Properties of Chitosan/Poly(vinyl alcohol) Films for Drug-Controlled Release

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ABSTRACT: With bovine serum albumin (BSA) as a model drug, drug-loaded films of chitosan (CS) and poly(vinyl alcohol) (PVA) were obtained by a casting/solvent evaporation method and crosslinked by tripolyphosphate (TPP). The films were characterized by FTIR, XRD, and SEM. The influential factors of drug-loaded films on drug-controlled release were studied. These factors included, primarily, the component ratio of CS and PVA, the loaded amount of BSA, the pH and ionic strength of the release solution, and the crosslinking time with TPP. The results showed that within 25 h, when the weight ratios of CS to PVA in the drug-loaded films were 90 : 10, 70 : 30, 50 : 50, and 30 : 50, the cumulative release rates of BSA were 63.3, 72.9, 81.8, and 91.8%, respectively; when the amounts of model drug were 0.1, 0.2, and 0.3 g, the release rates were 100, 81.8, and 59.6%, respectively; when the pH values of the drug release medium were 1.0, 3.8, 5.4, and 7.4, the release rates reached 100, 100, 37.9, and 7.8%, respectively; the cumulative release rates of BSA were 78.4, 82.3, 84.3, and 91.7% when the ionic strengths of the release solution were, respectively, 0.1, 0.2, 0.3, and 0.4*M*; when the crosslinking times of these drug films in the TPP solution were 0, 5, 15, 30, and 60 min, the release rates attained 100, 100, 81.8, 65, and 43.3%, respectively. All the results indicated that the CS/PVA film was useful in drug delivery systems. J Appl Polym Sci 96: 808–813, 2005

Key words: crosslinking; drug delivery systems; films; modeling; chitosan

INTRODUCTION

Chitosan (CS), the deacetylated derivative of chitin, is one of the most abundant naturally occurring polysaccharides. Recently, it has attracted much interest in the biomedical industry because of its excellent biodegradability, biocompatibility, antimicrobial activity, and accelerated wound-healing properties.[1–4] Because of its unique polymeric cationic character, net negatively charged compounds such as DNA, glycosaminoglycans, and most proteins can be incorporated into CS without the use of harsh and denaturing organic solvents, such as methylene chloride. Therefore, CS has been extensively examined in the pharmaceutical industry for its potential use in the development of a controlled release implant system.[5–8]

Poly(vinyl alcohol) (PVA), a water-soluble polymer, also has good characteristics of biodegradability and biocompatibility. It is a good biomedical material in the pharmaceutical industry.[9,10]

With respect to the excellent film-forming properties of CS, many new and original film materials have been achieved.[11,12] Drug-loaded film is one of the applications for those films in the pharmaceutical technology. In addition, numerous controlled or sustained-delivery systems have been described in the literature, whereby the active ingredient has been dissolved or dispersed within these films.[13] For continued development of film-based controlled-release devices, testing of these films is of paramount importance.[14–16] CS/PVA blend films are also novel film materials and have not previously been reported to be used as drug release media. To use these films in several controlled-release applications, it is necessary to have an overall understanding of their properties in drug-controlled release. Thus using bovine serum albumin (BSA) as a model drug, we studied some of the influential factors on CS/PVA drug-loaded films. These factors included, primarily, the component ratio of CS and PVA, the loaded amount of BSA, the pH and ionic strength of the release medium, and the crosslinking time in tripolyphosphate (TPP) solution.

EXPERIMENTAL

Materials

CS from shrimp shells [degree of deacetylation (DD): 87%; $M_v = 8.0 \times 10^5$] was purchased from Yuhuan Ocean Biochemical Co. (Zhejiang, China). The DD was measured by pH titration method[17] and the M_v was

