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Influence of mannitol concentration on the physicochemical, mechanical and pharmaceutical properties of lyophilised mannitol

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ABSTRACT

Mannitol is a pharmaceutical excipient that is receiving increased popularity in solid dosage forms. The aim of this study was to provide comparative evaluation on the effect of mannitol concentration on the physicochemical, mechanical, and pharmaceutical properties of lyophilised mannitol. The results showed that the physicochemical, mechanical and pharmaceutical properties of lyophilised mannitol powders are strong functions of mannitol concentration. By decreasing mannitol concentration, the true density, bulk density, cohesivity, flowability, netcharge-to-mass ratio, and relative degree of crystallinity of LM were decreased, whereas the breakability, size distribution, and size homogeneity of lyophilised mannitol particles were increased. The mechanical properties of lyophilised mannitol tablets improved with decreasing mannitol concentration. The use of lyophilised mannitol has profoundly improved the dissolution rate of indomethacin from tablets in comparison to commercial mannitol. This improvement exhibited an increasing trend with decreasing mannitol concentration. In conclusion, mannitols lyophilised from lower concentrations are more desirable in tableting than mannitols from higher concentrations due to their better mechanical and dissolution properties.

1. Introduction

Industrially, the ordinary method to produce pharmaceutical compounds in the micrometer size range is the 'top-down' size reduction by milling (Kaialy and Al Shafiee, 2015). However, despite its popularity, milling has several disadvantages (Parrott, 1990). For example, milling offers low opportunity to produce particles with controlled characteristics such as size, shape and surface properties (Snow et al., 1984). Jet-milled particles usually exhibit broad size distributions, irregular shapes (Rasenack and Müller, 2004), and high levels of electrostatic charges, resulting in increased interparticle cohesive forces and potentially leading to poor product performance (Brodka-Pfeiffer et al., 2003; Kaialy, 2016). Moreover, jet-milling is incompatible with thermally sensitive materials and may raise safety worries due to dust exposure during processing (Tong and Chow, 2006).

Particle engineering techniques have been a subject to continuous improvement (Blagden et al., 2007). In contrast to jet-milling, particles with precisely engineered physical properties were, for instance, engineered using antisolvent crystallization (Kaialy et al., 2014, 2010), batch cooling crystallization (Kaialy et al., 2012), spray drying (Vehring, 2008), spray-freeze drying (Rogers et al., 2003), etc. Freeze-drying (lyophilisation) is a technical procedure that involves the removal of frozen water by sublimation. Lyophilised formulations commonly contain mannitol ($C_6H_{14}O_6$) as a bulking agent to increase the drug volume and thus preventing the 'blow-out' phenomenon that may occur in the case of a solution having a content of solute less than 1%, *w/v* (Franks and Auffret, 2008). The relatively high melting

Abbreviations: ΔH_0, Endothermic enthalpy of CM melting; ΔH_s, Endothermic enthalpy of LM melting; ANOVA, One way analysis of variance; API, Active pharmaceutical ingredient; c.opt, Optimal concentration; CI, Carr's index; CM, Commercial mannitol; C_{man}, Concentration of mannitol; $d_{10\%}$, particle size at 10% volume distribution; $d_{50\%}$, particle size at 50% volume distribution; $d_{90\%}$, particle size at 90% volume distribution; D_b, Bulk density DE Dissolution efficiency; DSC, Differential scanning calorimeter; D_t, tap density; EB, Ease of breakage; Eq, Equation; FT–IR, Fourier transform infrared; GI, Gastro intestinal; HSD, Honestly Significant Difference; *I*, Relative intensity; $I_{amorphous}$, the input to the intensity from the amorphous region; $I_{crystalline}$, the input to the intensity from the crystalline region; LM, Lyophilised mannitol; MDR, Mean dissolution rate; MDT, Mean dissolution time; *P*, Statistical probability; PXRD, Powder X–ray diffraction; Q_{10min}, The mean percentage of drug dissolved in the first 10 min; Q_{30min}, The mean percentage of drug dissolved in the first 30 min; Q_{4min}, The mean percentage of drug dissolved in the first 4 min; Q_{50min}, The mean percentage of drug dissolved in the first 50 min; RDB, Relative degree of breakage; SD, Standard deviation; SEM, Scanning electron microscopy; SM, Supplementary material; T_g, Glass transition temperature; TS, tensile strength.

