



Correlation between molecular dynamics and physical stability of two milled anhydrous sugars: Lactose and sucrose

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ABSTRACT

The process of milling often results in amorphization and the physical stability of amorphous phase is linked with its molecular dynamics. This study focuses on a propensity of two disaccharides (lactose and sucrose) to amorphize on ball milling and the stability of the resultant amorphous phase. The amorphous content in milled sugars is estimated by Differential Scanning Calorimetry (DSC) and the stability was measured in terms of the tendency to recrystallize by Broadband Dielectric Spectroscopy (BDS). The results show that the amorphous content increases with milling time and is greater for lactose than sucrose. At the same degree of amorphization, sucrose recrystallize at temperature ~ 15 °C higher than lactose, indicating higher stability. The molecular dynamics (beta relaxation process), suggest that milled sucrose is more stable with higher activation energy (~ 9 kJ mol⁻¹) than that of lactose. The moisture content of amorphous phase also impacts its molecular dynamics in terms of increase in activation energy as the moisture decrease with increasing the milling times. The study suggests a greater stability of amorphous sucrose and susceptibility of milled lactose to recrystallize, however, on extended milling when the moisture content decreases, lactose was seen to become relatively more stable.

1. Introduction

Amorphous solids are produced in pharmaceutical industry by quench cooling of melts, (Angell, 1995) freeze drying, (Liu et al., 2002) spray drying, (Gharsallaoui et al., 2007) precipitation from solution (Li et al., 2000), vapor condensation (Kearns et al., 2007) and melt extrusion (Crowley et al., 2007). However, certain processes (including milling, a common process used for particle size reduction) causes the unwanted generation of amorphous phase (Willart et al., 2004).

The amorphous phase has the advantage of increasing the super-saturated solubility and dissolution rate of poorly soluble drug substances owing to its high surface free energy and enormous surface area (Dudognon et al., 2006; Hancock and Parks, 2000; Murdande et al., 2010). At the same time, this phase is metastable and may ultimately reverts back (i.e. recrystallizes) to its original crystalline form, or even a different crystalline form, thus compromising the stability and efficacy of the product during its shelf life (Fisher, 2007). The amorphous phase

produced during milling is probably the most unstable because of the presence of residual crystallites that act as nuclei for crystallization. Therefore the benefits of milling could only be achieved until the post-milling crystallization is prevented, for example by co-milling with an agent that stabilizes the amorphous phase.

The physical stability of amorphous phase is related to its molecular mobility which itself is defined by glass transition temperature (T_g), the temperature above which long range co-operative molecular mobility is manifest owing to the high internal energy and specific volume, thereby creating opportunities for the material to crystallize.

There is a range of techniques available for studying the molecular mobility and thus stability of the amorphous phase. Parameters such as structural relaxation time, enthalpy relaxation time, glass transition and/or fragility index (obtained from dielectric spectroscopy, DSC or isothermal micro-calorimetry techniques) have been used to provide certain measures of molecular mobility (Aso et al., 2000; Graeser et al., 2009; Kawai et al., 2005; Pokharkar et al., 2006; Rodrigues et al.,

Abbreviations: BDS, broadband dielectric spectroscopy; DSC, differential scanning calorimetry; τ , relaxation time; E_a , activation energy; T, Fröhlich parameter B
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2013). Recently, T_g of β -relaxation (Kissi et al., 2018) and THz spectroscopy (Sibik et al., 2015; Sibik and Zeitler, 2016) have also been employed to study molecular mobility and crystallization dynamics of amorphous phase. Interestingly, it has also shown that there are certain energy barriers behind this molecular dynamics of the disordered amorphous phase (Ruggiero et al., 2017).

In dielectric studies the dynamics of amorphous materials is usually described by primary and secondary relaxation processes; the former represents the structural (α -) relaxation process which is observed in all disordered materials while later can be described as Johari-Goldstein (β -relaxation) and non-Johari-Goldstein (sometimes termed as γ -relaxation) (K. Kaminski et al., 2008a,b). Of these processes, it is the structural relaxation (in terms of the characteristics of α -relaxation) that is expected to reflect a degree of freedom/molecular mobility that underpin the crystallization process (and hence instability) of materials containing an amorphous phase (Kolodziejczyk et al., 2013; Rodrigues et al., 2013). There are many studies in literature that show the correlation between molecular dynamics and crystallization; these are discussed below.

Zhou et al. (2002) in their study on amorphous pharmaceuticals demonstrated that the molecular mobility along with the configurational entropy are important parameters in determining the physical stability of the amorphous phase (Zhou et al., 2002). Whereas, Bhugra et al. (2007) from the correlation between crystallization onset time and dielectric relaxation time (of the α -process at temperatures above T_g) suggested that the molecular mobility can be used for the prediction of stability (Bhugra et al., 2007). Another study has suggested the involvement of some other factor in addition to global mobility i.e. α -process that predicts the instability in amorphous systems (Bhardwaj et al., 2013).