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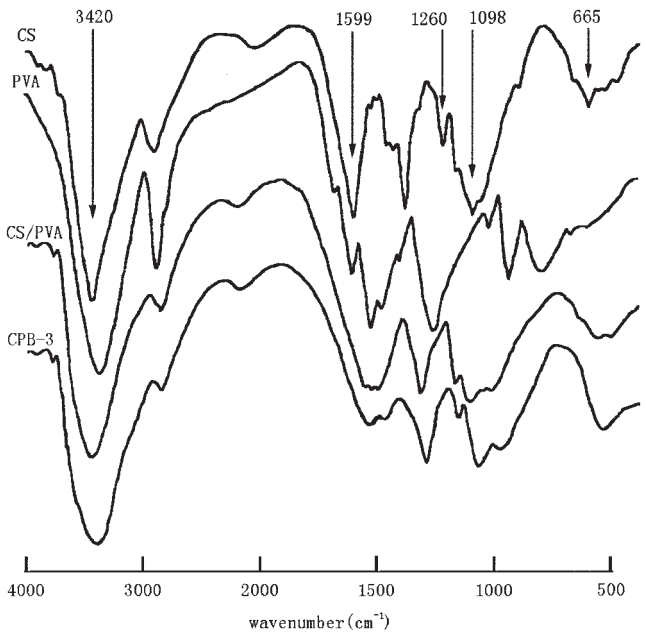

Figure 1 FTIR spectra of CS, PVA, CS/PVA, and CPB-3.

measured by viscometric method.[18] PVA (degree of polymerization: 1750 ± 50; degree of saponification ~ 99.8%) was purchased from Shanghai Chemical Reagent Co. (Shanghai, China). Bovine serum albumin (BSA, $M_v = 6.8 \times 10^4$), a biochemical reagent, was purchased from Sigma Chemical Co. (St. Louis, MO). TPP and other reagents were all analytical grade, all commercially available, and used as received.

Methods

The FTIR spectra of CS, PVA, CS/PVA, and CPB-3 films (weight ratio of CS to PVA: 70 : 30; amount of BSA: 0.2 g) were recorded with KBr pellets on a Nicolet 170SX FTIR spectrometer (Nicolet Instrument Technologies, Madison, WI).

The X-ray diffraction patterns of the films were taken with a Dmax-rA X-ray diffractometer (Rigaku, Tokyo, Japan), using nickel-filtered Cu–K_α radiation at 40 kV and 50 mA in the 2θ range of 5–40°.

The surface and cross-sectional morphologies of the drug-loaded films were examined using a Hitachi XA-650 scanning electron microscope (SEM; Hitachi, Osaka, Japan). Cross-sectional samples were prepared by fracturing films in liquid nitrogen. Before observation, samples were mounted on metal grids, using double-sided adhesive tape, and coated with gold under vacuum before observation.

Preparation of CS/PVA drug-loaded films with BSA

CS/PVA drug-loaded films were produced by a casting/solvent evaporation technique. CS was dissolved in a 2% (w/v) acetic acid water solution to prepare a 4% (w/v) CS solution; the 4% (w/v) PVA solution was achieved by dissolving PVA in hot distilled water. These two kinds of solutions were then blended in fixed ratios, from which four kinds of mixed solutions were obtained. The mass ratios of CS to PVA of these four blended solutions were 90 : 10, 70 : 30, 50 : 50, and 30 : 70, respectively. BSA (0.2 g) was dissolved in 50 mL of each of these four solutions. The solutions were thoroughly mixed by continuous stirring, after which they were sonicated, allowed to stand until trapped air bubbles were removed, and poured onto a Teflon plate of 20 × 15 cm^2. The films were dried in an oven at 37°C to a constant weight. Subsequently, the dried films were immersed in a 1% (w/v) TPP solution to crosslink for 15 min. Then the films were washed with distilled water, placed on a Teflon plate, oven-dried at 37°C for 48 h, and finally dried under vacuum at room temperature until reaching a constant weight. Thus a series of CS/PVA drug-loaded films with BSA were produced and designated as CPB-1, CPB-2, CPB-3, and CPB-4.

By the above method, 0.1 or 0.3 g BSA was dissolved in the mixed solution of CS and PVA, at a mass ratio of CS to PVA of 50 : 50, thus producing drug-loaded films CPB-5 and CPB-6, respectively. A blend film of CS and PVA without BSA was designated as CS/PVA.

