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Nicotine-loaded sodium alginate–magnesium aluminum silicate (SA–MAS) films: Importance of SA–MAS ratio

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ABSTRACT

The objective of this work was to investigate the influence of the sodium alginate–magnesium aluminum silicate (SA–MAS) ratio on film properties for nicotine (NCT) mucosal delivery. NCT-loaded SA–MAS films with varying SA–MAS ratios were prepared at acidic and basic pH, which represent the protonated and neutral species of NCT, respectively. The film characteristics, such as NCT content, muco-adhesive properties, NCT release and skin and mucosal membranes NCT permeation were examined. The result showed that increasing the MAS ratio in the films caused an increase in NCT retention and a decrease in the NCT release rate. The NCT release mechanism of the NCT-loaded SA–MAS films prepared at acidic and basic pH was an anomalous transport and a swelling controlled mechanism, respectively, and was primarily impacted by the SA content in the films. The NCT permeation rate across the mucosal membrane decreased with increasing MAS ratio of the films. The mucosal drug permeation kinetics suggested a matrix diffusion controlled mechanism, whereas skin penetration acted as a rate-limiting step of drug permeation. Film preparation pH also affected NCT release and permeation due to the unique charge characteristics of the various NCT species formed. Furthermore, films with a high MAS ratio could adhere to the mucosal membrane. These findings suggest the SA–MAS ratio remarkably influences the characteristics of the NCT-loaded SA–MAS films, and that these films demonstrate a promising mucosal drug delivery system.

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1. Introduction

Polymer–clay composites have been interestingly developed and characterized for their mechanical properties and their ability to improve polymer thermal behavior (Pavlidou & Papaspyrides, 2008). Changes in the physicochemical properties of polymers occur when clay is incorporated due to molecular interactions between the polymer and clay. This incorporation leads to an alteration of polymer matrix structure, which may slow drug release. For this reason, the polymer–clay composites with drugs incorporated have been studied for drug delivery systems (Campbell, Craig, & McNally, 2008; Stephen, Mark Saltzman, & Giannelis, 2003; Tammaro, Costantino, Nocchetti, & Vittoria, 2009; Wang, Du, Luo, Lin, & Kennedy, 2007).

Composites between sodium alginate (SA) and magnesium aluminum silicate (MAS) are materials that possess unique characteristics for pharmaceutical use (Aguzzi, Cerezo, Viseras, & Caramella, 2007; Lee, Moturi, & Lee, 2009). SA is a sodium salt of alginic acid, a natural polysaccharide found in marine brown algae. SA has been widely used as a food and pharmaceutical additive, a tablet disin-

tegrant, and a gelling agent (Kibbe, 2000). MAS is a mixture of montmorillonite and saponite clays (Kibbe, 2000) with a layered structure. Each layer is constructed from tetrahedrally coordinated silica atoms fused into an edge-shared octahedral plane of either aluminum hydroxide or magnesium hydroxide (Alexandre & Dubois, 2000; Kibbe, 2000). This layered structure of MAS possesses weakly positively charged edges and negatively charged faces. The positively charged edges on the MAS layers interact with SA to form a phase-separated microcomposite. Previous studies investigated the physicochemical properties and the drug and/or water vapor permeability of the SA–MAS composite films (Pongjanyakul, 2009; Pongjanyakul, Priprem, & Puttipipatkhachorn, 2005). Moreover, the SA–MAS composite dispersions were tested as a coating material for tablets and shown to effectively modulate drug release from the tablets (Pongjanyakul et al., 2005).

Nicotine (NCT), obtained from tobacco plants, is a volatile and strongly alkaline liquid. It has two well-separated pK_a values (pK_{a1} of 3.04 and pK_{a2} of 7.84), which cause the formation of diprotonated, monoprotonated, and neutral NCT species at acidic, neutral, and basic pH, respectively (Nair, Chetty, Ho, & Chien, 1997). Common NCT delivery sites are the skin and mucosal membranes, such as buccal and nasal mucosae, because both the neutral and protonated NCT forms can readily permeate the mucosal membrane (Chen, Chetty, & Chien, 1999; Nair et al., 1997). Due to the volatile liquid

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and oxidative degradation of the free base form of NCT, several researchers are seeking a material to adsorb the basic form of NCT to prevent evaporation and improve stability. Previously tested materials for NCT adsorption include cellulose powder (Mihranyan, Andersson, & Ek, 2004) and cation exchange resins (Borodkin, 1993; Cheng et al., 2000). Recently, the interaction between NCT and MAS at varying pH was also investigated. This composite led to the adsorption of NCT onto MAS particles and formation of NCT–MAS flocculates (Suksri & Pongjanyakul, 2008). The dry powder of NCT–MAS complexes could produce a sustained NCT release pattern in physiological fluids following mucosal administration (Pongjanyakul, Khunawattanakul, & Puttipipatkhachorn, 2009).

We recently tested SA–MAS films with a ratio of 1:1 at different pH. These composites demonstrated the potential to provide a film matrix for NCT delivery, especially through transmucosal delivery. The protonated and neutral NCT species could interact with the negatively charged MAS to form numerous NCT–MAS complexes that acted as microreservoirs in the films. This reservoir generation led to a reduction in NCT evaporation during film drying and sustained NCT release and mucosal membrane NCT permeation (Pongjanyakul & Suksri, 2009). Several researchers have also studied the effects of clay content on the physical properties of the polymer–clay composite films (Sothornvit, Hong, An, & Rhim, 2010; Magalhães & Andrade, 2009). Therefore, MAS content may affect the characteristics of the NCT-loaded SA–MAS films, particularly NCT retention in the films, NCT release kinetics and NCT permeation of the skin and mucosa.

