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Dry powder inhalers: Physicochemical and aerosolization properties of several size-fractions of a promising alterative carrier, freeze-dried mannitol

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ABSTRACT

The purpose of this work was to evaluate the physicochemical and inhalation characteristics of different size fractions of a promising carrier, i.e., freeze-dried mannitol (FDM).

FDM was prepared and sieved into four size fractions. FDMs were then characterized in terms of micromeritic, solid-state and bulk properties. Dry powder inhaler (DPI) formulations were prepared using salbutamol sulphate (SS) and then evaluated in terms of drug content homogeneity and in vitro aerosolization performance.

The results showed that the crystalline state of mannitol was maintained following freeze-drying for all size fractions of FDM. All FDM particles showed elongated morphology and contained mixtures of α-, β- and δ-mannitol. In comparison to small FDM particles, FDMs with larger particle sizes demonstrated narrower size distributions, higher bulk and tap densities, lower porosities and better flowability.

Regardless of particle size, all FDMs generated a significantly higher (2.2–2.9-fold increase) fine particle fraction (FPF, 37.5 ± 0.9%–48.6 ± 2.8%) of SS in comparison to commercial mannitol. The FPFs of SS were related to the shape descriptors of FDM particles; however, FPFs did not prove quantitative apparent relationships with either particle size or powder bulk descriptors. Large FDM particles were more favourable than smaller particles because they produced DPI formulations with better flowability, better drug content homogeneity, lower amounts of the drug depositing on the throat and contained lower fine-particle-mannitol.

Optimized stable DPI formulations with superior physicochemical and pharmaceutical properties can be achieved using larger particles of freeze-dried mannitol (FDM).

1. Introduction

Pulmonary drug delivery is one of the most ancient and successful methods of drug delivery systems (Washington et al., 1989). This delivery route is globally expected to grow to a reasonable market size of around $44 billion by 2016 (Nagavarapu, 2012), which contributes to its popularity within the pharmaceutical world. Good inhalation performance requires many characteristics such as stability, ease of processing, reproducibility and availability at the site of action. Particle deposition in the respiratory tract is affected by many physical properties of the aerosol such as size, shape, density and flowability (Telko and Hickey, 2005).

Dry powder inhalers (DPIs) are delivery devices that have been introduced in the 1970s. These dosage forms are stable, friendly to the environment, easy to formulate and cost-effective (Borgström et al., 2002). However, the relatively high variation in dose delivery was one disadvantage associated with DPIs that may lead to signif-

Abbreviations: ANOVA, one way analysis of variance; CI, Carr's compressibility index; CL, commercial lactose; CM, commercial mannitol; Copt, optical concentration; CV, coefficient of variation; D_{ae}, theoretical aerodynamic diameter; $D_{10\%}$, particle size at 10% volume distribution; $D_{50\%}$, particle size at 50% volume distribution (median diameter); $D_{90\%}$, particle size at 90% volume distribution; D_{equi}, equivalent diameter; DPI, dry powder inhaler; DSC, differential scanning calorimetery; ER, elongation ratio; FDM, freeze-dried mannitol; FPD, fine particle dose; FPF, fine particle fraction; FPM, fine particle mannitol; FR, flakiness ratio; FT-IR, Fourier transform infrared; GSD, geometric standard deviation; HSD, Honestly Significant Difference; I + M, inhaler with mouthpiece adaptor; IP, induction port; MMAD, mass median aerodynamic diameter; MSLI, Multi-Stage Liquid Impinger; OD, overall desirability; PSD, particle size distributions; PXRD, powder X-ray Diffraction; r^2, correlation coefficient; RD, recovered dose; RH, relative humidity; SD, standard deviation; SEM, scanning electron microscopy; SM, supplementary material; SS, salbutamol sulphate; TSE, transmissible spongiform encephalopathy; USP, United States Pharmacopeia; VMD, volume mean diameter; Y_i, the actual observed values; Y_{max}, the maximum acceptable values; Y_{min}, the minimum acceptable values.

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icant dose uniformity problems (Cegla, 2004). In addition, DPIs demonstrated low efficiency of drug delivery to the lower airway regions (Islam and Cleary, 2012). High drug-carrier adhesive forces and the consequent inadequate separation (drug re-dispersion) was one of the most important explanations for poor drug deposition efficiency of DPI formulations (Zhou and Morton, 2012).

DPI performance is essentially affected by particle–particle interactions (Xu et al., 2011). Therefore, engineered drug (Muhammad et al., 2013) and/or engineered carrier (Kaialy et al., 2012a) particles have been used to improve DPI performance. Recently, mannitol with promising aerosolization performance from a DPI was engineered by freeze-drying (Kaialy and Nokhodchi, 2013a). Freeze-drying process, also known as lyophilisation, is a particle-engineering technical procedure that encompasses three distinctive stages after the pre-treatment step, i.e., freezing, primary drying and secondary drying. In general, the procedure works by freezing the sample material, followed by reduction of the surrounding atmospheric pressure. This permits the frozen water in the product to sublimate directly from its solid-state to the gaseous state without liquid phase transition (Mellor, 1978). Several process and formulation factors should be optimized during the application of freeze-drying technique in order to insure stability of active ingredients (Carpenter et al., 1997). Sublimation is an endothermic process and therefore energy has to be supplied, by the heat transfer fluid in the channels within the shelves, in order to sustain the sublimation rate. The temperature of the shelf has to be maintained below the glass transition temperature (or 'collapse temperature') of the sublimate in order to avoid the formulation of amorphous (glassy) phase during freeze-drying (Adams and Ramsay, 1996).