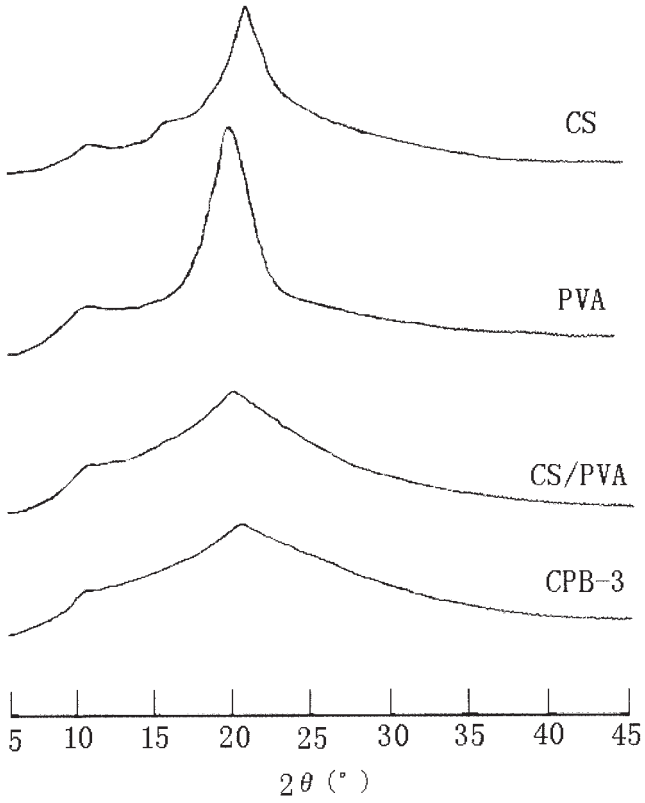

Figure 2 X-ray diffraction patterns of CS, PVA, CS/PVA, and CPB-3.

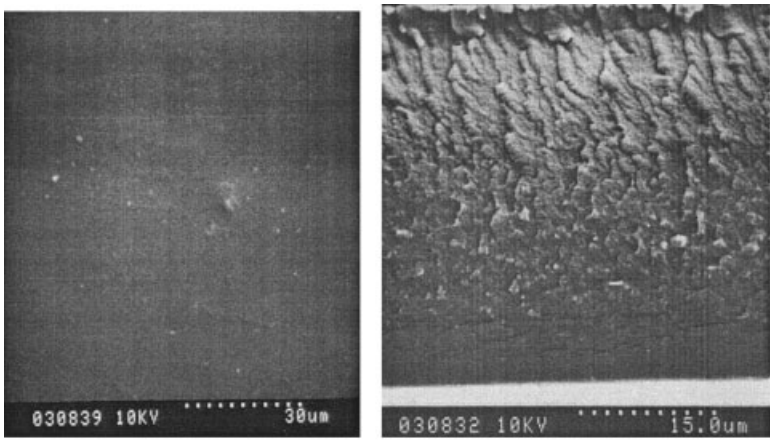

Figure 3 SEM micrographs of CS/PVA and CPB-3 drug-loaded film.

These dried films were cut into 3 × 3 cm^2 test sections. The thickness of the dried films was determined to be 40 ± 5 μm.

In vitro drug release studies

The drug-loaded films were suspended in glass vessels containing 50 mL of media, and incubated on a constant temperature shaking bed at 37°C and 130 rpm. At appropriate time intervals the solutions were withdrawn and the amounts of BSA released from the drug-loaded films were evaluated by UV spectrophotometry at 278 nm. Then an equal volume of the same dissolution medium was added to maintain a constant volume. The media for the controlled release studies were pH 1.0 (0.1*N* HCl solution), pH 3.8, 4.7 and 5.4 (10 m*M* HAc–NaAc buffered solution), and pH 7.4 (10 m*M* NaH_2PO_4–Na_2HPO_4 buffered solution). The ionic strength of these buffered solutions was carefully adjusted to a constant level by adding an appropriate amount of NaCl. All the experiments were done in triplicates.