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temperature of the mannitol/ice eutectic mixture (~ −1.5 °C) promotes efficient drying and physical stability of lyophilised mannitol (LM) solids (Kim et al., 1998). Mannitol can be lyophilised to produce a crystalline product, with the only precaution to maintain the temperature below that of incipient melting (Barresi et al., 2009). Therefore, the lyophilisation of 10% *w*/*w* solutions of mannitol and sucrose resulted in crystalline and amorphous materials respectively (Franks and Aufrett, 2007). Although amorphous mannitol can serve as a stabiliser for the active pharmaceutical ingredient (API) (Izutsu et al., 1994), the difficultly to maintain mannitol in the amorphous state during lyophilisation makes mannitol a poor choice as stabiliser (Pikal, 2002). However, the crystallisation of mannitol in frozen solutions during lyophilisation was inhibited by using phosphate buffer salts (Izutsu et al., 1994), polyvinylpyrrolidone (Cavatur et al., 2002) and NaCl (Telang et al., 2003).

During lyophilisation, mannitol was shown to crystallise as three common stable anhydrous polymorphic forms (i.e. α, β and *δ*) (Bauer et al., 2000; Berman et al., 1968; Botez et al., 2003; Burger et al., 2000; Kim et al., 1968) or as mannitol hemihydrate (Cavatur and Suryanarayanan, 1998; Cavatur et al., 2002; De Beer et al., 2007; Nunes et al., 2004; Romero-Torres et al., 2007; Yu et al., 1999). The polymorphic form of lyophilised mannitol was shown to have an effect on the stability of the lyophilised product during its storage (Cao et al., 2006; De Beer et al., 2009, 2007; Pisano et al., 2013). For example, the presence of hemihydrate mannitol in a lyophilised product could increase the rate of degradation, because hemihydrate mannitol is transformed during storage into anhydrous crystalline *δ*–mannitol by releasing its hydrate water within the amorphous phase containing the active pharmaceutical ingredient (Ahlneck and Zografi, 1990; Nunes et al., 2004). (Pisano et al., 2013) showed that a high content of mannitol in formulations containing mannitol and sucrose could better protect the enzyme molecules (acid phosphatase) from the dehydration stresses of lyophilization. Several studies showed the selection of the freezing method (Oddone et al., 2016) and the process conditions (Gan et al., 2004; Rene et al., 1993; Velardi and Barresi, 2008) as important parameters to be considered during cycle development. For example, (Kim et al., 1998) showed that a mixture of α– and β–mannitol was produced by slow freezing of 10% (*w*/*v*) mannitol, whereas fast freezing of 10% (*w*/*v*) and 5% (*w*/*v*) mannitol produced *δ*– and β–mannitol respectively. (Barresi et al., 2009) showed the temperature at which primary drying is carried out to affect the bulk density, rehydratability and residual moisture content of the lyophilised product. Higher rehydration rates were observed for products lyophilised at lower temperatures and lower initial concentrations. (Yu et al., 1999) showed the secondary drying conditions during freeze-drying as important parameters for the removal of the mannitol hemihydrate form. (Cannon and Trappler, 1999) showed slow cooling rates to promote the formation of α–mannitol. The use of surfactants, e.g. pluronic F68 (Hottot et al., 2008) and polysorbate (Haikala and Eerola, 1997), was shown to induce the formation of *δ*–mannitol phase and inhibit mannitol crystallisation.