Lactose is recognized as the excipient of choice for pulmonary delivery (Kou et al., 2012; Pilcer et al., 2012). However, lactose has some disadvantages when it is used as excipient for DPIs. For example, lactose is incompatible with drugs that have a primary amine group (e.g. budesonide and formoterol) and therefore it is less suitable for the next generation of inhalable products (e.g. proteins and peptides) (Patton and Platz, 1992). Lactose may demonstrate unpredictable physicochemical properties during pharmaceutical processing (Steckel et al., 2006). Moreover, lactose may carry a potential risk of transmissible spongiform encephalopathy (TSE) because it may be produced with traces of biovine (EC Statement, 2002). Therefore, engineering alternative carriers for DPI formulations appears to be scientifically warranted. Mannitol is a polyol broadly used in freeze-drying (Al-Hussein and Gieseler, 2012). Unlike lactose, mannitol does not have a reducing effect, and furthermore, it displays desirable properties for DPI formulations such as high crystallinity, non-hygroscopicity, excellent mechanical properties and chemically inert nature (D'Addio et al., 2013).

Particle size is an important design variable of DPI formulations. Several researchers highlighted that the presence of fine carrier particles had a positive influence on DPI performance (Jones and Price, 2006; Kaialy and Nokhodchi, 2013b). The mechanism by which fine particle excipients improve the performance of drug-carrier DPI formulations remains speculative; nevertheless, several hypotheses have been suggested including the active-sites theory (e.g. Zeng et al., 1998), agglomeration theory (e.g. Louey and Stewart, 2002), fluidisation theory (e.g. Shur et al., 2008) and buffer hypothesis (e.g. Dickhoff et al., 2006). However, caution should be kept in mind on the development of the latter formulations since the long-term safety of fine excipient particles is not established yet, which may induce concerns among regulatory authorities (Jones and Price, 2006; Chan and Chew, 2003). Inhaled fine carrier particles may lead to annoyance, irritation, coughing and even bronchoconstriction (Karhu et al., 2000). Inhaled fine mannitol could increase bronchial hyperresponsiveness (Rademacher et al., 2013). Therefore, we believe that preparing engineered carrier particles that would enhance the performance of drug-carrier binary DPI formulations without the use of a ternary additive of fine carrier is significantly justified. To this end, aerodynamically light powders of freeze-dried mannitol were prepared and the influence of physicochemical properties of freeze-dried mannitol on the performance of a DPI was investigated.

2. Materials and methods

2.1. Materials

Commercial mannitol (CM) was purchased from Fisher Scientific, UK. Micronized salbutamol sulphate (SS, $D_{10\%}$ = 0.5 ± 0.0 μm, $D_{50\%}$ = 1.7 ± 0.1 μm, $D_{90\%}$ = 3.1 ± 0.3 μm, SM–1)) was supplied from LB Bohle, Germany. Commercial lactose (CL, Pharmatose 100 M) was obtained from DMV International, Netherlands. Methanol (Fisher Scientific, UK) and 1-heptane sulfonic acid sodium salt (Sigma–Aldrich, Chemical Co., USA) used for HPLC experiments were obtained from the named sources.

2.2. Preparation of freeze-dried mannitols in different size fractions

Mannitol (5%, w/v in distilled water) was freeze-dried (SCANVAC CoolSafe™ freeze-dryer, CoolSafe 110-4, Lynge, Denmark) and then sieved (vibratory mechanical shaker, Endecotts Ltd, England) in different size fractions. The bulk fluffy FDM powder (the yield was >99% w/w) was poured above 125 μm sieve that was placed on top of different sieves (Retsch® Gmbh Test Sieve, Germany) with smaller aperture sizes above each other as follows: 90 μm, 63 μm, 45 μm, 20 μm and a metal collection plate. The mechanical shaker was tightened closely and then operated for 15 min. When the sieving process was complete, particles with different size fractions, i.e., FDM-A (90–125 μm), FDM-B (63–90 μm), FDM-C (45–63 μm) and FDM-D (20–45 μm), were collected and stored in sealed glass vials in laboratory (22 °C, 50% RH) until required. The sieved FDMs were stored for at least 7 days before further analyses to allow any possible charge relaxation to occur. The commercial mannitol (CM) and commercial lactose (CL) were as well sieved to separate the 63–90 μm fractions. The physicochemical properties of the sieved CM (Kaialy and Nokhodchi, 2013b) and CL (Kaialy and Nokhodchi, 2012b) were described previously.

2.3. Particle size measurements

Sieving is a rough method in determining particle size because it does not give exact measurements of any dimension of the particle. Therefore, volume-weighted particle size analysis of all mannitols was conducted using a Sympatec HELOS/RODOS (Clausthal-Zellerfeld, Germany) laser diffraction particle size analyser. The dispersion of air pressure was adjusted to 2.0-bar and a feed rate of 50% was applied. The particle size distributions (PSDs), i.e., particle size at 10% ($D_{10\%}$), 50% ($D_{50\%}$, median diameter), 90% ($D_{90\%}$) of the volume distribution and volume mean diameter (VMD) (mean ± SD, n = 9), were all calculated automatically using the WINDOX software based on Fraunhofer theory. Approximately 1 g of each powder was hand-fed into the VIBRI RODOS disperser through a funnel placed above the u-shaped groove of the rotating table. The sample container was cautiously tapped against the funnel to make sure the material was flowing through the vibrating chute into the groove of the rotary table. A background measurement was taken as the reference test. The measurements were set to trigger when the optical concentration (Copt) was higher than 1.1% and to end when the Copt fell below 1% for 5 s. The time-