RESULTS AND DISCUSSION

Structure and morphology characterization

Figure 1 shows the FTIR spectra of CS, PVA, CS/PVA, and CPB-3 drug-loaded films. With respect to pure chitosan, the characteristic absorption band at 3420 cm^{-1} was attributed to the stretching vibration of the N—H group bonded to the O—H group; bands at 1599 and 1260 cm^{-1} were attributed to the bending vibrations of the N—H group and the O—H group, respectively.[19] In drug-loaded film of CPB-3 the absorption band at 3420 cm^{-1} became wider, indicating that hydrogen bonding was enhanced.[11] The disappearance of crystalline-sensitive bands of CS at 1098

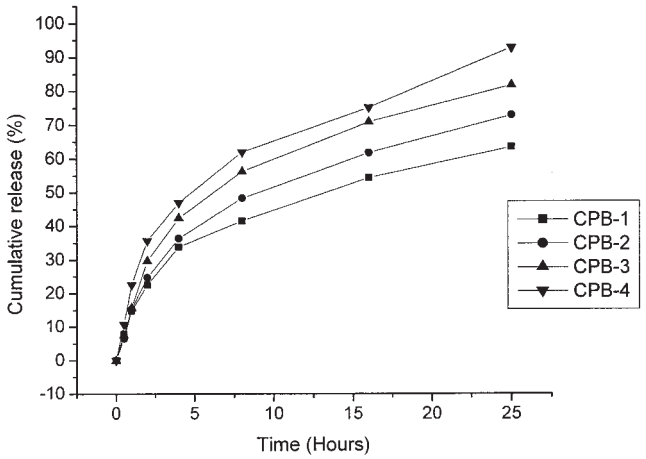

Figure 4 Influence of composition of drug-loaded film on drug-controlled release.

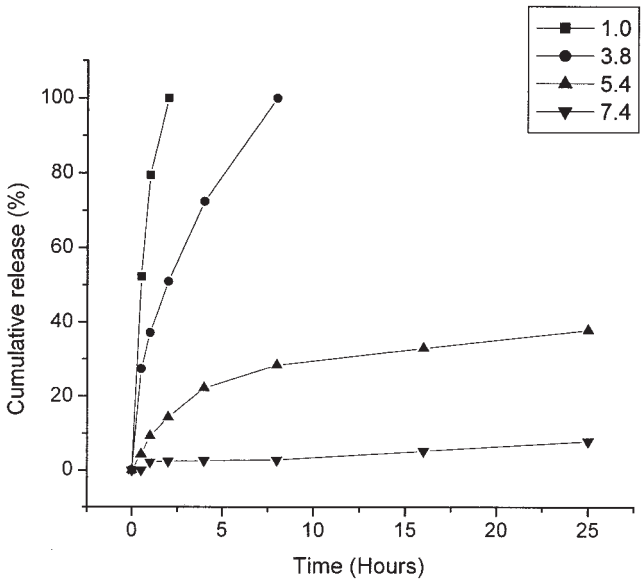

Figure 6 Influence of pH of release media on drug-controlled release.

and 665 cm^{-1} [20]demonstrated that blending disturbed the crystallization of CS, which was further confirmed by X-ray analysis. The 1599 cm^{-1} peak of the N—H bending vibration shifted to a lower band, indicating the linkage between phosphoric and ammonium ions.[21]

The X-ray diffraction patterns of the investigated films are shown in Figure 2. The diffractogram of CS films consisted of three major crystalline peaks at 2θ values of 10.5, 15.4, and 20.1°, in agreement with literature values.[22] PVA had two major crystalline peaks at 2θ values of 10 and 19.8°, although in the drug-loaded film, each component's characteristic crystalline peaks weakened or disappeared. This indicated that amino and hydroxyl groups in chitosan formed complexes with hydroxyl groups of PVA or combined with BSA, which then resulted in an amorphous structure of the polymer complex.[23]

Figure 3 shows the morphologies of CS/PVA and CPB-3 drug-loaded film. The upper surface of CS/PVA film [Fig. 3(a)] was very smooth, and its cross section [Fig. 3(b)] was very integrated and dense. However, incorporation of model drugs in the CPB-3 film resulted in a significant change of the surface and cross section morphologies. For example, large pores were observed on the upper surface of CPB-3 drug-loaded film [Fig. 3(c)], the cross section was very rough, and many deficiencies were observed [Fig. 3(d)].

