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Highly-porous mannitol particle production using a new templating approach

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ABSTRACT

A new method has been successfully developed to create highly-porous powder templates through the spray drying of mannitol, using citric acid as the templating agent and then removing the citric acid by ethanol washing of the spray-dried powders. It has been demonstrated that textural properties, such as the surface area and the pore volume of the resultant mannitol, can be tuned by varying the concentrations of citric acid, whey protein isolate (WPI), and Gum Arabic. The resulting powder structure is a mannitol network with significant porosity and high surface area of 8.0 ± 0.4 m^2/g and total pore volume of 0.075 ml/g. The scanning electron microscope micrographs were consistent with the Brunauer–Emmett–Teller (BET) surface area measurements. It has been found that higher concentrations of WPI, more than 0.5% w/w, have a detrimental effect on the porosity of the spray-dried powders from the solutions of mannitol/WPI with 2% (w/w) citric acid. For Gum Arabic, more than 1% (w/w) Gum Arabic causes lower porosities due to the lower citric acid removal by ethanol washing. The results of this study allow excipient powders to be produced with high specific surface areas.

1. Introduction

Recently, the use of mannitol as an alternative to lactose in food products and pharmaceutical formulations has significantly increased. Lactose is a reducing sugar, which is incompatible with some active pharmaceutical ingredients, such as peptides and proteins, and also has problems associated with lactose intolerance (Littringer et al., 2012; Steckel & Bolzen, 2004; Westermarck, Juppo, Kervinen, & Yliruusi, 1998). The non-hygroscopic nature of mannitol and consequently its low moisture content make it a desirable additive and excipient for moisture sensitive ingredients (Westermarck et al., 1998). Mannitol has also been used as a primary material for protein stabilization in dried protein formulations (Bakaltcheva, O'Sullivan, Hmel, & Ogbu, 2007; Hulse, Forbes, Bonner, & Getrost, 2009).

The most common application of mannitol in the pharmaceutical industry is its use as a diluent in tablet processing with both direct compression and wet-granulation methods (Kibbe, 2000). In general, compressibility of excipient powders has been reported to depend on properties, such as specific surface area, crystallinity, polymorph, particle size, and crystal habit (York, 1983).

Increasing the particle surface roughness increases the tablet crushing strength by promoting the bonding mechanisms between solid surfaces in the compact agglomerate (Karehill, Glazer, & Nyström, 1990; Riepma, Lerk, de Boer, Bolhuis, & Kussendrager, 1990). It has been suggested that dissolution rates of particles with large surface areas and porosities are relatively high, which results in fast tablet disintegration and dissolution (Danesh et al., 2001; Parikh, 2011; Simões, Sousa, & Figueiredo, 1996; Yamasaki, Kwok, Fukushige, Prud'homme, & Chan, 2011). It has been found that different crystal forms and polymorphs of theophylline have different physicochemical properties, which influences their tableting behavior (Suihko, Lehto, Ketolainen, Laine, & Paronen, 2001). The same result has been reported for different polymorphs of mannitol (Burger et al., 2000; Debord et al., 1987). McKenna and McCafferty (1982) reported that decreasing the particle size of spray-dried lactose increases the tablet tensile strength and results in stronger compacts. The effect of crystal habit on compressibility of powders has also been extensively reviewed (Garekani, Ford, Rubinstein, & Rajabi-Siahboomi, 1999; Marshall & York, 1991). Staniforth, Rees, Kayes, Priest, and Cotterill (1981) changed the crystal habit and porosity of mannitol and obtained a highly porous mannitol for direct compression by using a special crystallization technique.

Kanig (1964) improved the tableting properties of mannitol by decreasing the crystallinity of the particles through rapid solidification of the melted mannitol in a spray dryer. However, the produced amorphous fused mannitol was rather unstable, and its compressibility decreased as the crystallinity gradually increased during storage. Maas et al. (2011) produced spray-dried mannitol particles with different surface roughnesses by spray drying at different outlet temperatures. They found that increasing the outlet temperature of the spray dryer increased the crystal size and particle surface roughness, which was attributed to different crystallization mechanisms. In an attempt to increase the mannitol surface area, Yoshinari, Forbes, York, and Kawashima (2002) found that exposing the mannitol to a high relative humidity

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significantly changed the morphology of the particles and increased their surface areas from 0.4 to 2.3 $m^2 g^{-1}$, which are associated with the moisture-induced polymorphic transition of mannitol from the δ to β form. The high surface-area mannitol produced with this method has been shown to possess excellent compaction behavior (Yoshinari, Forbes, York, & Kawashima, 2003). Typical specific surface areas of mannitol powders have been reported to be between 0.3 and 0.6 $m^2 g^{-1}$ (Ho et al., 2012; Westermarck et al., 1998).

Different techniques can be used to obtain porous spray-dried particles, but the dominant method for producing porous inorganic particles by spray drying appears to be the use of aqueous solutions containing the main (core) material with a templating agent that is removed by heat treatment, including calcination (Balgis, Anilkumar, Sago, Ogi, & Okuyama, 2012; Lee, Gradon, Janeczko, Iskandar, & Okuyama, 2010; Nandiyanto et al., 2013; Zhang, Xie, Xu, Zhao, & Lei, 2010). The key challenge is to extend this understanding of the powder-templating process from inorganic materials to organic ones, thereby generalizing this understanding. A novel procedure has been used here to obtain highly-porous templates or frameworks of mannitol through the use of the low-cost and high-throughput spray-drying process for mannitol using citric acid as the templating agent. Then, the template material (citric acid) has been removed by ethanol washing of the spray-dried powders. We demonstrate that textural properties, such as surface area and pore volume of the resultant mannitol, can be tuned by varying the concentrations of citric acid, WPI, and Gum Arabic.

