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Research Paper

Particle agglomeration of chitosan–magnesium aluminum silicate nanocomposites for direct compression tablets

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ABSTRACT

Exfoliated nanocomposites of chitosan-magnesium aluminum silicate (CS-MAS) particles are characterized by good compressibility but poor flowability. Thus, the aims of this study were to investigate agglomerates of CS-MAS nanocomposites prepared using the agglomerating agents water, ethanol, or polyvinylpyrrolidone (PVP) for flowability enhancement and to evaluate the agglomerates obtained as direct compression fillers for tablets. The results showed that the addition of agglomerating agents did not affect crystallinity, but slightly influenced thermal behavior of the CS-MAS nanocomposites. The agglomerates prepared using water were larger than those prepared using 95% ethanol because high swelling of the layer of chitosonium acetate occurred, allowing formation of solid bridges and capillary force between particles, leading to higher flowability and particle strength. Incorporation of PVP resulted in larger agglomerates with good flowability and high strength due to the binder hardening mechanism. The tablets prepared from agglomerates using water showed lower hardness, shorter disintegration times and faster drug release than those using 95% ethanol. In contrast, greater hardness and more prolonged drug release were obtained from the tablets prepared from agglomerates using PVP. Additionally, the agglomerates of CS-MAS nanocomposites showed good carrying capacity and provided desirable characteristics of direct compression tablets.

1. Introduction

Tablets are a conventional platform that is widely used for the oral administration of drugs. They are mainly composed of drug powders and excipients such as fillers or diluents, disintegrants, anti-adherents and lubricants. The solid components are compacted under compression pressure to form disc-like or cylindrical specimens. The filler is important and is added to increase the amount of powder and to form the tablet after compaction. The crucial properties of tablet fillers are compressibility and flowability, especially when the tablets are produced using a direct compression method (Jivraj et al., 2000; Li et al., 2017). Direct compression fillers are mainly produced from natural polymers; for example, microcrystalline cellulose (MCC). MCC possesses excellent compressibility (Mitrevej et al., 1996; Shlieout et al., 2002; Mohammed et al., 2005; 2006) but poor flowability because it contains fibrous and elongated particles (Landín et al., 1993; Mohammadi and Harnby, 1997; Gamble et al., 2011; Horio et al., 2014). Improvement of MCC flowability could be achieved by changing the particle shape. Spherical MCC particles exhibit good flowability and higher compressibility under direct compression (Horio et al., 2014). In another study, rice starches were modified by a spray drying method to form an agglomeration of rice starch grains. Spray-dried rice starch has a spherical shape and good flowability for direct tableting (Mitrevej et al., 1996).

Chitosan (CS), an *N*-deacetylated derivative of chitin, is a positively charged biopolysaccharide composed of *N*-acetyl-D-glucosamine and D-glucosamine. It is a weak base with a pK_a value for the D-glucosamine residue in the range of 6.2–7.0 (Hejazi and Amiji, 2003). CS is in a protonated form in acidic media, causing the swelling properties of CS (Illum, 1998). It has been used as a matrix former for preparing drug delivery systems, such as films (Hermans et al., 2014; Tejada et al., 2017), beads (Chen et al., 2008; Varshosaz et al., 2009), tablets (Rege et al., 1999), microparticles and nanoparticles (Piccirilli et al., 2014; Unsoy et al., 2014). Furthermore, CS has been developed for use as a tablet diluent. Tray-dried CS has been studied, but it provided poor flowability and compressibility due to the irregular shape of the particles (Rege et al., 2003). Alternatively, CS particles produced by a spray-drying method possessed a spherical shape (Rege et al., 2003; Nunthanid et al., 2004; Khlibsuwan and Pongjanyakul, 2015), and thus better flowability and compressibility were observed in comparison to tray-dried CS (Rege et al., 2003). Spray-dried CS was alternatively employed as a binder in tablets, resulting in a sustained-release pattern

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because it could be swollen to form a gel matrix in an acidic medium (Nunthanid et al., 2004). In other experiments, CS was blended with water-soluble substances, such as lactose (Chinta et al., 2009) or gelatin (Kokil et al., 2005), to improve the micromeristic properties of spray-dried particles for use in tablets.

An alternative approach that could improve the micromeristics of spray-dried CS is to blend CS and water-insoluble materials before spray drying. Clays were used for this purpose; for example, magnesium aluminum silicate (MAS). MAS, a water insoluble clay with a negative charge (Suksri and Pongjanyakul, 2008), is composed of silicate layers where a component of each layer is a central octahedral sheet of aluminum or magnesium and two external silica tetrahedron sheets (Alexandre and Dubois, 2000). MAS can disperse and swell in water, and silanol (−SiO−) groups on the surface of the silicate layers can interact with a positively charged substance via electrostatic interaction (Suksri and Pongjanyakul, 2008; Rojtanatanya and Pongjanyakul, 2010; Rongthong et al., 2013). MAS and CS could immediately form flocculated particles in the dispersion after mixing because the amino groups of CS could strongly interact with MAS (Khunawattanakul et al., 2008). The cast CS-MAS films could form a nanocomposite material, with the types of nanocomposite dependent upon the incorporated MAS content (Khunawattanakul et al., 2010). As an exfoliate nanocomposite, MAS silicate layers disperse in the CS matrix with the addition of a small amount of MAS. In contrast, intercalated nanocomposites are created when CS molecules are intercalated into the space between the silicate layers of MAS at a higher MAS content.

