



Quantitative determination of micronization-induced changes in the solid state of lactose



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ABSTRACT

Lactose, in particular α -lactose monohydrate, is the most used carrier for inhalation. Its surface and solid-state properties play a key role in determining Dry Powder Inhalers (DPIs) performance. Techniques such as X-Ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC), which are commonly used for the characterization of lactose, are not always capable of explaining the solid-state changes induced by processing, such as micronization. In the present work, the evaluation of the effect of the micronization process on the solid-state properties of lactose was carried out by XRPD and DSC and a satisfactory, although not unequivocal, interpretation of the thermal behaviour of lactose was obtained. Thus, a new gravimetric method correlating in a quantitative manner the weight change in specific sections of the Dynamic Vapour Sorption (DVS) profile and the amount of different forms of α -lactose (hygroscopic anhydrous, stable anhydrous and amorphous) simultaneously present in a given sample was developed and validated. The method is very simple and provides acceptable accuracy in phase quantitation (LOD = 1.6, 2.4 and 2.7%, LOQ = 5.4, 8.0 and 8.9% for hygroscopic anhydrous, stable anhydrous and amorphous α -lactose, respectively). The application of this method to a sample of micronized lactose led to results in agreement with those obtained by DSC and evidenced that hygroscopic anhydrous α -lactose, rather than amorphous lactose, can be generated in the micronization process.

The proposed method may find a more general application for the quantification of polymorphs of compounds different than lactose, provided that the various solid phases afford different weight variations in specific regions of the DVS profile.

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1. Introduction

Lactose is a widespread excipient and the most commonly used carrier in dry powder formulations for inhalation (Marriott and Frijlink, 2012). Its surface and solid-state properties are of paramount importance in determining the drug aerosolization performance (Pilcer et al., 2012).

Lactose is a disaccharide composed of a moiety of galactose linked to a moiety of glucose through a β 1-4 glycosidic linkage. It exists in two forms, α -lactose and β -lactose, which differ from each other for the configuration of the anomeric carbon of the glucose moiety. Moreover, lactose can be amorphous (L_{am}), with variable anomeric composition, or crystalline. Different

polymorphs (or pseudopolymorphs) are known, each of which has a specific crystalline structure (Kirk et al., 2007; Platteau et al., 2004): α -lactose monohydrate ($L\alpha \cdot H_2O$), hygroscopic anhydrous α -lactose ($L\alpha_H$), stable anhydrous α -lactose ($L\alpha_S$), β -lactose and mixed α/β compounds co-crystallized with different stoichiometries. Among these, α -lactose monohydrate is the most common lactose grade used as coarse material or fine particles (Kou et al., 2012; Pilcer et al., 2012).

To produce fine particles, inhalation grade lactose is often subject to unit processes such as micronization or spray drying that may alter its physico-chemical properties, thus affecting the product performance and stability (Kou et al., 2012). Changes in lactose anomeric composition induced by milling (Otsuka et al., 1991) and spray drying have previously been reported (Jawad et al., 2012). Moreover, the formation of amorphous material as a consequence of milling/micronization processes is a known phenomenon well documented in the literature (Briggner et al., 1994; Shariare et al., 2011; Willart et al., 2004; Young et al., 2007).

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Differently, the formation of other polymorphs, such as the α -anhydrous forms, has never been reported nor directly correlated to the above-mentioned unit processes.

Techniques such as X-Ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC), which are commonly used for the characterization of lactose, are not always capable of explaining the solid-state changes induced by processing. This is due to the fact that the “new” forms of lactose may be generated in quantities that are considerably lower than the detection limit of the aforesaid techniques or to the fact that certain behaviours still do not have an unambiguous interpretation. For example, considering the DSC trace of lactose, the presence of thermal events (peaks) in the region between the evaporation of crystalline water and the melting of lactose remains a source of different and sometimes conflicting interpretations (Figura and Epple, 1995; Kaiyal et al., 2012; Lerk et al., 1984a).

In this respect, a most suitable technique could be Dynamic Vapour Sorption (DVS). Few gravimetric methods that allow the quantification of amorphous material through the evaluation of vapour sorption/desorption isotherms are described in the literature (Sheokand et al., 2014). Among these, the “residual weight” method was used by Buckton and Darcy (Buckton and Darcy, 1995) for an approximate quantification of low levels of amorphous lactose (down to 0.05% w/w). The method was based on the assumption that the final weight gain of a lactose sample is a consequence of the crystallization of the amorphous lactose into α -lactose monohydrate (Buckton, 1997). However, the application of this method to samples of lactose containing larger amounts of amorphous led to unsatisfactory results (Buckton and Darcy, 1999). This was due to the fact that, in contrast with what was initially assumed, not all the amorphous lactose converts to α -lactose monohydrate, but both α - and β -lactose might be generated in different ratio upon crystallization (Timmermann et al., 2006; Vollenbroek et al., 2010). Therefore, the amorphous content calculated according to the final weight gain is indefinitely underestimated.

