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Preparation of an extended-release matrix tablet using chitosan/Carbopol interpolymer complex

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Abstract

A chitosan and Carbopol interpolymer complex (IPC) was formed using a precipitation method in an acidic solution. The chitosan and Carbopol IPC was characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and turbidity measurements. FT-IR demonstrated that the IPC formed a complex through an electrostatic interaction between the protonated amine (NH_3^+) group of chitosan and the carboxylate (COO^-) group of Carbopol. DSC indicated the IPC to have different thermal characteristics from chitosan or Carbopol. The turbidity measurement revealed the complexation ratio of IPC between chitosan/Carbopol to be 1/4. A theophylline tablet was prepared using the IPC as a matrix material. The drug release profile from this tablet was similar to that from the HPMC tablet and showed a pH-independent release profile. The mechanisms for drug release from the IPC tablet were diffusional release at pH 6.8 and relaxational release at pH 1.2.

Keywords: Chitosan; Carbopol; Interpolymer complex; Extended release

1. Introduction

Hydrophilic gel-forming matrix tablets are widely used as oral extended-release dosage forms (Nellore et al., 1998; Kranz et al., 2005). Since the overall rate of drug release is regulated by the viscosity and thickness of the gel layer formed from the matrix tablets, selecting the appropriate hydrophilic polymer with the appropriate viscosity and disintegration rate is very important for designing a controlled release tablet.

Carbopol is a cross-linked polymer of acrylic acid with a high molecular weight that forms a hydrogel in aqueous solutions depending on the degree of hydration of the carboxyl group in Carbopol (Singlga et al., 2000). Although Carbopol has many advantages as a candidate for an extended-release tablet matrix, e.g. a good gel-forming ability and mucoadhesive property, there are few reports on the application of Carbopol to the extended-release dosage forms (Meshali et al., 1996; Betageri et al., 2001). This might be due to the ionic nature and high sensitivity of Carbopol to the pH of the medium. It is difficult to control the drug release rate from the Carbopol matrix and correlate the in vitro drug release with the in vivo drug absorption due to its pH sensitivity (Singlga et al., 2000). pH-dependent drug release can cause in vivo variability (Kranz et al., 2005).

Recently, an interpolymer complex (IPC) has attracted considerable interest by pharmaceutical researchers (Wang et al., 1997) on account of its unique characteristics due to a specific interaction between constituent polymers such as hydrogen bonds, electrostatic interaction, van der Waals force, or hydrophobic interactions (Zhong and Guo, 1996). Among them, the formation of an IPC between poly(acrylic acid) and chitosan has been previously reported (Chavasit et al., 1988). The complexation is due to an electrostatic interaction between the carboxylate group of poly(acrylic acid) as the polyanionic polymer and the protonated amine group of chitosan as the polycationic polymer (Mi et al., 1999). In a similar manner, the formation of an IPC between Carbopol and chitosan would be expected. This might solve the problem of the pH dependency of Carbopol because carboxyl groups, which are the main factors affecting the pH-dependant drug release, are complexed with chitosan. Moreover, chitosan possesses some favorable properties, such as non-toxicity, high biodegradability and biocompatibility (Cho and Choi, 2005a).

In this study, a Carbopol/chitosan complex powder was prepared and evaluated as an extended-release tablet matrix. The

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drug release pattern at lower and higher pH was also examined. Theophylline was selected as the model drug because it is water-soluble and has an almost constant solubility between pH 2 and 7.5 (Vendruscolo et al., 2005).

2. Materials and methods

2.1. Materials

Theophylline anhydrous and low (viscosity of 1% acetic acid solution: 20–200 cP), medium (viscosity of 1% acetic acid solution: 200–800 cP) and high (viscosity of 1% acetic acid solution: 800–2000 cP) molecular weight Chitosan were purchased from Sigma–Aldrich (St. Louis, MO, USA). Carbopol 971 was obtained by Noveon, Inc. (Cleveland, OH, USA). Hydroxypropylmethylcellulose (HPMC; Metolose® 60SH 4000cp) was obtained from Shin-Etsu (Tokyo, Japan). All the other chemicals were of reagent grade or above and used without further purification.

