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Research Paper

Comminution-amorphisation relationships during ball milling of lactose at different milling conditions

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ABSTRACT

The purpose of the study was to investigate the relationship between comminution and amorphisation of α-lactose monohydrate particles during ball milling under different milling conditions, including ball-to-powder mass ratio, milling time and ball diameter. The results revealed that at a constant ball filling ratio, ball-to-powder mass ratio of 25:1 resulted in the lowest minimum particle diameter of ~5 μm and the highest degree of apparent amorphous content of 82%. The rate of comminution was high during early stage of milling whereas the degree of apparent amorphous content increased gradually at a slow rate. An increased ball-to-powder mass ratio during milling increased both the rate of comminution and the rate of amorphisation. Using a given ball-to-powder mass ratio, the ball diameter affected the degree of apparent amorphous content of the particles while the particle diameter remained unchanged. The relationship between comminution and amorphisation could be described as consisting of two stages, i.e. comminution dominated and amorphisation dominated stage. It was proposed that the rate constant of comminution and amorphisation are controlled by stress energy distribution in the milling jar and the stress energy distribution is regulated by the ball motion pattern that can be affected by the process parameter used.

1. Introduction

In the formulation of complex solid chemical systems, the control of the nature of the solid state of the ingredients is important. Since the amorphous state sometimes possesses valuable formulation properties compared to the crystalline state, such as increased particle dissolution rate (Bahl et al., 2008; Murdande et al., 2010) and powder compactibility (Sebhatu and Alderborn, 1999; Vromans et al., 1987), the interest in using and understanding amorphous powders is evident in order to prepare particles with tailored formulation properties.

Milling of powders is commonly used in chemical and pharmaceutical manufacturing and a frequently used milling apparatus is the planetary ball mill. An obvious and frequent use of ball milling is the size reduction (comminution) of particles into a suitable particle size distribution, e.g. to improve dissolution properties of a drug (Branham et al., 2012). However, the high stress level that particles are subjected to during ball milling may induce changes in other physical characteristics of the particles, such as the induction of crystal defects and the transformation to an amorphous solid or another polymorphic phase. Therefore, ball milling have also been used for other applications, including mechanical alloying and mechano-chemical reactions (Alex et al., 2014; Zdujić et al., 2009), preparation of cocrystals and coamorphous systems (Friščić and Jones, 2009; Sovago et al., 2016) and the preparation of an amorphous form of a crystal solid (Caron et al., 2011; Karmwar et al., 2012). There are thus three main applications of ball milling, i.e. particle size reduction, mechano-chemical synthesis (including the preparation of cocrystals) and solid state disordering or amorphisation of solids. Solid state disordering by milling may thus be an objective *per se* in order to functionalize particles to be used in a solid formulation. Since the disordered state shows different chemical and physical properties than the crystalline state, partial particle disordering may also represent an inadvertent effect when the primary application is another. Thus, the understanding of the mechanisms of amorphisation and how the apparent amorphous content of particles evolves during ball milling is important.

A single particle is considered (Newman and Zografi, 2014) to respond to the stress to which it is subjected during milling by fracturing followed by disordering or amorphisation, i.e. a

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sequential process of two events. Regarding the second event, two conceptions are used in literature to describe the mechanism of disordering. The first mechanism is the formation of amorphous domains through a melting-solidification process, i.e. a vitrification, and the nature of the disordered particle is represented by a two-state system with amorphous and crystalline domains. The other disordering mechanism is the creation of defects and the formation of amorphous regions at a critical defect density. Thus, the nature of the disordered particle is in this case represented by a one-state system. These two disordering mechanisms have been denoted (Newman and Zografi, 2014) type 1 (vitrification) and type 2 (defect induction) disordering respectively. In other papers (Dujardin et al., 2013), the type 2 disordering process has alternatively been described in terms of crystallite fragmentation followed by a fusion of crystallites into an amorphous phase at a critical crystallite size.

The milling conditions inside a planetary ball mill are complex and depend on the material properties and on the processing parameters used. According to the literature, important examples of process parameters affecting the milling process are the size and mass of the balls, the ball-to-powder mass ratio (charge ratio), the ball filling ratio, the mill velocity, and the milling time (Descamps and Willart, 2016; Rosenkranz et al., 2011; Sato et al., 2010; Shashanka and Chaira, 2015). A fundamental aspect of ball milling is the force or energy that is transferred from the balls to the particles during ball milling which has been addressed for example by modelling of the milling process (Ashrafizadeh and Ashrafizaadeh, 2012; Feng et al., 2004; Mio et al., 2004; Sato et al., 2010; Stender et al., 2004). It is suggested that high forces or energies are generated by impaction and that the average energy transferred to the powder at each impact and the frequency of impacts are the two most important factors determining the outcome of a comminution process. However, it has also been suggested (Pazesh et al., 2013) that another contact process between particles, i.e. sliding, may also lead to the disordering of particles. Thus, both compression forces due to impaction and friction forces due to sliding may play a role in the evolution of particle amorphicity.

