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Chitosan-clay matrix tablets for sustained-release drug delivery: Effect of chitosan molecular weight and lubricant

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ABSTRACT

Matrix tablets prepared using chitosan-clay microparticles with various molecular weights (MWs) of chitosan were characterized in terms of hardness, swelling, and drug release. Moreover, the effect of magnesium stearate on the physical properties and drug release of the tablets was also examined. Montmorillonite clay, magnesium aluminum silicate (MAS), was used in this study. The results showed that chitosan-MAS microparticles with different chitosan MWs prepared by spray drying had similar micromeritic properties but displayed different nanocomposite types. The microparticles possibly possessed plastic deformation under the compression pressures to form matrix tablets. The tablets had greater hardness with increasing chitosan MW. Increasing the chitosan MW caused greater swelling of the tablets in acidic medium but reduced swelling in neutral medium. Chitosan-MAS tablets presented sustained-release patterns in both acidic and neutral media, and the drug release of the tablets in neutral medium decreased when using chitosan of higher MW. Furthermore, the introduction of up to 5%w/w magnesium stearate provided the tablets with lower hardness, higher friability, and lower drug release in acidic medium. These findings suggest that chitosan MW and lubricant content are important factors in the formulation of chitosan-MAS tablets and these tablets present good potential for oral sustained-release drug delivery.

1. Introduction

Polymeric matrix tablets have been widely used for oral sustained-release dosage forms. They can be prepared from hydrophobic and hydrophilic polymers [1]. Hydrophobic polymers, such as ethylcellulose [2], are insoluble in water, preventing the matrix tablets from swelling; drug release from this tablet type is mainly controlled by drug diffusion through water-filled channels. Conversely, hydrophilic matrix tablets can be prepared from semi-synthetic and natural polymers. The semi-synthetic polymer hydroxypropyl methylcellulose [3] has been used as a matrix-former in tablets from which drug release kinetics were controlled by both drug diffusion and polymeric swelling. Natural polymers, such as xanthan gum [4], sodium alginate [5,6], and chitosan [7,8], have been used for this purpose because of their biodegradability and biocompatibility.

Chitosan is a deacetylated derivative of chitin, which consists of *d*-glucosamine and *N*-acetyl-*d*-glucosamine units. Chitosan is a weak base (pK_a = 6.2–7.0) [9] that is insoluble at neutral and alkaline pH but swells and becomes soluble in acidic medium due to protonation of its amino groups [10]. Chitosan has been widely used for fabricating drug delivery systems, including matrix tablets, in which chitosan could be used to modify or sustain drug release from the tablet formulations [7]. Unfortunately, natural chitosan is bulky, and it produces flaky particles that have poor micromeritic properties for tablet production, particularly if a direct compression method is used. For this reason, modification of chitosan is necessary. Thus, chitosan dispersions in acidic medium were prepared and dried using tray drying and spray drying methods for comparison. Tray-dried chitosan provided irregularly-shaped chitosan, resulting in poor flowability and compressibility [11]. In contrast, spray-dried chitosan particles were spherical in shape [12], thus providing better flowability and compressibility than tray-dried chitosan [11]. Moreover, chitosan was combined with water-soluble substances, such as gelatin [13] or lactose [14], to improve the micromeristic properties of spray-dried particles. However, tablets prepared using particles of chitosan blended with these substances and could not sustain drug release for long periods of time.

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Montmorillonite clay, also known as magnesium aluminum silicate (MAS), has a layered structure consisting of tetrahedrally coordinated silica atoms fused into an edge-shaped octahedral plane of either aluminum hydroxide or magnesium hydroxide [15]. The structural layers of MAS that bear silanol (-SiOH) groups with negative charges can be separated upon hydration in water. Thus, the negatively charged silicate layers were able to interact electrostatically with a positively charged substance [16,17]. Upon mixing chitosan and MAS, particles flocculated immediately to form a dispersion because the amino groups of chitosan could strongly interact with MAS [18]. The chitosan-MAS dispersions were cast onto a plastic plate and dried to obtain a nanocomposite film [19]. The chitosan-MAS nanocomposite types were dependent on the MAS content. The addition of a small amount of MAS could form exfoliated nanocomposites, with the MAS silicate layers entirely dispersed in the chitosan matrix. In contrast, adding a large amount of MAS allowed the chitosan molecules to insert into the space between the two silicate layers of MAS, resulting in intercalated nanocomposites. The nanocomposite formation had a significant effect on the chitosan-MAS films, showing decreased water uptake, swelling and drug permeability than the chitosan films [19].

