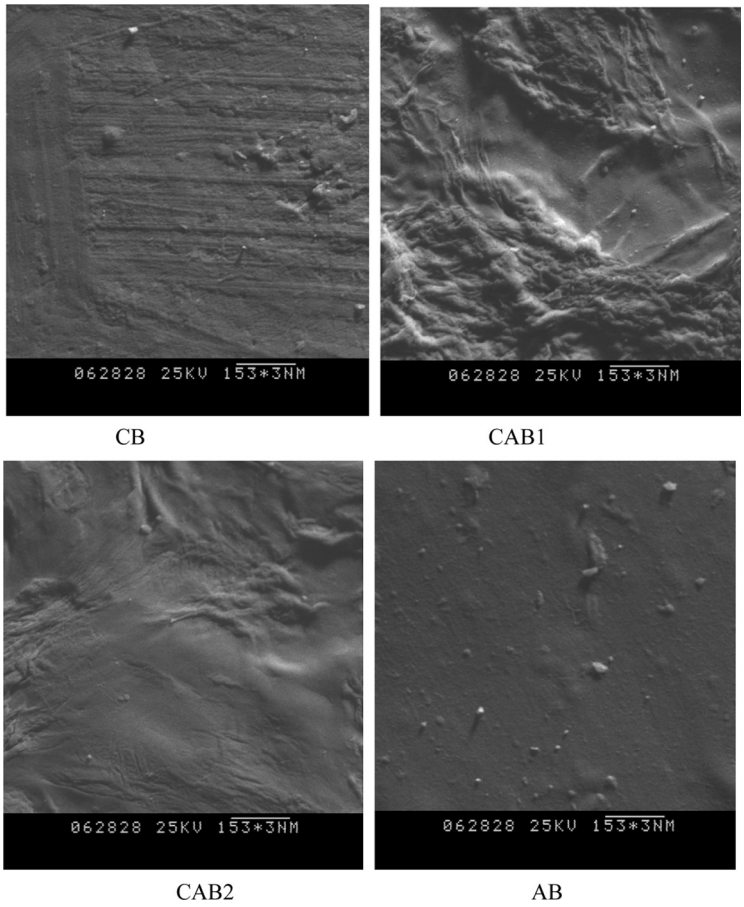

Figure 1: SEM micrographs of drug-loaded membrane.

in CAB1 and CAB2. It was explained that the blend system could have formed a random fibrillar network [8].

FTIR Spectra of Complex Membranes

FTIR spectra of the complex membranes are shown in Figure 2. The spectrum of chitosan and berberine blended film (CB) shows the characteristic absorption band at 1552 cm^{-1} ($-NH_2$ bending vibration). The bands at 1606 cm^{-1} and 1413 cm^{-1} present in the spectrum of sodium alginate drug-loaded film (CB) were assigned to antisymmetric and symmetric stretching of $-COO^-$. In spectra of complex membranes with different mass ratios, antisymmetric stretching of $-COO^-$ in sodium alginate moved to lower bands and appeared at 1546 cm^{-1} (in CAB2) and 1595 cm^{-1} (in CAB1). With the addition of sodium alginate, the bending of amino in CB moved to a higher

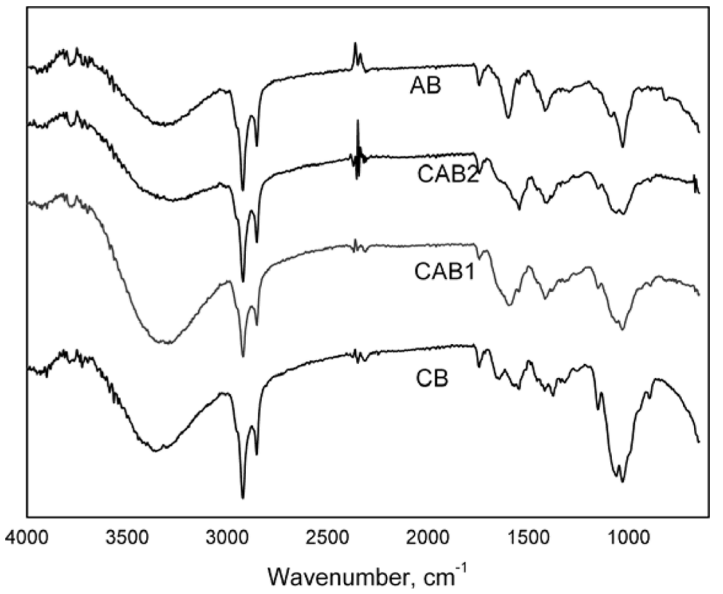

Figure 2: FTIR spectra of various membranes.

wavenumber and overlapped the peak of antisymmetric stretching of $–COO^-$, which confirmed the presence of polyionic interaction of cationic chitosan with anionic sodium alginate through electrostatic interactions.

If the stretching peak of the hydroxide group strengthens and moves to lower absorption bands, hydrogen bonding would be expected to increase, that is, intermolecular interactions would increase [9]. The bands at 3365.8 cm^{-1} and 3307.9 cm^{-1} were attributed to stretching of –OH in CB and AB, respectively, while it is observed that the peak of –OH stretching in a complex membrane moved to a lower wavenumber, 3296.3 cm^{-1} in CAB1 and 3280.9 cm^{-1} in CAB2, resulting from strong hydrogen bonding between chitosan and sodium alginate in polyion complex.

TG-DTA Analysis of Complex Membrane

TG and DTA curves are presented in Figures 3 and 4. DTA curves of pure drug-loaded membrane and complex membranes showed the formation of an endothermic peak at near 133°C and 143°C, respectively, resulting from water elimination. TG curves showed that CAB1 began to lose weight quickly at 238°C and the weight loss reached 45% at 310°C. The weight loss of CAB1 reached 40% between 238°C and 310°C, which was the main extent of weight loss. CAB2 lost weight quickly from 238°C and the weight loss reached 40% between 238°C and 310°C. The weight loss of drug-loaded chitosan film reached about 60% at 310°C. DTA curves indicated that

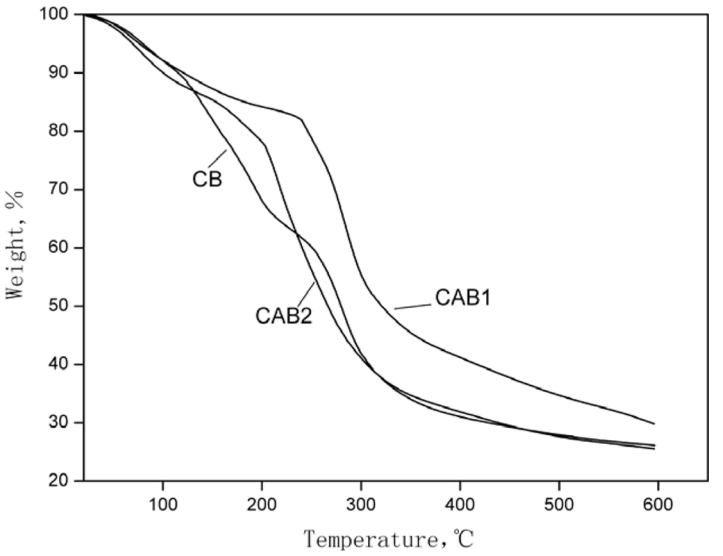

Figure 3: TG curves of complex membranes.

during thermal degradation there appeared two endothermic peaks in CAB2 and CB, however, only one in CAB1 near 265°C. The difference may be due to the stronger electrostatic interaction and intermolecular hydrogen bonding in polyion complex CAB1. The results of thermal analysis