In spite of relation of α -process to instability of amorphous phase, its exploitation is compromised, as it is sometimes difficult to clearly observe the structural relaxation in some materials (i.e. sugars) at temperatures above T_g due to the contribution from ionic conductivity in quenched systems (K Kaminski et al., 2008a,b). It was also ascertained by Ermolina and Smith (2011), that the structural relaxation of freeze dried amorphous disaccharides is masked by the percolation of protons and dc conductivity within the hydration shell on the extensive surface area of such material (Ermolina and Smith, 2011).

Therefore, various attempts have been made to find some other features of the dielectric relaxation behavior that may have some relation with the structural relaxation, and might therefore be used to predict the stability of the amorphous phase.

Alie et al., (2004), in their dielectric relaxation study of a quench cooled amorphous phase of a proprietary drug molecule, has suggested that it is the β - relaxation process (the Johari-Goldstein β -relaxation) not α - that defines the specific molecular dynamics and underpin the physical stability of the amorphous phase (Alie et al., 2004). This Johari-Goldstein process can be clearly identified by subtraction of dc conductivity and annealing (Bhardwaj and Suryanarayanan, 2011).

There are many other studies that demonstrate the faster secondary relaxation has in fact a close relation to the structural relaxation. Evidence for this comes from Paluch et al. (2003) who showed that the β - process deviates from Arrhenius behavior in a similar way to the α -process (Paluch et al., 2003) while Ngai and Capaccioli (2004) have shown that the activation energy of this process correlates well with the dynamic glass transition which is determined from the α -relaxation, when $\tau \sim 100$ s (Ngai and Capaccioli, 2004). In the other studies Kaminski et al. (2012) and Ermolina and Smith (2011) have shown that the β - process mimics the features of structural relaxation in terms of its response to pressure (i.e. shift towards lower frequencies by increasing pressure) or moisture (the activation energy of the beta process decreases with increasing the moisture) respectively (Ermolina and Smith, 2011; K Kaminski et al., 2006). Hence the beta relaxation might be considered in some way as a precursor of structural relaxation, possibly in the sense that the cooperative unit of the beta process represents the

minimal scale length for the otherwise more long range cooperative process. Certainly, it has been suggested that the activation energy of the beta process is the indicator of flexibility of the molecule, i.e. the greater the value of the energy barrier, the more inflexible is the molecule (K. Kaminski et al., 2012) i.e. fewer its degrees of freedom.

Another fact concerning the dielectric studies of amorphous phase is that in the majority ($\sim 95\%$) of these cases the amorphous phase was usually produced by quench cooling of the melt; a procedure which is not commonly applied in the pharmaceutical industry as it may degrade the material. As the method of preparation influences the molecular mobility of the amorphous phase as previously stated (Surana et al., 2004) there is a need to study the specific molecular dynamics of amorphous phases, as they are generated by unwantedly during milling in order to have any chance to understand and even predict the stability of such materials after milling.

Another important aspect to consider when milling crystalline materials is the fact that, the amorphous phase inevitably contains some quantity of moisture (either generated from within the material in case of crystalline hydrates or adsorbed from the environment). A recent study on ball milled indapamide (Wojnarowska et al., 2013) has suggested the presence of a water relaxation peak rather than the typical relaxation processes of amorphous phase. The distribution of this water affects the molecular dynamics of the amorphous phase and is therefore important in defining the stability of this phase. Therefore the cooperative molecular dynamics of this amorphous phase, as modulated by the so called 'plasticization' effect of water (Gupta et al., 2013) may be of greater relevance to the stability of amorphous system obtained by milling than on quench cooled systems.

In this work, our aim is to quantify the impact of milling on the amorphization of two anhydrous disaccharides (lactose and sucrose) and to elucidate the molecular mechanisms underlying the stability of the amorphous phases. In the first part of the study DSC was used to investigate the extent of amorphization of crystalline materials as a function of milling times and the relative stability of the amorphous phase determined via an evaluation of the onset temperatures for recrystallization. In the second part of this study, an assessment of possible contribution of the molecular dynamics was made. For this purpose BDS (in terms of activation energies for the γ and β - processes) was employed. The results from DSC experiments were compared to the onset temperature of recrystallization obtained by BDS to establish whether its parameters can be used, in part to predict the relative stability of milled amorphous sugars. This may help to establish the approaches for the prediction of the stability of milled pharmaceuticals, in general.

2. Materials and methods

Lactose and sucrose used in this study were purchased from Fluka (UK) and used as received from the supplier. Lactose occurs as a white crystalline powder with finely divided particles ($< 100 \mu\text{m}$) while sucrose was presented as a coarse crystalline material with the particle size $< 500 \mu\text{m}$.

Note: The lactose used in this study was of a commercial grade and contained mainly beta lactose with a small proportion of α -lactose (as indicated by THz spectra, unpublished data), therefore wherever the word lactose is used in this study means the anhydrous beta lactose.

2.1. Ball milling

Milling of both lactose (particle size $< 100 \mu\text{m}$) and sucrose (particle size $400\text{--}500 \mu\text{m}$) was performed at ambient conditions (40–45% RH and 20–22 °C temperature) in a vibratory MM 301 ball mill (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 sugar was loaded into each jar, which were then closed tightly and clamped in position of the mill. The mill was operated at frequency of

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