The objective of this work was to study the influence of the SA–MAS ratio on the film characteristics of NCT-loaded SA–MAS films. The NCT-loaded SA–MAS films were prepared at pH 5 and 10, which represented the protonated and neutral NCT species, respectively. Film preparations were made by following a casting/solvent evaporation method. The surface morphology, internal structure, NCT content and muco-adhesive properties of the films were investigated. Furthermore, the NCT release and permeation across shed snake skin (a model skin) and porcine esophageal epidermis (a model mucosa) were also examined.

2. Materials and methods

2.1. Materials

MAS (Veegum®HV) and NCT (liquid state and free base form) were obtained from R.T. Vanderbilt Company Inc. (Norwalk, CT, USA) and Fluka (Buchs, Switzerland), respectively. SA (Manugel®DMF) was obtained from ISP Thailand Ltd. (Bangkok, Thailand). All other reagents used were analytical grade and used as received.

2.2. Preparation of the NCT-loaded SA–MAS films

The NCT-loaded SA–MAS films were prepared with SA–MAS ratios of 1:0.25, 1:0.5, and 1:1. The solid content in the dispersion for film casting was a total of 3 g of materials. The SA was initially dispersed in 100 ml of distilled water to obtain a homogeneous dispersion; subsequently the MAS was pre-hydrated with 100 ml of hot water and then added to the SA suspension. The composite dispersions were then mixed for 5 min at 5000 rpm using a homogenizer (Ystral T1500, Dottingen, Germany). NCT (0.3 g, 10% of the solid content in the dispersion) was subsequently added to the composite. The pH of the SA–MAS dispersion containing NCT was adjusted by titration with either 1N HCl or 1N NaOH. The final solution pH of either 5 or 10 was verified with a pH meter (Ion Analyzer 250, Coring, USA). After pH titration, the composite dispersions were adjusted to a final volume of 300 ml with distilled water. The dispersions were then mixed and incubated at 37 °C

for 24 h. The dispersions with NCT at SA–MAS ratios of 1:0.25 and 1:0.5 by weight were also prepared using the same procedure as mentioned above. Two-hundred and fifty milliliters of each of the SA–MAS dispersions with NCT at different pH was poured onto a plastic plate (15 cm × 20 cm) and allowed to evaporate at 50 °C for 24 h. The films were peeled off and stored in a desiccator (40 ± 2% RH).

To obtain the NCT-loaded SA films, SA (3 g) was dispersed in 200 ml of distilled water and the dispersions were then mixed for 5 min at 5000 rpm using a homogenizer. NCT (0.3 g, 10% of solid content in the dispersion) was then added to the SA dispersions. The pH of the SA dispersion with NCT was adjusted by adding a small amount of 1N HCl or 1N NaOH with stirring, while monitoring with a pH meter until the final pH of the dispersions was 5 or 10. After that, the dispersion was adjusted to a final volume of 300 ml with distilled water and incubated at 37 °C for 24 h before use. The film casting of the SA dispersion with NCT was done using the methods described above.

2.3. Determination of film thickness

The films were placed on a control plate and the film thickness was measured in 20 places using a microprocessor coating thickness gauge (Minitest 600B, ElektroPhysik, Germany). The probe was connected to a measurement gauge and calibrated using a standard film.

2.4. Determination of NCT content

The films (0.98-cm diameter) were cut and weighed. Discs were soaked in 50 ml of 2N HCl and incubated at 37 °C with intermittent shaking for 24 h (Pongjanyakul & Suksri, 2009). The solution was collected, filtered using a 0.45-μm cellulose acetate membrane and analyzed with a UV–visible spectrophotometer at a wavelength of 259 nm (Shimadzu UV1201, Japan). The NCT content was calculated as the percentage by weight.

2.5. Surface morphology and internal structure of the films

The surface morphology and internal structure of the films was observed by scanning electron microscopy (SEM). For internal structure studies, the films were immediately fractured after immersion in liquid nitrogen for 2 s. The films were mounted onto stubs, sputter coated with gold in a vacuum evaporator and photographed using a scanning electron microscope (Jeol Model JSM-6400, Tokyo, Japan).

2.6. In vitro release studies

A 6 ml modified Franz-diffusion cell (1-cm diameter) was used and the receptor solution (pH 5.6 citrate–phosphate buffer solution (CPBS) at 37 °C) was stirred at 600 rpm. A piece of 0.45-μm cellulose acetate (Sartorius Stedim Biotech Gmbh, Germany) was used as a membrane for release testing. The membrane was soaked in CPBS overnight and then mounted on a diffusion cell. The films (0.68-cm diameter) were placed on the hydrated membrane and the cells were fixed and tightly fastened with a clamp. At appropriate intervals, 0.4 ml aliquots of the receptor solution were withdrawn and immediately replaced by fresh solution. The concentration of NCT in the receptor medium was collected and analyzed via HPLC.

The total time until 25% NCT content release ($T_{25\%}$) was calculated to compare NCT film release rates. The mechanism of NCT release was determined by using a semi-empirical equation or the power law as follows (Peppas, 1985; Siepmann & Siepmann, 2009):