In the present work, the effect of the micronization process on the physico-chemical properties of lactose was evaluated by using different techniques. A previously described method (Jawad et al., 2012) based on the use of proton Nuclear Magnetic Resonance (^1H NMR) was employed to determine the anomeric composition of the lactose samples under investigation. Then, a first evaluation of the effect of the micronization process on the solid-state properties of lactose was carried out by XRPD and DSC and a satisfactory interpretation of the thermal behaviour of lactose was obtained. However, the analyses performed also confirmed that these techniques are not sufficient for the unequivocal identification and quantification of all the forms of lactose induced by the process, especially when they are simultaneously present in the same sample.

Thus, starting from the work of Burnett et al. (Burnett et al., 2009), a new method correlating the weight variations in specific sections of the DVS profile and the amount of different forms of lactose (L_{α_H} , L_{α_S} and amorphous α -lactose) simultaneously present in the specimen was developed and validated.

2. Materials and methods

2.1. Materials

Coarse $L\alpha\cdot\text{H}_2\text{O}$ ($d_{V50} = 91.7 \mu\text{m}$) was supplied by Kerry (Ireland). Lacto-Sphere[®] MM50 (sieved $L\alpha\cdot\text{H}_2\text{O}$, $d_{V50} = 53.1 \mu\text{m}$) and Lacto-Sphere[®] MM3 (micronized lactose, $d_{V50} = 2.5 \mu\text{m}$) were provided by Micro-Sphere SA (Switzerland). Coarse and sieved $L\alpha\cdot\text{H}_2\text{O}$ were fully compliant with the relevant Ph.Eur. 8.0 monography.

2.2. Methods

2.2.1. Micronization

The micronization of coarse $L\alpha\cdot\text{H}_2\text{O}$ was performed using a laboratory scale J-70 fluid jet micronizer (Tecnologia Meccanica, Italy). Nitrogen was used as fluid for the micronization. Samples with different particle size were obtained by varying three process parameters on the basis of a previous preliminary design of experiments (data not shown): the Venturi pressure P_V , the ring pressure P_R and the feed rate R_F . The experimental matrix and the resulting particle size distributions are reported in Table 1.

2.2.2. Preparation of hygroscopic anhydrous α -lactose (L_{α_H})

L_{α_H} was prepared by modifying the procedure described by Garnier et al. (Garnier et al., 2002). 7 g of Lacto-Sphere[®] MM50 were placed with 250 glass beads ($\varnothing = 3 \text{ mm}$) inside a 32 mL (14 mm internal diameter x 20 cm length) stainless steel column (Applied Separations, USA), kept in an oven at 25 °C for 2 h under a dry nitrogen flow of 50 mL min⁻¹ and then heated at 120 °C for 9 h under the same nitrogen flow. After production, L_{α_H} was always handled in a glove-box filled with dry nitrogen (RH < 5%) in order to prevent possible rehydration.

2.2.3. Preparation of stable anhydrous α -lactose (L_{α_S})

L_{α_S} was prepared by modifying the procedure reported by Kirk et al. (Kirk et al., 2007). 7 g of Lacto-Sphere[®] MM50 were placed with 250 glass beads ($\varnothing = 3 \text{ mm}$) inside a 32 mL (14 mm internal diameter x 20 cm length) stainless steel column (Applied Separations, USA), kept in an oven at 25 °C for 2 h under a dry nitrogen flow of 50 mL min⁻¹ and then heated at 145 °C for 6 h under the same nitrogen flow.

2.2.4. Preparation of amorphous lactose (L_{am})

Different samples of L_{am} were produced by spray drying starting from 10% w/v aqueous solutions of α -lactose monohydrate. In order to obtain samples of L_{am} with different anomeric composition, the solutions were kept under stirring for variable times and at different temperatures: 20 min and 40 min in ice bath, 1 h and 20 h at 20 °C. Thereafter, they were spray dried using a Büchi Mini Spray Dryer B-290 (Büchi, Switzerland) set with an inlet temperature of 130 °C, an outlet temperature of 60 °C, a feed rate of 5 mL min⁻¹, a spray flow of 600 L h⁻¹ and an aspiration of 35 m³ h⁻¹ (similar conditions were reported by Hill et al. (Hill et al., 1998)). The spray dried material was then stored under vacuum in a desiccator in the presence of P₂O₅ and handled in a dry glove-box (Relative Humidity < 5%).

2.2.5. Proton nuclear magnetic resonance (^1H NMR)

^1H NMR spectra were recorded at 25 °C using a Bruker AV400 spectrometer (Bruker, USA). The samples were prepared by dissolving approximately 5 mg of lactose in 0.5 mL of DMSO-*d*₆ 99.9 atom% D (ARMAR Chemicals, Switzerland) and then immediately analysed. Each measurement lasted about 10 min and was performed at least in triplicate. The anomeric composition of each sample was determined by integrating the peaks at $\delta = 6.3 \text{ ppm}$ and $\delta = 6.7 \text{ ppm}$, corresponding to the protons of the hydroxyl group at carbon C1 in the α - and β -anomer, respectively (Jawad et al., 2012). Spectra were processed using MestReNova software (Mestrelab Research, Spain). An apodization of 0.2 Hz was applied and spectra were manually phase corrected prior to automatic baseline correction and final peak integration.

2.2.6. X-Ray powder diffraction (XRPD)

X-ray diffraction patterns on powder were recorded on a MiniFlex diffractometer (Rigaku, Japan) using Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$) generated with 30 kV. The samples of lactose powder

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