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Controlled release of ciprofloxacin hydrochloride from chitosan/polyethylene glycol blend films

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Abstract

Films of chitosan and polyethylene glycol (PEG), with ciprofloxacin hydrochloride as model drug incorporated at different concentrations, have been obtained by a casting/solvent evaporation method. Interrelated chemical, morphological and mechanical characterizations included the component ratio of chitosan and PEG, the loaded amount of ciprofloxacin hydrochloride, the pH and ionic strength of the release solution, the thickness of the drug loaded films, the coating layer of sodium alginate and the cross-linking time with tripolyphosphate (TPP) and others. The results of controlled release tests showed that the amount of ciprofloxacin hydrochloride released increased with an increase in the proportion of PEG and decreased as the amount of drug loaded in the film increased; however, the cumulative release amount of the drug increased. The chitosan/PEG films were also sensitive to pH and ionic strength. In simulated intestinal fluid, the thickness of the film increased from 35 to 85 μm with a concomitant reduction of the ciprofloxacin hydrochloride concentration from 100% to 71%. Differing the concentration of sodium alginate coating solution reduced the release of ciprofloxacin hydrochloride by as much as 16% in simulated gastric fluid and 38% in simulated intestinal fluid. When the cross-linking time of these films in the TPP solution were 0, 5, 15 and 30 min, the drug release rate attained 100%, 100%, 70% and 42%, respectively, within 24 h.

Keywords: Chitosan; PEG; Ciprofloxacin hydrochloride; Blend films; Drug delivery systems

1. Introduction

Chitosan, 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 (Hirano, Seino, & Akiyama, 1994; Malette, Euiglem, & Gaines, 1983; Qurashi, Blair, & Allea, 1992; Wel, Hudson, & Mayer, 1992). Chitosan has good gel and film forming properties. When it is dissolved in dilute acetic acid solutions, the amino groups become protonated and associated with acetate counter-ions, making the charged polymer soluble. Therefore, net negatively charged compounds such as DNA, glycosaminoglycans, and most proteins can be incorporated into chitosan without the use of harsh and denaturing organic solvents, such as methylene chloride, which are needed for film preparation of many biodegradable polymers. Therefore, chitosan has been investigated extensively in the pharmaceutical industry for its potential use in the development of controlled release implant systems (Aspden, Mason, Jones, Lowe, & Illum, 1997; Karlson, 1991; Mao, Troungle, & Janes, 2001; Oungbho & Muller, 1997; Wang, Du, & Fan, 2005).

Polyethylene glycol (PEG) is a biocompatible polymer with excellent biocompatibility and non-toxicity (Zhang, Gong, Zhao, & Zhang, 2002). It is often blended or compounded with other polymers to be used in the field of drug-controlled release (Chandy, Mooradian, & Ral, 1998; Won, Chu, & Lee, 1998; Won, Chu, & Lee, 1998).

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With regard to the excellent film forming properties of chitosan, many new and original films materials has been achieved (Tang, Du, Zheng, & Fan, 2001; Yu, Du, & Zheng, 1999). Drug-loaded film is one of the applications of those films in 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 (Carmen & Roland, 1997). For the development of film-based controlled release devices, tests carried out with them are very important and needed (Chad et al., 2001; Graeme, John, & John, 1999; Shu, Zhu, & Song, 2001). It was reported that when PEG was blended with chitosan to form films, it could promote the proliferation of cells. Most important, it could not reduce the activities of the protein in the cells (Zhang et al., 2002). In the present study, chitosan/PEG blend films were prepared and used in several controlled release applications to give a better overall understanding of their properties. Using ciprofloxacin hydrochloride as a model drug, some factors that may have influence the drug release from chitosan/PEG films as function of the ratio of chitosan and PEG used, the loaded amount of ciprofloxacin hydrochloride, the pH and ionic strength of the release solution, the thickness of the drug loaded films, the coating layer of sodium alginate and the cross-linking time with tripolyphosphate (TPP), have been studied. It is anticipated that the films reported herein may lead to a successful application for localized drug delivery in *in vivo* and *in vitro* environments.

