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Characterization of chitosan–magnesium aluminum silicate nanocomposite films for buccal delivery of nicotine

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ABSTRACT

The objective of this study was to prepare and characterize chitosan–magnesium aluminum silicate (CS–MAS) nanocomposite films as a buccal delivery system for nicotine (NCT). The effects of the CS–MAS ratio on the physicochemical properties, release and permeation, as well as on the mucoadhesive properties, were investigated. Molecular interactions between the components of the film were also investigated. The results indicated that NCT-loaded CS–MAS films provided a higher NCT content than NCT-loaded films containing only CS. The greater the MAS ratio in the films, the higher the NCT content that was observed because intercalated nanocomposites could be formed by electrostatic interactions of MAS with NCT and CS. These interactions caused an insignificant loss of NCT by evaporation during film drying. The release and permeation of NCT were related to the square root of time, indicating that a diffusion-controlled mechanism via the NCT–MAS complex particles and the film matrix controls NCT release. NCT release and permeation rates decreased with as the MAS ratio of the films was increased. However, the NCT-loaded CS–MAS films may have a potential adhesion to the mucosal membrane. These findings suggest that NCT-loaded CS–MAS films can be used as a buccal NCT delivery system.

1. Introduction

In recent years, polymer-layered silicate nanocomposites were widely fabricated and characterized as a novel material that provides both good mechanical and barrier properties. These nanocomposites are composed of both synthetic and natural polymers as well as clays, including montmorillonite [1,2], rectorite [3], laponite [4], and magadiite [5]. Chitosan (CS), a positively charged polysaccharide, has been widely used to prepare nanocomposites with many different types of clay. CS–clay nanocomposites are capable of enhancing the thermal stability and mechanical properties of CS [6], while simultaneously retarding the swelling properties of CS, since clay can act as a multi-functional cross-linker of CS when intercalated nanocomposite structures are formed [5]. CS–clay nanocomposites have been used as biosensors [4], packaging materials [7], and superabsorbent materials [8].

Pharmaceutics research lead to the discovery that the nanocomposite formulation of CS with clay improved the antimicrobial activity of CS and provided a good barrier against water vapor and protein [9]. Moreover, CS–montmorillonite nanocomposites could retard CS matrix dissolution in acidic medium, resulting in slower drug release from the nanocomposite matrix when compared to the rate of drug release from CS or montmorillonite matrices [10]. In previous studies, CS was observed to form a nanocomposite with magnesium aluminum silicate (MAS), which is a mixture of natural montmorillonite and saponite clays and is used in pharmaceuticals [11]. The CS–MAS nanocomposite films showed good mechanical properties and could limit water vapor and drug permeation [12]. In addition, the CS–MAS nanocomposite could be applied as a coating material for tablets. The release of drugs from coated tablets could be modified by varying the CS–MAS ratios and coating levels, and in vitro release studies clearly indicated that the CS–MAS coated films had superior stability against acidic medium and pancreatin than conventional CS-coated films [13].

Nicotine (NCT), a volatile liquid alkaloid with pK_a values of 3.04 and 7.84 [14], is used as an aid for smoking cessation. NCT undergoes very high first pass metabolism in the liver, resulting in an

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oral bioavailability of less than 20% [15]. However, NCT can permeate through the buccal mucosa by passive diffusion [14,16]. Therefore, buccal delivery is an alternative route of administration that can be used to enhance the bioavailability of NCT. CS is one of the polysaccharides used as a film matrix for buccal delivery because of its mucoadhesive properties [17]. Therefore, investigation of CS–MAS nanocomposite films for NCT buccal delivery is of interest because NCT may electrostatically interact with MAS, which may reduce NCT volatilization during film preparation and nanocomposite matrix formed may also control the delivery of NCT.

In the present study, NCT-loaded CS and CS–MAS films were prepared using a casting/evaporation method. The effect of the CS–MAS ratio of the films on NCT content, water uptake, nanocomposite formation, and NCT release and permeation was investigated. Moreover, this study marks the first report of the molecular interactions of three components in nanocomposite films. These interactions were characterized using ATR-FTIR, Raman, and solid state ^{29}Si NMR spectroscopic methods. Additionally, the mucoadhesive properties of the films were also examined.

2. Materials and methods

2.1. Materials

CS (800 kDa with a degree of deacetylation of 85%) was purchased from Seafresh Chitosan (Lab) Co., Ltd. (Bangkok, Thailand). MAS (Veegum®HV) was obtained from R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA). NCT (free base) and HPMC (viscosity 4000 mPa s) were purchased from Fluka Chemical Co. (Buchs, Switzerland). All other reagents used were of analytical grade.