Mannitol is an attractive pharmaceutical excipient that is becoming more and more popular in solid dosage forms (Ohrem et al., 2014). Mannitol shows the lowest hygroscopicity among the frequently used excipients as filler/binder and hence it can be utilized for moisture-sensitive drugs. Furthermore, mannitol does not increase the levels of blood glucose to such an extent as lactose (Geil, 1996) and thus it is especially suitable for pharmaceutical formulations that are used for diabetics (Zumbe et al., 2001). There is currently a strong driving force to use mannitol as an alternative excipient to lactose in pharmaceutical formulations (Eadala et al., 2009). This is because lactose exhibits unpredictable physicochemical properties during pharmaceutical production processes such as milling (Steckel et al., 2006) and crystallization (Zeng et al., 2000). Although lactose monohydrate is the most commonly used filler in tablet manufacture, lactose particles are required to have small size distributions to show good compactibility, leading to poor flow properties (Vromans, 1987). Additionally, lactose has a degree of security as inert excipient due to its incompatibility with compounds that have primary amine moieties (e.g. budesonide and formoterol), since Maillard-type condensation reaction is likely to occur (Bharate et al., 2010). Furthermore, although the side effects of lactose intolerance will sometimes not be observed in a patient using the small amounts of lactose present in tablets, the NOCEBO-effect should not be ignored. Therefore, lactose-free formulations may be needed for lactose-intolerant patients (Picksak and Stichtenoth, 2009). Moreover, lactose is produced from bovine milk or with bovine-driven additives, thus it carries a potential risk of transmissible spongiform encephalopathy (EMA, 2002). Mannitol is valuable in the production of tablets due to its excellent mechanical compressing properties, physical and chemical stability (Ohrem et al., 2014). Toxicity studies indicated that mannitol did not cause any considerable adverse effects (Lawson, 2000).

This study contributes to the development of mannitol as a potential excipient of the first choice. The purpose was address the theory that the physicochemical, mechanical and pharmaceutical properties of lyophilised mannitol (LM) powders are strongly dependent on the concentration of mannitol solution subjected to lyophilisation as one variable.

2. Materials and methods

2.1. Materials

Commercial mannitol (CM) was purchased from Fisher Scientific, UK. Indomethacin was purchased from Sigma-Aldrich, USA. Dissolution buffers were prepared according to the USP using potassium phosphate monobasic-white crystals (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for pH 7.2.

2.2. Preparation of lyophilised mannitols

A series of mannitol solutions with concentrations of 15%, 10%, 5% and 1% (*w*/*v*) were prepared by separately dissolving 15 g, 10 g, 5 g and 1 g of mannitol in distilled water such that the final volume of each solution is 100 mL. Each solution was then filtered (< 0.45 μm, cellulose filter paper), filled into 250 mL round-bottomed flasks (50 mL per flask), and consequently lyophilised using a similar protocol as follows. The flasks were kept in a freezer (−80 °C) for 12 h. The flasks containing the frozen mannitol solutions were quickly placed on the shelves of a Christ Beta 1–8 LD Freeze Dryer (Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany) using manifolds. The primary drying was performed at a shelf temperature of −27 °C, vacuum pressure of 0.518 mbar and a safety pressure of 0.700 mbar, whereas the final drying was performed at a shelf temperature of −35 °C, vacuum pressure of 0.224 mbar and a safety pressure of 0.380 mbar. For safety reasons (especially for mannitols lyophilised from the lowest concentrations, i.e. 1% *w*/*v*), the primary drying was carried out at a fixed low temperature for all samples in order to avoid collapse or 'blow-out' and to promote faster rehydratability of the LM products (Barresi et al., 2009; Franks and Auffret, 2008; Pikal-Cleland et al., 2000). The LMs were collected after 48 h. Fluffy LM powders were obtained with yields above 99% (*w*/*w*). The LM powders were sieved through a 0.50 mm sieve (Retsch® Gmbh Test Sieve, Germany), and stored in sealed glass vials in laboratory conditions (22 °C, 50% RH) until used. The preparations were