Recently, CS-MAS nanocomposite particles produced by spray drying were used as matrix formers in controlled release tablets (Khlibsuwan and Pongjanyakul, 2015, 2016) and drug delivery systems (Khlibsuwan et al., 2017). An exfoliated nanocomposite structure was formed upon immediate drying at high temperatures, which was not dependent on the MAS content. However, the use of low molecular weight CS with MAS could form the intercalated nanocomposites (Khlibsuwan and Pongjanyakul, 2016). Interestingly, spray-dried CS-MAS nanocomposites possessed better flowability than spray-dried CS. The incorporation of MAS at higher ratios resulted in an increased hardness of tablets prepared from spray-dried CS-MAS nanocomposites when increasing the compression pressure. The swelling capacity of the tablets decreased with increasing MAS content in both acidic and neutral media, allowing for time-controlled drug release from the matrix tablets (Khlibsuwan and Pongjanyakul, 2015). Unfortunately, spray-dried CS-MAS nanocomposites still had poor flowability; therefore, it is of interest to enhance flowability of spray-dried CS-MAS nanocomposites by the agglomeration method. Additionally, the preparation and characterization of the CS-MAS agglomerates for use in direct compression tablets is not previously reported.

The objectives of this study were to prepare and characterize the agglomerates of spray-dried CS-MAS nanocomposites by using agglomerating agents and to evaluate their potential for use as direct compression fillers. The agglomerating agents used were water, an aqueous ethanol solution, and polyvinylpyrrolidone (PVP) in 95% ethanol. Characteristics of the CS-MAS agglomerates such as particle size, particle strength, flowability, thermal behavior, and crystallinity, were investigated. The physical properties and drug release from tablets prepared from the CS-MAS agglomerates were investigated. In addition, the dilution potential or carrying capacity of the CS-MAS agglomerates as direct compression fillers was examined in this study.

2. Materials and methods

2.1. Materials

CS (85% degree of deacetylation) with MW 800 kDa was purchased from Bio 21 Co., Ltd. (Chonburi, Thailand). MAS in granular form (Veegum® HV) was purchased from R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA). Propranolol HCl (Changzhou Yabang Pharmaceutical Co., Ltd., Jiangsu, China), acetaminophen (Pharma Thai Co., Ltd., Bangkok, Thailand), PVP K90 (K Science Center & Medical Ltd., Khon Kaen, Thailand) and magnesium stearate (Mallinckrodt Inc., St. Louis, MO) were also used in this study. All other reagents were of analytical grade and were used as received.

2.2. Preparation of CS-MAS nanocomposites

A CS dispersion (3% w/v) was prepared by dispersing CS powder into a 1% w/v acetic acid solution. MAS suspensions (4% w/v) were prepared using hot water and were adjusted to the final volume using purified water. Then, the MAS suspension was diluted using 10 mm acetate buffer at pH 4 to achieve a concentration of 3% w/v. After that, 10 L of a 3% w/v CS dispersion was mixed with 6 L of a 3% w/v MAS dispersion to achieve 1:0.6 ratios of CS and MAS with a 3% w/v solid content. The final pH of the mixture was adjusted to 4 using glacial acetic acid. Finally, the mixtures were stirred and stored at room temperature (27 ± 2 °C) for 24 h before spray drying. The composite dispersions were dried using a spray dryer (Mobile MINOR™ GEA Niro A/S Soeborg, Denmark) under the following conditions: diameter of nozzle size = 1.5 mm; inlet temperature = 150 °C; outlet temperature = 80 ± 3 °C; air pressure for feeding = 80 kPa; and feed rate = 1.7 L h^{-1}. CS-MAS nanocomposites were collected from the cyclone and stored in a desiccator before testing.

2.3. Preparation of CS-MAS agglomerates

CS-MAS nanocomposites (75 g) were mixed with 11.3, 22.5 or 33.8 mL of water produced by reverse osmosis, which yielded 15, 30 or 45% v/w of nanocomposites, respectively. The wet mass was pressed through an 841-μm sieve, dried at 50 °C in a hot air oven, and then passed through a 150-μm sieve. The agglomerates were divided into 2 fractions of large and small particles using a 75-μm sieve. The large particle fraction (75–150 μm) was retained on the sieve and the small particles (< 75 μm) passed through the sieve. Each fraction was weighed and the % yield was calculated. In addition, the effect on the characteristics of agglomerates of ethanol concentration (50, 70, or 95% v/v) and PVP in 95% ethanol (2.5, 5.0, or 7.5% w/v) at the volume of 45% v/w of nanocomposites was investigated.

2.4. Characterization of CS-MAS agglomerates

2.4.1. Particle morphology studies

The particle morphology of the agglomerates 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-3000N, Tokyo, Japan).

2.4.2. Flowability studies

Flowability of the agglomerates was determined using the angle of repose and Carr's index. For the repose angle, the samples were poured through a funnel onto a horizontal surface, forming a conical pile. The height (h) and radius (r) of the pile were measured, and the angle of repose (α) was computed using following equation:

$$\tan \alpha = \frac{h}{r} \quad (1)$$

The samples (30 g) were weighed and poured into a 100 ml cylinder. The initial volume of the sample was recorded and the bulk density (D_B) was calculated. Then, the cylinder was tapped 500 times 1.5 inches from the bottom, and the final volume was used to compute the tapped density (D_T) of the sample. Carr's index (%) was calculated using the following equation:

$$\text{Carr's index}\,(\%) = \frac{(D_T - D_B)}{D_T} \times 100 \quad (2)$$