2.2. Preparation of Carbopol/chitosan complex

A Carbopol aqueous solution (1 mg/ml) and chitosan acetic acid solution (5 mg/ml) were mixed. The resulting precipitate (Carbopol/chitosan IPC) was washed with distilled water and dried under vacuum over a 24-h period. The dried complex was ground with a grinder and ball milled. The powder was passed through a 200-μm sieve and used for further study.

2.3. Fourier transform infrared (FT-IR) spectroscopy study

The infrared absorption spectra of Carbopol, chitosan and their IPC were analyzed using a FT-IR spectrophotometer (LX30-7012, Perkin Elmer, MA, USA). The pellets were prepared by pressing the sample with potassium bromide.

2.4. Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a differential scanning calorimeter (DSC 50, Shimadzu Scientific Instruments, MD, USA). The samples were placed in an aluminum-sealed pan and preheated to 200 °C. The sample was cooled to room temperature and then reheated from 40 to 450 °C at a scanning rate of 10 °C/min.

2.5. Turbidity measurements

The Carbopol/chitosan ratio in the complex was examined by monitoring the transmittance of the solution at a wavelength of 600 nm using a spectrophotometer (UV-1601, Shimadzu, Japan). An aqueous Carbopol solution (0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 mM) and a chitosan acetic acid solution (0.5, 1, and 2 mM) were used. The concentration was calculated by dividing the weight of chitosan and Carbopol by the formula weight of each monomer unit. Each Carbopol solution (3 ml) was mixed with the 0.5 mM chitosan solutions (3 ml), and each chitosan solution (3 ml) was mixed with a 0.5 mM Carbopol solution (3 ml). Each mixture was shaken vigorously. The mixtures were then left to stand for 10 min before measuring the transmittance as a function of the various mixing ratios (chitosan/Carbopol).

2.6. Preparation of extended-release matrix tablet

The extended-release matrix tablets with a total weight of 250 mg were prepared using a mixture of theophylline and an excipient at 1:1. The mixture was compressed using a hydraulic press with a 13-mm diameter. The compression force was 10 kN/cm^2 with a dwell time of 1 s. Carbopol, chitosan, HPMC and three types of Carbopol/chitosan complexes (three different molecular weight of chitosan) were used as the excipient.

2.7. Dissolution of theophylline from the tablet

A dissolution test was carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). The dissolution tester was calibrated using an USP Dissolution Calibrator, salicylic acid (Lot O) and prednisone (Lot O0C056) tablets. The rate of theophylline dissolution was measured using the USP paddle method at 50 rpm using 900 ml of a pH 1.2 or pH 6.8 medium at 37 °C. The samples were withdrawn at predetermined times and then analyzed using a HPLC system (Shimadzu Scientific Instrument, Kyoto, Japan) at a wavelength of 280 nm with a flow rate of 1.2 ml/min using an ODS column (Luna C8, 4.6 mm × 150 mm, 5 μm, Phenomenex, USA). The mobile phase used was pH 3.8 100 mM acetate buffer/acetonitrile = 93/7.

2.8. Determination of matrix erosion and water uptake

Matrix erosion and water uptake of a Carbopol/chitosan complex tablet were evaluated by measuring the amount of water uptake and weight loss in a dissolution tester. The tablets were placed in 900 ml of pH 1.2 or pH 6.8 medium at 37 °C using USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. The tablets were then pulled out of the vessel at predetermined times. The weight of the hydrated tablet (W_h) was measured after removing the surface medium with filter paper. The weight of the dried tablet was measured after drying the tablet under a vacuum for 24 h. The water uptake ratio and level of matrix erosion were calculated using the following equations:

$$\text{Water uptake } (\%) = \frac{W_h - W_d}{W_d} \times 100 \quad (1)$$

$$\text{Matrix erosion } (\%) = \frac{W_i - W_d}{W_i} \times 100 \quad (2)$$

where W_i is the initial weight of the tablet. W_d was corrected by subtracting the weight of the buffer components (KH_2PO_4, NaOH, NaCl) present in the absorbed medium from the measured weight after drying.