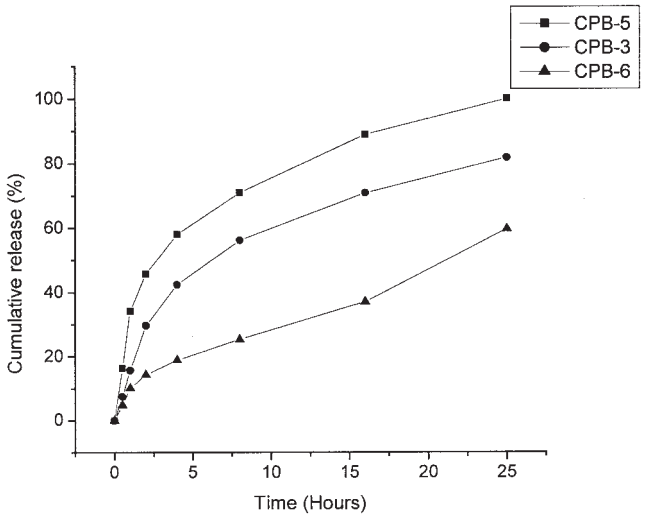

Figure 5 Influence of amount of drug loaded on drug-controlled release.

In vitro drug release studies

Effect of the composition ratio of drug-loaded film

Drug-loaded films CPB-1, CPB-2, CPB-3, and CPB-4, with different composition ratios of CS to PVA, were conducted in this experiment. The release medium was the same: 10 m*M* HAc–NaAc buffered solution with pH = 4.7 and ionic strength (I) = 0.145*M*. Figure 4 shows that the release decreased with increasing content of CS, perhaps because the N—H group and the –COOH group of BSA were combined with the NH_3^+ of the CS.

Effect of the amount of drug loaded

Films CPB-5, CPB-3, and CPB-6 with different amounts of drug loaded were studied. The 10 m*M* HAc–NaAc buffered solution with pH = 4.7 and I = 0.145*M* was used as the release solution. From

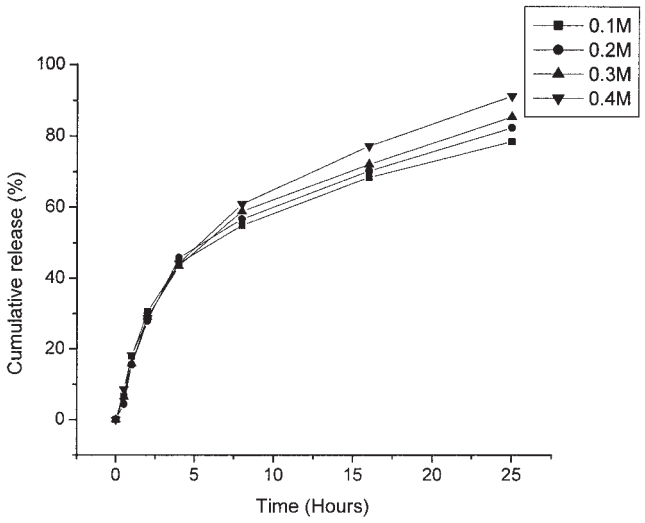

Figure 7 Influence of ionic strength of release on drug-controlled release.