2. Materials and methods

2.1. Sample preparation

D-Mannitol ($C_6H_{14}O_6$), citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$), Gum Arabic from acacia trees and whey protein isolate (Balance, Vitaco Health Ltd, Auckland, New Zealand) were used in this study and dissolved in deionized water. The package label of this whey protein isolate (WPI) indicated the composition (per 100 g) as being 92 g protein, 0.4 g fat (total) including 0.2 g saturated fat, 0.5 g carbohydrate, and sodium 0.6 g.

In order to investigate and report the effects of citric acid, WPI, and Gum Arabic concentrations on the BET surface areas of mannitol, experiments were carried out by varying the composition of the solutions with additions of citric acid, WPI, and Gum Arabic to the mannitol solution. For all experiments, the mannitol concentrations were kept constant at 10% (w/w). The composition of the solution was varied with additions of citric acid % (w/w) to the 10% (w/w) mannitol solutions. Also, different concentrations of whey protein isolate or Gum Arabic % (w/w) have been added. Each solution was made up to a total weight of 100 g. All solutions were magnetically stirred at the room temperature of 25 °C for at least 30 min, so a clear solution was obtained without any visible crystals being present. The clear solutions were then spray dried. The pH of the solutions was measured with a pH electrode, InPro 3250 series (Mettler Toledo, M 300, Switzerland).

2.2. Operating conditions for spray drying

A Buchi B-290 laboratory-scale spray dryer was used to dry the solutions with an inlet gas temperature of 150 °C, a main air flow rate of 38 m^3/h (an aspirator setting of 100%), a pump rate of 8 mL/min (25% of the maximum rate), and a nozzle air flow rate of 470 L/h (40 on the nozzle rotameter scale). A collection vessel has been used to remove the freshly spray-dried powder from the bottom of a cyclone, and some of that powder has been mixed with ethanol for 24 h at the room temperature of 25 °C to remove the citric acid. This step has been followed by vacuum filtration (Fig. 1) and oven drying at 60 °C for 1 h. The dried cake was crushed and ground to produce the final powders. The yield of the drying process has been calculated as the mass of solids recovered from the collection vessel compared with the mass of solids in the feed solution, as a percentage. Gravimetric moisture analysis, Fourier transform infrared spectroscopy (FTIR), and BET have been performed on both the freshly spray-dried and ethanol washed powders immediately after spray drying; the remaining powders have been kept in sealed bags and in a refrigerator for scanning electron microscope (SEM) tests on the following day. Weighing the sample before and after drying in a fan-circulated oven (Labec, Australia) at 85 °C for 24 h has been used to measure the free moisture content (dry basis). For each concentration, experiment has been done three times and at least two replicate analyses have been done on samples. Data in this study are presented as means ± STD (standard deviation) and were obtained from at least three independent experiments.

3. Powder characterization

3.1. BET surface area analysis

N_2 adsorption and desorption isotherms have been used to determine surface areas and pore volumes (or pore size distribution) at the temperature of liquid N_2 (77 K) using a surface area analyzer (Quantachrome Autosorb-1). The Brunauer–Emmett–Teller (BET) equations have been used to calculate the surface areas, and the total pore volume has been calculated according to the Barrett–Joyner–Halenda (BJH) method. Outgassing of all samples has been carried out at room temperature overnight prior to measurements. Three replicates (at least) of each experiment have been done using fresh powder.

3.2. Fourier transform infrared spectroscopy (FTIR)

The extent of citric acid removal has been measured with FT-IR absorbance spectra using a single bounce diamond ATR (Universal ATR) in a Nicolet 6700 FTIR spectrometer (Thermo Fisher Scientific Inc.) controlled by OMNIC 8.2.387. Collection of the FT-IR spectra has occurred at a resolution of 4 cm^{-1} with 32 scans over a wavelengths range from 600 cm^{-1} to 2000 cm^{-1}. Baseline correction has been done using the OMNIC 8.2.387 software, with Microsoft Excel being used for further analysis. There is a stretching band at 1625 cm^{-1} in the spectrum of the pure citric acid solution, which may be attributed to the C═O in the dissociated carboxylic acid, while the stretching band is 1730 cm^{-1} when not dissociated (Masoudpanah & Seyyed Ebrahimi, 2011; Socrates, 2001). Five replicates (at least) for each sample have been performed.

3.3. Scanning electron microscope (SEM)

The powders have been observed using a scanning electron microscope, to show the structures of both the surface and bulk material. Sample preparation has included placing a small amount of the sample onto a carbon tape on an aluminium sample stab. A standard thickness of 30 nm gold coating has been given for each sample for producing the conductive surface (Emitech, K550X, Quorum Technologies, UK). A Zeiss EVO 50 scanning electron microscope, fitted with a LaB6 filament, has been used. The operating conditions were 10 keV beam energy, 2A filament current, and a spot size of 360. A range of 900 to 2500 times magnification was used in the images and the images were captured using the software ImageSlave v2.11.

3.4. Particle size analysis

Laser diffraction using a Malvern Mastersizer 3000 (Malvern Instruments, UK) with a dry powder feeder unit has been used to measure the particle size distributions. Two replicates have been carried out for each test, and we have reported the average mean particle size.