A critical aspect on the translation of the conception of sequential steps of comminution and disordering from the single particle scale to the powder scale is the rate constants of the respective process. It is reported (Caron et al., 2011) that amorphisation upon milling occurs during long times while particle size reduction occurs at an early stage of milling with only limited amorphisation of the particles. Thus, the conception of a step wise processing on the single particle scale may also be applicable to the collective response of the particles during powder milling. The rate constants of both processes are probably strongly affected by the energy conditions in the milling jar and the energy condition in the milling jar is dependent on the ball motion pattern (Burmeister and Kwade, 2013; Rosenkranz et al., 2011).

We conclude that in order to understand how milling operations should be designed to reach the desired purpose of the process, there is a need to increase our knowledge on the kinetics of comminution and amorphisation and how the rate constants of the processes can be controlled by the energy conditions. The objective of this paper is to investigate the relationship between particle comminution and amorphisation during ball milling under different milling conditions, i.e. ball-to-powder mass ratio, milling time and ball size, which are expected to give different ball motion patterns and stress energy conditions in the milling jar. α-lactose monohydrate, a commonly used pharmaceutical excipient in solid formulations, was used as model material.

2. Materials and methods

2.1. Materials

Two qualities of α-lactose monohydrate with different labelled particle size, Pharmatose® 200M and 450M (DFE Pharma, the Netherlands) were used.

2.2. Methods

2.2.1. Milling operation

Ball milling of lactose powders was performed in a planetary ball mill (PM 100 CM, Retsch, Germany). The milling operation was carried out in a stainless steel milling jar with a constant volume of 12 cm^3 and a diameter of 3 cm using balls of the same material of 1, 5 and 10 mm in diameter. The rotation speed of the solar disk (revolution speed) and the rotation speed of the milling jar (rotational speed) were set to 400 rpm, where the solar disk was moved in normal and the milling jar was moved in counter direction, i.e. a speed ratio of 1:-1 was used. The milling experiments were performed in humidity controlled room at 25 °C and 30 ± 3% relative humidity (RH).

Three milling experiments with different set-ups were done, summarized in Table 1. In all milling experiments, a constant volumetric ball filling ratio (the ratio between the total volume of the milling balls to total volume of the milling jar (Schmidt et al., 2015)) of 0.27 was used. In the first set-up of milling experiment, ball-to-powder mass ratios, hereafter denoted BPM, of 25:1, 13:1 and 6:1 were used and the samples were milled for 1, 10, 30, 60, 300, 600 and 1200 min using balls with a diameter of 5 mm. In the second set-up of milling experiment, balls with a diameter of 5 mm and BPM ratios of 25:1 and 13:1 were used. For the BPM ratio of 25:1, the samples were milled for 1, 3, 5, 7 and 10 min and for the BPM ratio of 13:1, the samples were milled for 1, 3, 5, 7, 10, 15, 30 and 45 min. In the third set-up of milling experiment, balls with diameter of 1 mm and 10 mm were used. For these samples a BPM ratio of 25:1 were used and the sample were milled for 300 min and 1200 min. For the milling times exceeding 20 min, a combination of milling periods and pause periods was applied to allow cooling of the jar and thus minimize heating of the sample, i.e. after each milling period of 20 min a pause period of 5 min was used.

2.2.2. Particle size distribution

The particle size distributions of the original crystalline and the milled lactose powders milled in the first set-up of milling experiment were measured using a laser diffraction instrument (Malvern Mastersizer, long bed instrument, Malvern, U.K.) equipped with a 300 mm Reverse Fourier lens. Particle size distributions of milled lactose powder milled in the second and the

Table 1
Milling condition used during ball milling.

Milling experimental set-up	1	2	3
Ball-to-powder mass ratio	25:1, 13:1 and 6:1	25:1 and 13:1	25:1
Ball diameter (mm)	5	5	1 and 10
Milling time (min)	1, 10, 30, 60, 300, 600 and 1200	1, 3, 5, 7, 10 and 1, 3, 5, 7, 10, 15, 30, 45	300 and 1200