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Spherical agglomerates of lactose with enhanced mechanical properties

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ABSTRACT

The aim of this study was to prepare spherical agglomerates of lactose and to evaluate their physicochemical properties, flow properties, particle friability and compaction properties, and to compare them to commercially available types of lactose for direct compression (spray-dried, granulated and anhydrous β-lactose). Porous spherical agglomerates of α-lactose monohydrate with radially arranged prism-like primary particles were prepared exhibiting a high specific surface area. All types of lactose analysed had passable or better flow properties, except for anhydrous β-lactose, which had poor flowability. Particle friability was more pronounced in larger granulated lactose particles; however, particle structure was retained in all samples analysed. The mechanical properties of spherical agglomerates of lactose, in terms of compressibility, established with Walker analysis, and compactibility, established with a compactibility profile, were found to be superior to any commercially available types of lactose. Higher compactibility of spherical agglomerates of lactose is ascribed to significantly higher particle surface area due to a unique internal structure with higher susceptibility to fragmentation.

1. Introduction

In recent decades, extensive attention has been devoted to engineering pharmaceutical materials to tackle challenges in formulating solid dosage forms connected to their micromeritic properties. In the case of tablets, these comprise flowability and compaction properties, which are associated with particle size and its distribution, morphology, density, porosity, specific surface area and the crystal form of the substance (Paradkar and York, 2011). These properties of pharmaceutical substances govern the performance of powders during tableting and are therefore key to attaining tablets with desired properties. Direct compression is the preferred method of tablet production. To apply it, a tableting blend must have good flowability and compaction properties. Generally, such properties can be improved with an intermediate granulation step; however this demands substantial time and energy and is therefore undesirable. Another possibility is the use of high-functionality excipients, usually diluents specifically engineered for direct compression, which possess suitable flow and compaction qualities.

Lactose is the most common diluent in tablets due to its good physical and chemical stability (excluding Maillard reaction with amines), water solubility, availability and cost effectiveness (Gohel and Jogani, 2005). It is frequently produced with crystallization in the first stage, followed by milling and/or sieving. The outcomes of the milling process are often particles with a small size, irregular shape and sharp edges that have poor tableting properties. Lactose for direct compression is therefore commonly subjected to improvement. This is often achieved by procedures involving granulation, spray drying and co-processing (Gohel and Jogani, 2005). These additional stages of manufacturing after crystallization are time consuming and uneconomical. However, this step can be avoided if the agglomeration of crystals takes place simultaneously with crystallization. Spherical crystallization is a method in which primary crystals are transformed into spherical agglomerates during crystallization under controlled conditions (Kawashima et al., 1982). Such agglomerates have improved flowability and compaction properties, thus they are more readily compressed into a tablet by direct compression compared to primary particles (Kawashima et al., 1984a, 2003).

Various methods of spherical crystallization are applied depending on the material's physicochemical properties; however, spherical agglomeration and quasi-emulsion solvent diffusion are most commonly employed (Kovačič et al., 2012; Pawar et al.,

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2004a; Puechagut et al., 1998). In all methods, a solvent that dissolves the material to be crystallized and a non-solvent–generating supersaturation are required. In addition, a third solvent is typically added in spherical agglomeration and crystal-co-agglomeration, which acts as a bridging liquid to stimulate the formation of spherical agglomerates (Katta and Rasmuson, 2008; Pawar et al., 2004b). Additives such as emulsifiers or polymers are commonly introduced in the quasi-emulsion solvent diffusion method to stabilize the system and ensure proper diffusion of non-solvent into the dispersed phase (Kovačič et al., 2012; Nocent et al., 2001).

Adequate crystallization conditions are essential for attaining spherical agglomerates. It was shown that process parameters, such as the temperature of the crystallization system (Kawashima et al., 1984b; Ré and Biscans, 1999), agitation rate, amount and type of bridging liquid, feeding rate and concentration of solids, are of critical importance for agglomerates' micromeritic properties (Kawashima et al., 1995; Thati and Rasmuson, 2011, 2012). Spherical crystallization techniques have already been successfully applied to obtain spherical particles of various model drugs (Gupta et al., 2007; Kachrimanis et al., 1998; Usha et al., 2008). Furthermore, agglomerates of combinations of two drugs (Pawar et al., 2004a) or one drug and one excipient (Nokhodchi and Maghsoodi, 2008; Pawar et al., 2004b) have been reported. However the literature is still scant on obtaining agglomerates of an excipient (Nokhodchi et al., 2007).

The purpose of this study was to prepare spherical agglomerates of lactose for application in direct compression using a spherical crystallization method and to evaluate their physicochemical and mechanical properties, such as compressibility and compactibility. The study further aimed to critically compare the attained spherical agglomerates of lactose to the most common commercially available types of lactose for direct compression in terms of physicochemical properties, morphology, particle friability and mechanical properties of the tablets produced.