Recently, chitosan-MAS microparticles were produced by a spray drying method [20]. An exfoliated nanocomposite of the microparticles was formed by immediate drying at high temperatures, which was not dependent on the MAS content added. The chitosan-MAS microparticles provided better flowability than the spray-dried chitosan. The swelling capacity of the chitosan-MAS tablets decreased with increasing MAS ratios in both acidic and neutral media. Additionally, the tablets prepared using chitosan-MAS microparticles at a 1:0.6 ratio displayed the slowest drug release in acidic conditions. For additional development of chitosan-MAS microparticles as matrix forming agents in tablets, the effect of chitosan molecular weight (MW) on the physical properties of microparticles is worth investigating because several studies have reported changes in the micromeritic properties and drug release of spray-dried chitosan microparticles when using different chitosan MWs [21]. In addition, the amount of lubricant, which has been used as an additive to reduce friction in tablet preparations, also affects the physical properties of tablets [22,23]. Thus, lubricants may effect a change in the characteristics and drug release of chitosan-MAS tablets.

The objective of this study was to prepare spray-dried chitosan-MAS microparticles using different chitosan MWs and to characterize the resulting particles. Characteristics of the chitosan-MAS microparticles, such as particle morphology, particle size, thermal behavior, crystallinity, flowability, and compressibility, were investigated. In addition, the effects of chitosan MW and lubricant content on the physical properties of and drug release from chitosan-MAS tablets were examined. Propranolol HCl, a freely soluble drug in 0.1 M HCl and pH 6.8 phosphate buffer [24], was used as a model drug for investigating a sustain release property of chitosan-MAS tablets.

2. Materials and methods

2.1. Materials

Chitosan (85% degree of deacetylation) with MWs of 80, 400, and 800 kDa, which were defined as low, medium, and high MWs of chitosan (LCS, MCS, and HCS), respectively, was purchased from Bio 21 Co., Ltd. (Chonburi, Thailand). MAS (Veegum® HV) was purchased from R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA). Propranolol hydrochloride (Changzhou Yabang Pharmaceutical Co., Ltd., Jiangsu, China) and magnesium stearate (Mallinckrodt Inc., USA) were also used in this study. All other reagents were of analytical grade and were used as received.

2.2. Preparation of chitosan-MAS microparticles

A chitosan dispersion (3% w/v) in 1% acetic acid was prepared by stirring overnight at room temperature. A MAS suspension (4% w/v) was prepared in hot water using distilled water to adjust to the final volume. Then, the 4% w/v MAS suspensions were diluted using 10 mM acetate buffer at pH 4 to achieve the final 3% w/v MAS dispersion. The 3% w/v chitosan (62.5 ml) and 3% MAS dispersions (37.5 ml) were then mixed to achieve a chitosan-MAS mass ratio of 1:0.6, with the solid content of the composite dispersion kept constant at 3% w/v. For the chitosan microparticles, 3% w/v chitosan was prepared without MAS. Then, the final pH of the dispersions was adjusted to 4 using glacial acetic acid. The dispersions were then mixed for 30 min using a homogenizer and stored at room temperature for 24 h before spray drying. The dispersions were dried using a spray dryer (Mobile MINOR™ GEA Niro A/S Soeborg, Denmark) under the following conditions: inlet temperature = 150 °C; outlet temperature = 80 ± 3 °C; air pressure for feeding = 80 kPa; and feed rate = 1000 ml h^{-1}. Chitosan and chitosan-MAS microparticles were collected from the cyclone and stored in a desiccator before testing.

2.3. Characterization of chitosan and chitosan-MAS microparticles

2.3.1. Particle size and morphology studies

The size of chitosan and chitosan-MAS microparticles was determined using a laser diffraction particle size analyzer on a Mastersizer2000 (Malvern Instruments Ltd., UK) using a Scirocco2000 dry powder sampling accessory. The size-frequency distributions were plotted, and the particle sizes, volume-weighted mean diameter, were reported. Moreover, $D_{10\%}$, $D_{50\%}$, and $D_{90\%}$, which were the volume-number diameters where the given percentage of the particles was smaller than that size, were also determined. In addition, the size distribution was computed in terms of a polydispersity index (PI) expressed as:

$$PI = \frac{D_{90\%} - D_{10\%}}{D_{50\%}} \quad (1)$$

The particle morphology of the microparticles was assessed using scanning electron microscopy (SEM). The samples were mounted on dummies, sputtered with gold in a vacuum evaporator, and then viewed using a scanning electron microscope (Hitachi S-3000 N, Tokyo, Japan).

2.3.2. Differential scanning calorimetry (DSC)

The DSC thermogram of the samples was recorded using a differential scanning calorimeter (DSC822^e, Mettler Toledo, Switzerland). An accurately weighted sample (2.5–3.5 mg) was placed into 40-μl aluminum pans without an aluminum cover. Measurements were performed over a temperature range of 30–450 °C at a heating rate of 10 °C min^{-1}.

2.3.3. Powder X-ray diffractometry (PXRD)

The PXRD pattern of the samples was recorded using a powder X-ray diffractometer (Bruker D8 ADVANCE diffractometer, Germany) using Cu kα radiation generated at 40 kV and 40 mA as the X-ray source, an angular scan step of 2–25 °2θ and a step angle of 0.02 °2θ s^{-1}. The thickness of the silicate MAS layers was calculated using Bragg's equation: