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Research Paper

Quantification of residual crystallinity in ball milled commercially sourced lactose monohydrate by thermo-analytical techniques and terahertz spectroscopy

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ABSTRACT

The quantification of crystallinity is necessary in order to be able to control the milling process. The use of thermal analysis for this assessment presents certain challenges, particularly in the case of crystal hydrates. In this study, the residual crystallinity on ball milling of lactose monohydrate (LMH), for periods up to 90 min, was evaluated by thermo-analytical techniques (TGA, DSC) and terahertz spectroscopy (THz). In general, the results from one of the DSC analysis and the THz measurements agree showing a monotonous decrease in relative residual crystallinity with milling time (~80% reduction after 60 min milling) and a slight increase at the 90 min time point. However, the estimates from TGA and two other methods of analyzing DSC curve do not agree with the former techniques and show variability with significantly higher estimates for crystallinity. It was concluded that, the thermal techniques require more complex treatment of the data in the evaluation of changes in crystallinity of a milled material (in particular to account for the de-vitrification and mutarotation of the material that inevitably occurs during the measurement cycle) while the analysis of THz data is more straightforward, with the measurement having no impact on the native state of the material.

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1. Introduction

Milling is one of the conventional methods used in pharmaceutical technology for the reduction of particle size [1]. Among the various milling methods, ball milling is possibly the most aggressive technique, resulting in significant damage to the crystalline particles and a partial conversion to the amorphous state, the extent of which depends on the frequency and time of milling. The amorphous phase has the advantage of increased solubility and dissolution rate [2,3]. However, the process of milling inevitably leaves some crystals in a partially damaged state that provide seeds for de-vitrification, resulting in the potential loss of the

additional advantage conferred by the amorphous phase and creating a stability issue during shelf life of the product [4].

The quantification of this crystalline/amorphous content at various milling times, and over a range of ball-oscillation frequencies, is important in order to be able to control the milling process as well as explaining the impact of milling on solubility and dissolution rate and thereby investigating the stability of the material during storage.

The techniques commonly employed for quantification of crystalline materials, include DVS, isothermal micro-calorimetry, DSC, hyper-DSC, NIR, Raman spectroscopy and PXRD. Some of these are based on the analysis of the crystalline phase (PXRD, NIR) whereas others (Hyper-DSC, DVS and Microcalorimetry) are based on the analysis of the amorphous phase, while DSC can determine both crystalline and amorphous phases.

DVS is based on water vapor sorption and may give misleading results for materials in which the crystals also sorb water, alongside the amorphous phase under scrutiny. Organic vapor sorption is a possible alternative method [5] but this technique is not universal in its application. Isothermal micro-calorimetry detects the heat associated with the sorption of water by the amorphous phase

Abbreviations: THz-TDS, terahertz time domain spectroscopy; THz, terahertz; DVS, dynamic vapor sorption; NIR, near infrared; DSC, Differential Scanning Calorimetry; TGA, thermogravimetric analysis; PXRD, powder X-ray diffraction; PLS, partial least square; LMH, lactose monohydrate; SEM, scanning electron microscopy; RRC, relative residual crystallinity.

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but it requires crystallization of the amorphous to be favored kinetically [6]. PXRD might be considered as gold standard for crystallinity estimation but the results are inconsistent as it requires the preferred orientation of crystals in the path of beam, therefore whole pattern fitting is required for the complete characterization of a powder [7]. Measurement by Raman spectroscopy can induce photo-chemical reaction in the materials. In NIR, amorphization is inferred from a shift in the baseline of the spectral region rather than any change in the specific absorption peaks [8], therefore the first or second derivative of spectra is taken for quantification [9]. In addition, the NIR measurements are influenced by moisture [7]. Although both these vibrational techniques (Raman and NIR) are sensitive and quick methods, each require a calibration curve to be constructed from known crystalline and amorphous mixtures [10].

TGA measures the weight change associated with the loss of adsorbed water (if any) and the water of crystallization, in the case of a hydrated material. From the weight of the latter, the changes in crystallinity in milled hydrated materials may be estimated [11,12]. In order to use the TGA technique, one has to assume that the water of hydration in the residual crystalline material (within the milled material) provides an opportunity to quantify the proportion of un-damaged crystalline material remaining. However, there is always the possibility that the hydration water of the partially compromised crystalline particles will behave differently to the material in its native state, resulting in some uncertainty in the estimates of crystallinity so derived.

DSC is routinely used for the analysis of crystalline/amorphous materials. The quantification of crystallinity may be determined from the analysis of either the crystalline form or the amorphous state. The endothermic event associated with the melting of the crystalline phase that remains post milling may be used to determine the change in crystallinity on milling. However, the presence of an amorphous phase in a milled material may also manifest in the curve as a step in the baseline (indicating a glass transition) and/or exothermic peak in the curve (indicating a de-vitrification event). This devitrified amorphous phase will then contribute to the enthalpy of melting. Therefore one must subtract this contribution from the enthalpy of crystallization, in order to calculate the crystalline content of the milled material prior to analyzing the DSC curve.

In addition one should also recognize that milling may also result in defected or partially compromised crystals along with the amorphized phase and yet, the principle assumption is that, the specific enthalpy of melting of the defected crystalline material is the same as that of the starting material and is not impacted by the milling process.

Terahertz time domain spectroscopy (THz-TDS) produces pulses in the femtosecond time scale and therefore has the ability to probe crystal lattice and hydrogen bonding vibrations, which occur at frequencies in the low terahertz region (0.1–4 THz). The intensity of the specific absorption peaks can be used to quantify the degree of crystallinity in a mixed phase system. This technique has been used previously for the characterization [13] and quantification [14] of the crystallinity of APIs. Also, it has been employed to differentiate hydrated and anhydrous forms [15] and for studying the dehydration process in various pharmaceuticals [16]. This technique has been used recently for the measurement of crystallinity in amino acids [17] and freeze dried sugars [18]. The benefit of this technique is that one can analyze the material in its native state.

Lactose monohydrate (LMH) is one of the most commonly used excipients in the pharmaceutical industry. Its main use is as a diluent in tablet formulations and as a carrier in dry powder inhalers [19]. The milling of LMH not only reduces its particle size but may also impact its hydration status, moreover, the raised

temperature during the course of milling may cause instability in the amorphous phase that results in the anomeric transition of crystalline lactose [20]. There is therefore a need for a technique that could analyze a milled hydrated material in its native state. In this paper, a reliable method for determining the residual crystallinity (in respect to specific anomeric form, i.e. alpha lactose) in milled LMH, in its native state, is researched and compared that to the thermal methods in an attempt to highlight the issues related with the latter techniques for quantification of the residual crystallinity of milled LMH. The LMH studied in this work is taken from a commercial source and therefore there is inevitably a proportion of the sample which will be in the form of beta lactose. Typically the beta lactose content can be between 3 and 4 percent [21]. The residual crystallinities quoted through this article are therefore stated as a relative measure of the change in crystallinity from the original starting material. To that end the term relative residual crystallinity (RRC) has been adopted through this article.

2. Materials and methods

Lactose monohydrate (EP/BP) was sieved at room temperature ($\sim 23^\circ\text{C}$) and 45% relative humidity. The particles that pass through a 80 mesh sieve and retained on a 100 mesh sieve, were taken for analysis (corresponding to a linear size between 150 and 180 μm). The measured average particle size by SEM was $\sim 172 \mu\text{m}$. Laser diffraction technique has shown that 50% of particles (d_{50}) were of the size less than 154 μm .

2.1. Ball milling

The material was milled in the oscillatory ball mill (MM 301, Retsch, Germany) equipped with two 50 ml stainless steel cylindrical jars each containing one stainless steel ball of 25 mm diameter. A weight of 2.5 g of LMH was loaded into each jar, which were then closed tightly and clamped in position of the mill. The mill was operated at frequency of 18 Hz for 5, 10, 15, 30, 45, 60 and 90 min. The sample was collected into a glass bottle and immediately used for thermal and terahertz analysis.

Note: The mill frequency of 18 Hz was selected after an initial screening of three speeds i.e. 15, 18 and 25 Hz as previously used by [22] based on the fact that this frequency had a significant impact on crystallinity without a marked increase in the temperature of the mill. The temperature of milled material was $\sim 40^\circ\text{C}$, estimated by the insertion of a thermocouple probe into the powder immediately after milling.

2.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) of un-milled and milled materials was carried out in a TGA instrument with auto-sampler system (Perkin Elmer, US) according to the method already described by [23]. The empty aluminum pan was loaded into the TGA instrument and tarred. Then the sample was placed in the pan and the pan returned to the instrument. The weight of sample was recorded in the temperature range from 25°C to 250°C at the rate of $20^\circ\text{C min}^{-1}$.

2.3. Differential Scanning Calorimetry (DSC)

DSC experiments were performed according to method described in [23] using a Jade DSC (Perkin Elmer, US). The heating rate and heat flow were calibrated at $20^\circ\text{C min}^{-1}$ using indium and zinc standard. Approximately 7 mg sample was taken in a 50 μL aluminum pans, sealed non-hermetically with perforated lids for the evaporation of water and then loaded in the analyzer by the

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