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Milling induced amorphisation and recrystallization of α-lactose monohydrate

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ABSTRACT

Preprocessing of pharmaceutical powders is a common procedure to condition the materials for a better manufacturing performance. However, such operations may induce undesired material properties modifications when conditioning particle size through milling, for example. Modification of both surface and bulk material structure will change the material properties, thus affecting the processability of the powder. Hence it is essential to control the material transformations that occur during milling. Topographical and mechanical changes in surface properties can be a preliminary indication of further material transformations. Therefore a surface evaluation of the α-lactose monohydrate after short and prolonged milling times has been performed. Unprocessed α-lactose monohydrate and spray dried lactose were evaluated in parallel to the milled samples as reference examples of the crystalline and amorphous lactose structure. Morphological differences between unprocessed α-lactose, 1 h and 20 h milled lactose and spray dried lactose were detected from SEM and AFM images. Additionally, AFM was used to simultaneously characterize particle surface amorphicity by measuring energy dissipation. Extensive surface amorphicity was detected after 1 h of milling while prolonged milling times showed only a moderate particle surface amorphisation. Bulk material characterization performed with DSC indicated a partial amorphicity for the 1 h milled lactose and a fully amorphous thermal profile for the 20 h milled lactose. The temperature profiles however, were shifted somewhat in the comparison to the amorphous reference, particularly after extended milling, suggesting a different amorphous state compared to the spray-dried material. Water loss during milling was measured with TGA, showing lower water content for the lactose amorphized through milling compared to spray dried amorphous lactose. The combined results suggest a surface-bulk propagation of the amorphicity during milling in combination with a different amorphous structural conformation to that of the amorphous spray dried lactose. The hardened surface may be due to either surface crystallization of lactose or to formation of a low-water glass transition.

1. Introduction

Tableting performance is influenced by the chemical and mechanical properties of the formulation ingredients. In order to assure a good tableting performance, the powders are preprocessed using different unit operations such as granulation, drying, milling and blending, to achieve an optimal particle size, particle size distribution, stability, good flowability and a homogeneous mixture between the formulation components. However, the excipients or active ingredients might suffer from undesired structural changes which alter their surface properties during the different pre-conditioning steps (Gaisford, 2012). An example of this phenomenon is surface amorphisation due to milling – a common processing step prior to tableting in order to generate the desired particle size. High shear friction, crushing and collision forces in combination with arise in temperature during milling contribute to the amorphisation of the particles (Trasi et al., 2010; Willart and Descamps, 2009). The modifications induced through milling have been extensively studied in both drugs and excipients (Curtin et al., 2013; Willart et al., 2007). While amorphisation might be considered a side effect of the milling process, it is by no means always undesirable, for example the benefit of the amorphous state in increasing the dissolution rates for some poorly soluble drugs has been reported (Kawabata et al.,

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2011). On the other hand, problems related to the instability of the amorphous phase and the impact of particle surface amorphicity on the flowability of the powder have also been investigated (Caron et al., 2013; Fitzpatrick et al., 2007; Prescott and Barnum, 2000). A controlled degree of amorphicity in some excipients has shown an increase in tablet tensile strength while an extended level of amorphicity has led to a reduction in the tablet strength (Paterson et al., 2005). Thus, particle amorphisation, both at the surface and in bulk, can influence tableting performance leading to sticking and picking problems if adhesion and cohesion forces within the tablet become weaker (Badal Tejedor et al., 2015). Therefore uncontrolled particle amorphisation could have a detrimental effect on the final properties of the powder (Vromans et al., 1987). The unintended modification of the properties of the particles after milling introduces an uncertainty into the later performance of the powders. Therefore, it becomes important to study the changes in surface and bulk properties of the particles induced by milling (Gaisford, 2012; Hancock and Zografi, 1997) and the propagation of the amorphous content.

Milling induced amorphisation of particulate solids has been reported by several researchers. It has been suggested that the solid state amorphisation upon milling occurs during prolonged processing times (Caron et al., 2011). And the relationship between comminution and amorphisation was described as two stages, comminution dominates stage (early stage of milling) and amorphisation dominates stage (prolonged milling time) (Pazesh et al., 2017). However, the possibility of "surface-only" amorphisation, leading to a low overall level of amorphicity, was not discussed. Surface amorphisation during milling through melt mediated solid transformation has been proposed by Höckerfelt et al (Höckerfelt et al., 2009) and Pazesh et al (Pazesh et al., 2013). Here, the solid transformation is due to friction developed at the inter-particle contacts during the particle flow, thus it can be ascribed to a surface process. One of the bulk amorphisation approaches suggested in the literature is mechanical activation where the mechanical energy transferred through impact is stored in form of defects in the material. Frictional heat when the particles are sliding against each other followed by a solidification process and fracture of the particles contribute to disorder the initial crystalline structures (Lei et al., 2012). However, this process of activation is reversible resulting in recrystallization followed by a release of energy from the system (Hüttenrauch et al., 1985).