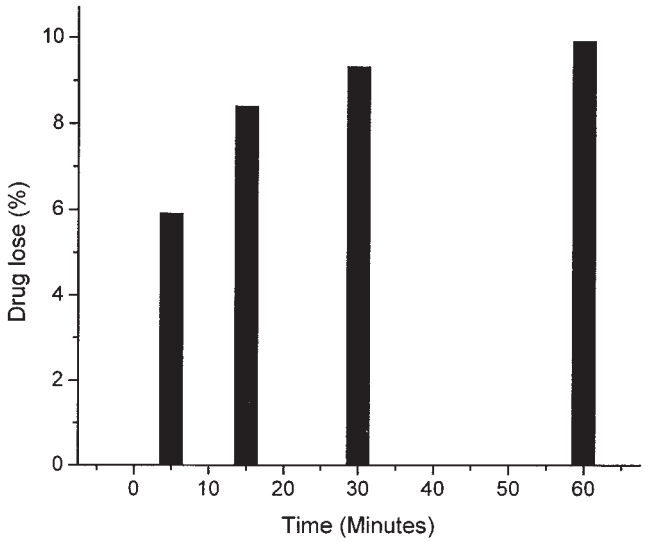

Figure 8 Influence of crosslinking time on drug loss rate.

Figure 5 we can conclude that the greater the amount of drug loaded, the slower the release of drug.

Effect of pH

Drug-loaded film CPB-3 released in four different buffered solutions with pH values of 1.0, 3.8, 5.4, and 7.4. The ionic strengths of these solutions were all adjusted to 0.145*M* by adding an appropriate amount of NaCl. Figure 6 shows that the release was accelerated with decreasing pH because the electrostatic interaction between anions and chitosan was substantially influenced by solution pH.[15] The decrease of pH weakened the salt bonds and ionic crosslinking and thus facilitated film swelling, and thus the drug release was accelerated.

Effect of ionic strength (*I*)

Drug-loaded film CPB-3 was used in this experiment as the release matrix. Adding appropriate amounts of NaCl to the 10 m*M* HAc–NaAc buffered solution with pH = 4.7 produced the four different release media. Figure 7 shows that with increasing ionic strength the drug release rate also increased, a result possibly related to the decrease of osmotic pressure inside the film with increasing salt concentration and the weakened salt bond between TPP and CS destroyed by the salt ion.[24]

Effect of crosslinking time

Drug-loaded CPB-3 films with different crosslinking times were produced by the casting/solvent evaporation method. The drug loss during the course of crosslinking was estimated by UV spectrophotometry at 278 nm. These films were then induced to release in a HAc–NaAc buffered solution with pH = 4.7 and I = 0.145*M*. Figure 8 shows that the drug loss amounts scarcely changed with increasing time and were all <10%. Figure 9 shows that the longer the crosslinking process continued, the slower the release of drug because an expanded crosslinking structure formed in the case of longer crosslinking time, thus prolonging the release process.

CONCLUSIONS

A novel drug-loaded film based on CS and PVA was produced by a casting/solvent evaporation method and crosslinked by TPP. With BSA as a model drug, we studied the film's structures and characterizations, especially its potential capacity in drug delivery sys-

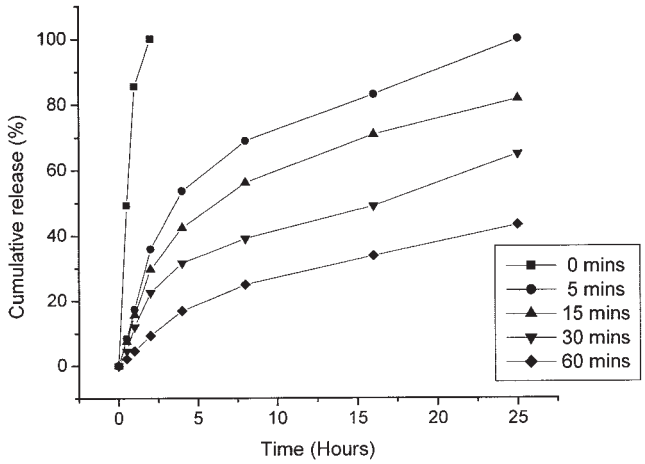

Figure 9 Influence of crosslinking time on drug-controlled release.

tems. The results indicated that the blended film was sensitive to pH and ionic strength of the release medium. Furthermore, the film's composition, amount of drug loaded, and crosslinking time all had relevant influence on the release properties of the film. Thus, we can control the drug release rate through changing some influential factors of the drug-loaded film. The film can lead to a successful application for localized drug delivery to the intestinal environment.

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