International Journal of Pharmaceutics 392 (2010) 178–188

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The enhanced aerosol performance of salbutamol from dry powders containing engineered mannitol as excipient

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ARTICLE INFO

Article history:
Received 20 January 2010
Received in revised form 12 March 2010
Accepted 27 March 2010
Available online 2 April 2010

Keywords:
Dry powder inhaler
Mannitol
Micromeritic
Deposition study
Crystallisation
Ratio of acetone/water

ABSTRACT

The aim of the present study was to investigate the effect of crystallising mannitol from different binary mixtures of acetone/water on the resultant physical properties and to determine the effects of any changes on *in vitro* aerosolisation performance, when the different mannitol crystals were used as a carrier in dry powder inhaler formulations containing salbutamol sulphate. Mannitol particles were crystallised under controlled conditions by dissolving the sugar in water and precipitating the sugar using binary mixtures of acetone/water in different percentages as anti-solvent media. For comparison purposes the physical properties and deposition behaviour of commercially available mannitol were also studied. SEM showed that all crystallised mannitol particles were more elongated than the commercial mannitol. Solid state studies revealed that commercial mannitol and mannitol crystallised using acetone in the presence of 10–25% v/v water as anti-solvent was β-polymorphic form whereas mannitol crystallised in the presence of a small amount of water (0–7.5%) was the α-form. All the crystallised mannitol samples showed poor flowability. Nevertheless, the powdered crystallised mannitol and commercial samples were blended with salbutamol in the ratio 67.5:1. The aerosolisation performance of the formulations containing the engineered mannitol (evaluated using Multi Stage Liquid Impinger) was considerably better than that of the commercial mannitol formulation (the fine particle fraction was increased from 15.42% to 33.07–43.99%, for the formulations containing crystallised mannitol). Generally, carriers having a high tapped density and high fraction of fine carrier particles produced a high FPF. The improvement in the DPI performance could be attributed to the presence of elongated carrier particles with smooth surfaces since these are believed to have less adhesive forces between carrier and the drug resulting in easier detachment of the drug during the inhalation.

1. Introduction

Since dry powder inhalers (DPIs) are pharmaceutical dosage forms which deliver drugs effectively to the respiratory tract but do not incorporate propellants as components, they have become of increasing popularity as both industry and consumers continue to appreciate the importance of 'green' issues. In addition they have a long history of successful use in the treatment of both local and systemic diseases (Timsina et al., 1994).

One of the methods designed to improve DPI performance has been to use engineered drug particles or indeed, carrier particles (Maa and Prestrelski, 2000; Thompson, 1998; Chan and Chew, 2003). DPI formulations usually incorporate at least one other component, as a carrier to facilitate aerosolisation of the active agent, lactose being the most common. This sugar has been employed owing primarily to its long history of use and consequent well-established stability and safety profile. Particles of lactose can also be produced pre-determined properties such as with a smooth surface and good flow properties (Smyth and Hickey, 2005). However, the use of lactose has some disadvantages, such as its incompatibility with drugs (such as formoterol, budesonide and peptides) that have primary amine moieties (Smyth and Hickey, 2005). Furthermore, lactose can be produced with traces of their bovine source (proteins), which, therefore, carries a theoretical risk of transmissible spongiform encephalopathy (TSE) (EC Statement, 2002). Other excipients such as mannitol have been suggested as possible alternative carriers for DPI formulations (Steckel and Bolzen, 2004; Tee et al., 2000).

Mannitol is an attractive alternative carrier to lactose because it does not have a reducing effect, it is less hygroscopic than some of the other sugars, gives a high sweet after-taste which could be used

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doi:10.1016/j.ijpharm.2010.03.057

to confirm to the patient that a dose has been successfully administered, and it has the capacity to provide a high fine particle dose of incorporated drug upon powder aerosolisation (Saint-Lorant et al., 2007). However, the effects of engineered mannitol as a carrier on DPI performance have to date not been investigated. In this study mannitol particles were crystallised using binary combinations of acetone/water as anti-solvent. The resultant batches of crystallised mannitol powders, produced using different acetone concentrations were then tested to explore their suitability for inclusion as DPI excipients.

2. Materials and methods

2.1. Materials

Salbutamol sulphate (LB Bohle, Germany), mannitol (Fisher Scientific, UK) and acetone (Fisher Scientific, UK) were purchased from the named suppliers.