2. Materials and methods

2.1. Materials

Chitosan from shrimp shell was purchased from Yuhuan Ocean Biochemical Co., Ltd (Zhejiang, China); the degree of deacetylation (*DD*) was 87%, and M_v was 8.0×10^5. The *DD* was measured by pH titration method (Lin, Jiang, & Zhang, 1992) and the M_v was measured viscosimetrically (Wang, Bo, & Qin, 1990). PEG6000 was purchased from Shanghai Chemical Reagent Co., Ltd (Shanghai, China). Ciprofloxacin hydrochloride was purchased from Jingxin Pharmacy Co., Ltd (Zhejiang, China) and used as model drug. Other reagents were all analytical grade.

2.2. Preparation of drug loaded films

Chitosan/PEG drug loaded films were produced by a casting/solvent evaporation technique. Solutions of chitosan and PEG, 2 wt%, were prepared with 2 wt% acetic acid solution and distilled water, respectively; and the PEG was dissolved in a higher temperature. These solutions were mixed in different proportions to obtain final PEG solution concentrations of 2.0, 3.5, 5.5 and 8.0 wt% of total. Ciprofloxacin hydrochloride (0.2 g) was dissolved, under stirring, in each one of these four resulting solutions (50 ml) to make them completely homogeneous. After that, they were sonicated in a sonication bath (FS-20, Jingrong Sonic Electronics Co. Ltd., Beijing, China), left to stand until trapped air bubbles were removed, and poured on a Teflon plate of $20 \times 15\,cm^2$. These films were dried in an oven (GDW-250, Saiou Test Machine Co. Ltd., Shanghai, China) at 37 °C for 48 h, and finally dried under vacuum at room temperature until constant weight. These dried films, with an average thickness of 55 μm determined by WHS-10A Portable Thickness Instrument (Tianfa Test Machine Co. Ltd., Jiangdou, China), were cut into $3 \times 3\,cm^2$ sections for tests. The several chitosan/PEG drug loaded films, prepared with ciprofloxacin hydrochloride, were designated as CP-1, CP-2, CP-3 and CP-4 (PEG contents were 2.0, 3.5, 5.5 and 8.0 wt%, respectively). The blank matrix film, without the drug, was marked with CP (PEG was 3.5 wt%).

Following the above method, different amount ciprofloxacin hydrochloride (0.1 and 0.3 g) was dissolved in solutions (PEG contents ratio was 3.5 wt%), producing drug loaded films designated as CPC-1 and CPC-2, respectively. By changing the volume of the forming solution of CP-2 poured onto the Teflon plate, drug loaded films were achieved with different thickness of 35 and 85 μm, marked as CPD-1 and CPD-2, respectively. Finally, CP-2 films dipped in sodium alginate coating solutions different concentrations (0.3 and 0.6 wt%) for 20 min were then dried. The thickness of the coating layer was determined to be 5 and 8 μm by aforementioned methods and they marked were as CPA-1 and CPA-2, respectively. Finally, a CP-2 film sample immersed in a 1 wt% TPP solution for different times to achieve different degrees of cross-linking. After being washed with distilled water, these films were dried using the aforementioned methods.

2.3. FT-IR analysis

The FT-IR spectra of pure chitosan, PEG, ciprofloxacin hydrochloride, CP and CP-4 films were recorded within KBr pellets on a Nicolet FTIR spectrometer, Model 170SX (USA).

2.4. X-ray diffraction studies

The X-ray diffraction patterns of pure chitosan, PEG, ciprofloxacin hydrochloride, CP and CP-4 films were determined on a Shimadzu Lab-XRD-6000X diffractometer (Japan), using Nickel-filtered CuKα radiation at 40 kV and 50 mA in the 2θ range of 5°–40°. From the results of CP and CP-4 films, the effects of ciprofloxacin hydrochloride on the degree of crystallization of the blend films were determined.

2.5. Morphology observations

The cross-sectional morphologies of the CP and CP-4 films were examined using scanning electron microscopy (SEM) Hitachi S-570 (Japan). Cross-sectional samples were prepared by fracturing films in liquid nitrogen. Prior to