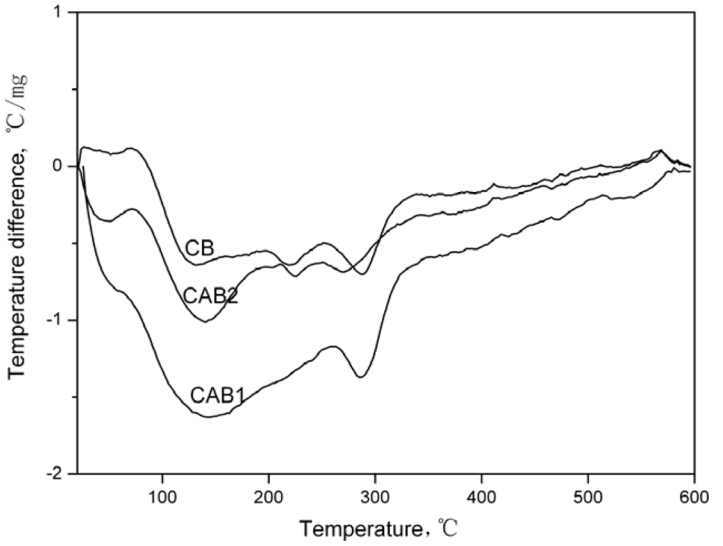

Figure 4: DTA curves of complex membranes.

showed the blended system of chitosan and sodium alginate was not a simple mixure, and blending the two polymers in appropriate proportions could restrain the degradation of chitosan and increase heat-resistant properties of the complex membrane.

Drug Release in vitro

Figure 5 showed the berberine release curves in 0.9% NaCl solution. It is indicated that the release profile of all drug-loaded membranes was similar, since in all formations there was a sudden release at an early stage, and subsequently the berberine release speed slowed down. The reason is that drug on the surface of the film was released first and subsequently drug from the interior was released slowly through diffusion. The cumulative release percentage of AB was the highest and the membrane was unstable. After being in the release medium for 20 h, the AB film disintegrated. The release speed of the complex membranes was slower than pure chitosan film-loaded drug(CB) and CAB1 showed the least cumulative release percentage. Berberine is a drug of cationic type. Accordingly, the addition of anionic polysaccharide sodium alginate increased the retention of the drug. In addition, a polyelectrolyte complex was formed and a strong charge to charge interactions had been demonstrated between chitosan and sodium alginate (blended in mass ratio 5:1), which decreased the drug release rate.

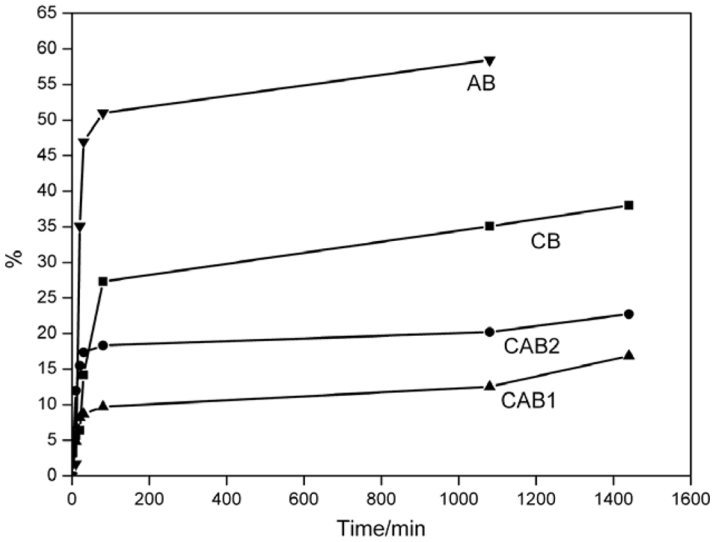

Figure 5: Release profile of various membranes in vitro.

CONCLUSIONS

Chitosan-sodium alginate-berberine complex membranes were prepared by solution casting method. FTIR analysis indicated that polyion complex was formed due to the occurrence of ionic crosslinking between chitosan and sodium alginate. The results of TG/DTA analysis showed that blending two saccharide polymers in appropriate ratios could increase the thermal stability of the complex membrane. The addition of sodium alginate could decrease the release speed of drug-loaded chitosan film, and the release control of CAB1 was better than CAB2.

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