The potential impact of even partial amorphisation of the material on processing and product performance calls for careful characterization of the powders (Çelik, 2011). Different analytical methods have been used to characterize and quantify the degree of amorphicity of the milled powders in previous studies. Calorimetric methods such as differential scanning calorimetry and isothermal microcalorimetry are the most widespread methods mainly because of their sensitivity (lower than 1% w/w of the amorphous material) and the low mass of sample required. However, data interpretation and method design are critical for successful characterization. Near-Infrared spectroscopy (NIR), Raman spectroscopy and solid-state NMR offer an evaluation of the sample at the molecular and particulate level. They are quick and non-invasive methods detecting amorphous content of 1% w/w. Some of the drawbacks for these methods are the need for suitable reference spectra of the characterized samples, local heating by the beam and complex mathematical determination of the amorphous content (Gaisford, 2012; Willart et al., 2007). Dynamic vapor sorption (DVS) analyzes the sample at the particulate level providing additional information regarding the surface properties. Inverse-gas chromatography methodology offers a more accurate analysis on the particle surface properties (Einfalt et al., 2013; Vollenbroek et al., 2010). A less extensively used surface characterization technique is atomic force microscopy. AFM is surface sensitive to the material mechanical properties at the nanoscale (Badal Tejedor et al., 2017; Mahlin et al., 2004). In a recently developed method, the energy dissipation of the surface is analyzed as a property that differentiates between amorphous and crystalline surfaces of fully amorphous and crystalline lactose (Badal Tejedor et al., 2017).

The objective of this study was to elucidate whether amorphisation of α-lactose monohydrate during milling is a surface induced phenomenon, and how the amorphicity evolves over time in the particulate structure. To this end, AFM is used to characterize the sample's surface mechanical properties, and hence amoprhicity, by means of a recently developed methodology (Badal Tejedor et al., 2017). AFM measurements were performed on the very top layer of the particles; therefore other bulk measurements were used to elucidate the non-linear evolution of the particles' amorphisation over time. Analytical techniques such as differential scanning calorimetry and thermogravimetrical analysis were used in combination with BET (Brunauer, Emmett and Teller) surface area. Thus, the nature of the mechanically amorphized material, effects of prolonged milling times and amorphous content propagation mechanisms can be suggested.

2. Experimental

2.1. Materials

The material used in this study is α-lactose monohydrate. The lactose used to prepare the milled samples was obtained from DFE Pharma (Pharmatose® 200M, Veghel, Netherlands) and the lactose used for spray drying was purchased from Merk KGaA (Darmstadt, Germany).

2.2. Milling of the powders

Ball milling of received crystalline lactose was performed in a planetary ball mill (PM 100 CM, Retsch, Germany). Crystalline lactose was stored in desiccator over P_2O_5 before use. The milling operation was carried out in a stainless steel milling jar of a volume of 12 cm^3 containing 50 balls with a diameter of 5 mm of the same material and 1 g of lactose, corresponding to a ball to powder mass ratio of 25:1 was used. The rotation speed of the solar disk was set to 400 rpm and the samples were milled for 1 and 20 h. Every 20 min of milling was followed by a pause period of 5 min and the milling experiments were performed in humidity controlled room at 30 ± 5% relative humidity and 22 ± 3 °C. The milled powder was stored in a desiccator at room temperature and 0–5% relative humidity.

2.3. Spray drying

A solution of a 10% solid content of lactose was spray dried in a laboratory spray dryer built at RISE (Research Institutes of Sweden). The feed solution was pumped with a 5 ml/min flow rate through a 2 mm diameter orifice nozzle, and dried with an air flow of 0.8 m^3/min in a 0.75 × 0.15 m drying chamber. The dryer operates in co-current mode with a jacketed two-fluid nozzle operated with pressurized air. The jacket temperature was 20 °C. The inlet and outlet temperatures of the drying air flow were 150 °C and 70–75 °C respectively. The powder produced was collected in a cyclone, but only the powder gravitationally deposited in the attached vessel below the cyclone was used for further analysis. The spray dried powder was stored in a desiccator at room temperature and 0–5% relative humidity.

2.4. Scanning electron microscopy

The morphology of the powder materials (lactose, milled lactose and spray dried lactose) was examined by scanning electron microscopy (FEI-XL, 30 series) with an accelerated voltage of 5 kV in high vacuum. The particulate samples were sprinkled over a double-sided carbon tape mounted on an aluminium holder and blown out with nitrogen gas to remove the excess of powder. Afterwards the samples were coated with gold (120 s, 40 mA) using a Balzers SCD050 coater to allow evaluation at high magnifications without damaging the sample with the beam.

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