2.2. Preparation of crystallised mannitol powder by multi-solvent crystallisation

Mannitol is poorly soluble in acetone, and therefore, this organic solvent was selected as anti-solvent to recrystallise mannitol powder, using an anti-solvent precipitation technique. Mannitol (20 g) was dissolved in water (100 ml) to obtain a near-saturated solution at 70 °C under stirring conditions. A series of anti-solvent media with different ratios of acetone:water (100:0, 95:5, 92.5:7.5, 90:10, 85:15, 80:20 and 75:25 ml) were prepared (the total volume of each combination being 100 ml). These anti-solvent media were heated to 30 ± 1 °C, and the temperature was maintained constant for 10 min. After temperature equilibration, 20 ml of the saturated solution of mannitol was added to 100 ml of the anti-solvent medium at a constant rate of 2.5 ml/min under constant stirring condition. After adding the total volume of saturated mannitol, all the beakers containing the crystallised mannitol were removed from the heat, covered tightly with parafilm, and stored unstirred at room temperature (22 ± 2 °C) for 24 h. The suspensions were then filtered under vacuum through a filtration unit containing a Whatman filter paper (<0.45 μm). Crystallised mannitol samples obtained using the lower ratios of acetone:water (80:20 and 75:25) (high amounts of water) were stored for 48 h before filtering due to the low yield obtained after 24 h. The harvested crystallised mannitol samples were dried for 24 h in an oven at 75 °C before being transferred to a glass vial, which was, subsequently, sealed and the samples retained for further investigation.

2.3. Particle size analysis

Particle size analysis was conducted on an aerosolised dry sample using a Sympatec (Clausthal-Zellerfeld, Germany) laser diffraction particle size analyser. The volume mean diameter (VMD), and other particle size parameters corresponding to the size of the 10th, 50th and 90th percentile of particles ($D_{10\%}$, $D_{50\%}$ and $D_{90\%}$) were calculated automatically using the software provided. Approximately 2–3 g of the sample was transferred into the funnel of the VIBRI. The sample container was cautiously tapped against the funnel to ensure all the contents emptied. A test reference measurement was performed with the HELOS sensor using WINDOX software followed by a standard measurement. This was to ensure the material was flowing through the vibrating chute into the groove of the rotary table. The results are the mean and standard deviation of three to five determinations.

2.4. Powder flow measurement

The bulk and tapped densities were measured. Carr's Index and Hausner ratio were calculated and employed as an indication of flowability of the mannitol samples. The powder was filled into a 5 ml measuring cylinder and after recording the volume (bulk volume) the cylinder was tapped 100 times under ambient conditions (20 °C, 50% RH) and the new volume was recorded (tapped volume). The preliminary results showed that the use of 100 taps was sufficient to attain the minimum volume of the powders under study. Carr's Index and Hausner ratio were calculated using the following equations (Carr, 1965a,b).

$$\text{Carr's Index} = \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}\right] \times 100 \quad (1)$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (2)$$

Carr's Index values of less than 25% and Hausner ratio values less than 1.25 indicate acceptable flow properties.

2.5. True density measurement

The true density of all mannitol samples was measured using an ultrapycnometer 1000 (Quantachrom, USA) and helium gas according to the manufacturer's guidelines. The true density was taken as the mean of three determinations.

2.6. Fourier transition infrared spectroscopy (FT-IR)

FT-IR spectra were used to investigate any possible changes in crystallised mannitol that may have occurred at the molecular level during the crystallisation or drying processes. These spectra were recorded using ATR, FT-IR (PerkinElmer, USA) equipment for the different crystallised mannitol crystals. The scanning range was 450–4000 cm^{-1} and the resolution was 1 cm^{-1}.

2.7. Scanning electron microscope (SEM)

Electron micrographs of the original and crystallised mannitol samples were obtained using a scanning electron microscope (Philips XL 20, Eindhoven, Netherlands) operating at 15 kV. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation.

2.8. Different scanning calorimetry (DSC)

A differential scanning calorimeter (DSC7, Mettler Toledo, Switzerland) was used to measure the enthalpy and melting point of the different mannitol samples. The equipment was calibrated using indium and zinc. Samples weighing between 4 and 5 mg were crimped and sealed in aluminium DSC pans with pin-hole lids. Samples were heated from 25 to 300 °C at a scanning rate of 10 °C/min under nitrogen gas. The melting points and enthalpies of fusion were calculated using the supplied software (Mettler, Switzerland).

2.9. Shape factors determination

A micro-spatula was used to sample about 20 mg of powder, and a microscope slid and the powder was gently finger-tapped above the microscope slide. The microscope slide was then also manually tapped to remove accumulated powder until very thin powder dust was homogenously scattered over the slide. Particle size and shape were assessed using image analysis software (designed in-house at King's College London) installed on an Archimedes computer,