2. Materials and methods

2.1. Materials

α-lactose monohydrate (200 mesh) for spherical crystallization was provided by FrieslandCampina DMV, the Netherlands. Distilled water and 96% ethanol were used in the crystallization process. Tablettose® 70, Tablettose® 80, DuraLac® H and FlowLac® 100 were obtained from Meggle, Germany. Lactopress® SD 250, SuperTab® 11 and SuperTab® 14 were obtained from DFE Pharma, Germany. Copovidone (Kollidon® VA 64, BASF, Germany) was used as a dry binder and magnesium stearate (Ligastar MG 700, Peter Greven, Germany) as an antiadhesive and lubricant.

2.2. Methods

2.2.1. Spherical crystallization of lactose

The quasi-emulsion solvent diffusion method of spherical crystallization was used to prepare lactose particles in this study. Fifty grams of α-lactose monohydrate was dissolved in 220 ml of distilled water at an elevated temperature (in a range from 70 to 80 °C) in order to obtain a solution. The solution was maintained at an elevated temperature (in a range from 40 to 50 °C). Afterwards, the lactose solution was added drop by drop at a rate of 4.7 ml/min with a peristaltic pump into laboratory vessel filled with 500 ml of 96% ethanol adjusted to a temperature of 10 °C. The crystallization system was continuously stirred at a constant rate (350 rpm) with a pitched-blade turbine impeller. After complete addition of the lactose solution, the crystallization system was stirred for further 30 min. The spherical agglomerates obtained were filtered and dried at 40 °C for 12 h in a drying oven.

2.2.2. Thermal analysis

Thermal analysis was performed using differential scanning calorimetry (DSC) with a DSC 1 calorimeter (Mettler Toledo, Switzerland). Before recording the DSC curves, the calorimeter was calibrated with indium. Samples were weighed (4–6 mg) and sealed in an aluminium pan with a pierced lid. They were heated from 278 to 523 K at a rate of 10 K/min under nitrogen flow (50 ml/min).

2.2.3. Particle size distribution

The volume distribution of the particle size parameters of lactose particles was measured using the laser diffraction method (Mastersizer S, Malvern, UK). D10, D50 and D90 represent 10%, 50% and 90% points in the cumulative undersize particle size distribution (PSD), respectively. We used 96% ethanol as a dispersion medium and an adequate amount of the sample was introduced into the dispersion cell to achieve the required obscuration rate (10–20%). The stirring rate inside the dispersion cell was set at 1500 rpm. The diffraction indexes of ethanol (1.33) and lactose particles (1.356) were assigned. Measurements were made in triplicate. The width of PSD, also designated *span*, was calculated using the following equation (Merkus, 2009):

$$Span = \frac{D90 - D10}{D50} \quad (1)$$

2.2.4. Scanning electron microscopy

The particle morphology of the prepared spherical agglomerates of lactose and other commercially available types of lactose was observed through a scanning electron microscope (SEM) (Supra 35 VP, Carl Zeiss, Germany). The particles were set up on double-sided carbon tape (Oxon, Oxford Instruments, UK). The particle imaging was performed using an acceleration voltage of 1 kV and a secondary electron detector.

2.2.5. Specific surface area

The specific surface area of spherical agglomerates of lactose, SuperTab® 14SD, Tablettose® 70 and DuraLac® H were measured using the Brunauer–Emmett–Teller (BET) equation (Brunauer et al., 1938). The adsorption data were acquired by recording the nitrogen adsorption-desorption isotherms with a Micromeritics TriStar 3000 (Georgia, USA) at 77 K in a relative pressure interval from 0.03 to 0.3. Preceding the measurement, the samples were dried overnight at 100 °C and outgassed in a vacuum oven at room temperature. The measurements were made in triplicate.

2.2.6. Pycnometric, bulk and tapped density

The bulk volume was determined by gently introducing an accurately weighed amount of a sample (99% lactose, 0.5% dry binder and 0.5% antiadhesive) into a dry, graduated, 100 ml cylinder. The sample was mechanically tapped 1250 times using a Vankel Tap Density Tester (VanKel, North Carolina, USA) to determine the tapped volume. The bulk and tapped densities in grams per millilitre were calculated from the ratio of the mass and volume of the sample (2.9.34. Bulk density and tapped density of powders). The pycnometric density was determined on tableting blends according to Ph. Eur. 8th Ed. (2.9.23. Gas pycnometric density of solids) using a helium pycnometer (AccuPyc 1330, Micrometrics, Norcross, Georgia, USA). All determinations were made in triplicate.