2.2. Preparation of NCT-loaded films

NCT-loaded CS and CS–MAS films were prepared using a casting/solvent evaporation technique. CS (1%, w/v) was dispersed using 1% (w/v) acetic acid as a solvent and stirring the mixture overnight at room temperature, whereas MAS (4%, w/v) was dispersed in hot distilled water and then diluted with 10 mM acetate buffer solution at pH to get 1% (w/v) MAS dispersion. NCT-loaded CS dispersions were prepared by incorporating 0.25 g NCT into 250 ml of 1% (w/v) CS dispersions and mixing for 30 min. NCT-loaded CS–MAS dispersions were prepared by mixing 0.25 g NCT with 1% (w/v) MAS dispersions for 30 min and then adding the 1% CS dispersion. CS–MAS ratios in the NCT-loaded CS–MAS dispersions were varied to 1:0.2, 1:0.6, and 1:1 by weight, and the total solid content of the dispersions was 2.5 g. The final volumes of the NCT-loaded CS–MAS dispersions were adjusted to 250 ml with 10 mM acetate buffer solution at pH 4 and were then stirred for an additional 30 min. All NCT-loaded dispersions were homogenized, and the final pH was adjusted to 4 using glacial acetic acid for complete protonation of CS and NCT, which the protonated CS and NCT could rapidly interact with MAS. The dispersions were then incubated in a water bath at 37.0 ± 0.5 °C for 24 h, after which they were poured onto a plastic plate (15 cm × 20 cm) and allowed to evaporate at 45 °C for 3–4 days. The dry films were peeled off and kept in a cool, dry place until use.

Hydroxypropyl methylcellulose (HPMC), which has been previously used as a film former for buccal delivery systems [18], was used to prepare NCT-loaded HPMC films to compare the NCT content and release to that of the NCT-loaded CS and CS–MAS films. HPMC (2.5 g) was dispersed in 250 ml of de-ionized water to obtain 1% (w/v) HPMC and 0.25 g of NCT was added. The HPMC dispersion with NCT was stirred for 1 h, homogenized, incubated at 37.0 ± 0.5 °C for 24 h, and dried at 45 °C for 2 days. The CS and CS–MAS (1:1) films without NCT were prepared using the same procedures outlined above. All films were stored in a cool, dry place prior to use.

2.3. Morphology and thickness of films

Surface and matrix morphologies of NCT-loaded films were observed using scanning electron microscopy (SEM). The films were immediately fractured after immersion into liquid nitrogen for 2 s. Samples were mounted onto the stubs, coated with gold in a vacuum evaporator, and photographed using a scanning electron microscope (Joel Model JSM-6480LV, Tokyo, Japan). The thickness of each film was measured at 10 different areas using a microprocessor coating thickness gauge (Minitest 600B, ElektroPhysik, Germany). The films were placed on the control plate. The probe, which had been connected to the measurement gauge and calibrated using the standard film, was gently moved downward to touch the film, and the thickness of the film was then recorded.

2.4. NCT content determination

The NCT content in the films was determined using an acid extraction. The films were cut to disc, weighed accurately, and then soaked in 50 ml of 2 M HCl in a volumetric flask. The flask containing the films was shaken at 37.0 ± 0.5 °C. Every 24 h, 25 ml of media was removed and replaced with fresh media. The medium taken was filtered through filter paper and diluted with 2 M HCl. NCT concentration in the collected medium was analyzed using a UV–visible spectrophotometer (Shimadzu UV1201, Japan) at the wavelength of 259 nm. The extraction was continued until constant amounts of NCT in the films were obtained. NCT content was calculated and reported as a percentage by weight of the films. Moreover, NCT retained in the films was calculated using the following equation:

$$\text{NCT retained}\,(\%) = \frac{\text{NCT content in the film}}{\text{NCT added}} \times 100 \qquad (1)$$

where the NCT added was 10% NCT in the solid content of the dispersion before film casting.

2.5. ATR-FTIR and Raman spectroscopies

ATR-FTIR spectra of both the films and the MAS powder were recorded using an ATR-FTIR spectrophotometer (Spectrum One, Perkin Elmer, Norwalk, CT). The samples were placed onto the ZnSe prism of a sample holder and scanned from 4000 to 650 cm^{-1} at the resolution rate of 4 cm^{-1}. FTIR spectra of NCT (free base in liquid form) were recorded using the KBr disc method at the same scanning rate and resolution rate. Furthermore, Raman spectra of the samples were characterized using a Bruker FRA 106/S FT-Raman spectrometer (Bruker Optik, Ettlingen, Germany). Data were collected from 500 to 3500 cm^{-1} at 4 cm^{-1} resolution using a Nd:YAG laser with an excitation wavelength of 1064 nm at a laser power of 450 mW.

2.6. Nuclear magnetic resonance (NMR) spectroscopy

The ^{29}Si NMR spectra of the samples were measured using a solid-state ^{29}Si cross-polarization, magic angle spinning (CP/MAS), and an NMR spectrometer (DPX-300, Bruker-BioSpin AG, Fällanden, Switzerland). The spectral parameters used were as follows: 1600 spins, a relaxation delay of 6 s, and a spin rate of 5 kHz.

2.7. Powder X-ray diffractometry

Powder X-ray diffraction (PXRD) patterns of MAS powder, CS film, CS–MAS (1:1) film, and NCT-loaded films were performed on a powder X-ray diffractometer (Philips PW3710 mpd control, The