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Short communication

Precipitating smooth amorphous or pollen structured lactose microparticles

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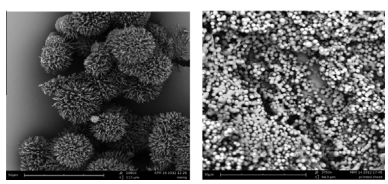
HIGHLIGHTS

- Hundreds of micro-particles can be precipitated from a single droplet.
- Precipitation map to produce particles with dendritic or smooth morphology.
- Smooth amorphous network structure formation.
- Potential surface tension dominated precipitation mechanism.

GRAPHICAL ABSTRACT



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ABSTRACT

Lactose microparticles with pollen-like or smooth amorphous morphology were produced using the convective antisolvent technique. The pollen-like particles was either composed of straight needle-like or short entwined dendrites. A possible threshold in the antisolvent humidity condition was found in which the smooth microspheres can be produced. Observation of a smooth network like structure suggested that a 'pinched off' mechanism might be one possible route in the formation of the precipitated smooth microspheres. A scenario based interfacial energy analysis elucidated the narrow (semi-monodispersed) size distribution of the precipitated smooth microspheres.

1. Introduction

Lactose is a widely used pharmaceutical excipient for tabletting and powder pulmonary drug delivery [1,2]. In such applications, the particle size and morphology of the lactose particles significantly affects the functionality of the resultant drug product. Lactose particles of different morphologies are produced using separate techniques. Spherical amorphous particles are typically produced via spray drying exploiting the rapid evaporation in the process [3]. Lactose crystals, with tomahawk or sharp and fine morphology, are mainly produced by slow precipitation or via the usage of antisolvents [4]. To date, there is no report in which a single process can be manipulated to produce both types of morphology for lactose particles. In this communication, we report the single droplet antisolvent vapour precipitation method, which can be controlled to produce lactose particles with spiky crystalline morphology or spherical amorphous morphology.

The underlying principle of technique is liquid antisolvent precipitation [5]. Instead of large bulk liquid, however, the current technique involves introducing a single aqueous droplet with dissolved lactose to a stream of convective ethanol vapour. Precipitation is induced when the ethanol is absorbed into the droplet at

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different degree and rate of oversaturation; by controlling the antisolvent vapour concentration. The larger aim of this experimental technique was to explore the possibility to produce precipitated particles from atomized droplets in spray systems. In some preliminary studies [6], we found that this method enables hundreds of 1–3 μm size pharmaceutical excipient particles to be produced from a single relatively large droplet of approximately 1200 μm (Supplementary Fig. 1). Following Zhang et al. [7], in this study, we initially set out to control the size of the precipitated particles by varying the concentration of the ethanol vapour in the convective stream. However, at different relative humidity and absolute humidity of the ethanol vapour (Fig. 1), an unexpected spiky morphology was observed from the experiments (Fig. 2). The occurrence of these two particle structure and a possible mechanism leading to the precipitation of smooth amorphous lactose will be discussed in great detail in the remainder of this communication.

2. Methodology

Experiments were undertaken using the single droplet drying concept developed in Monash University [8]. With this method, a single droplet is suspended with a glass filament and is exposed to a stream of convective drying medium. A new single droplet rig was constructed which allows antisolvent vapour to be used. Schematic of the new rig is shown in Supplementary Fig. 5. Compressed nitrogen is used to supply the bulk of the convective medium. The nitrogen is allowed to bubble through two conical flasks connected in series, filled with liquid antisolvent. The flow of nitrogen was adjusted to a flow rate of 0.3 m^3/h. As the nitrogen bubbles through the antisolvent, it will then carry any evaporated antisolvent vapour with it. Subsequently, the antisolvent vapour laden nitrogen stream will be heated within a heating coil submerged into a heated water bath maintained at 70 °C, prior to entering the drying chamber. It is noteworthy that temperature of the heated nitrogen stream will be less than that of 70 °C. The concentration of the ethanol vapour was controlled by adjusting the volume of the antisolvent in the conical flasks. In this work, ethanol was used as the antisolvent. For certain cases involving high absolute humidity of saturated ethanol vapour, the experimental set up was slightly modified by heating the conical flask containing the liquid ethanol in a slightly warm water bath with the aim of increasing the vapour concentration of the ethanol. Absolute humidity of antisolvent vapour laden stream was determined by bleeding of the stream and measuring the wet and dry bulb temperature just prior to the experiment and further reading off from the psychometric chart [9]. As the temperature of the chamber was not measured, the relative humidity reported here should be taken as an indicative value for the condition in the chamber. Three initial lactose concentration of 3 wt%, 5 wt% and 10 wt% were used representing dilute and moderately concentrated lactose solution at room temperature. The solubility of α-lactose in water is approximately 17.6 wt% at 24 °C [10].

Single lactose droplets were generated using a 5 μL gas chromatograph micro syringe (*Part# 001100, SGE Analytical Science Pty Ltd., Australia*). The initial size of the single droplet was chosen to be 1 μL for the present study. Lactose solutions were prepared by dissolving α-Lactose monohydrate *(L8783, Sigma–Aldrich, Australia)* with pure water for 4 h. Each experimental took about 30 min to allow sufficient dehydration of the particle. Scanning electron microscopy of the precipitated samples was undertaken using Phenom Benchtop SEM unit (FEI Company). Particle size analysis was undertaken by measuring the diameter of the precipitated microspheres from the SEM pictures using the ImageJ® freeware.

3. Results and discussions

3.1. Formation of spiky and smooth lactose microspheres

Fig. 1 is a three-dimensional plot of the experimental matrix rotated at different angles to illustrate the experimental matrix undertaken in this work. The initial lactose concentration, relative humidity and absolute humidity of the ethanol vapour in the nitrogen stream were varied in the experiments; the bulk of the experimental work was undertaken at the 3 wt% and 5 wt% initial lactose concentration. Most of the precipitated particles resembled particles with dendritic structures. These dendritic spheres vary in sizes and can be as large as 50–60 μm. These spiky morphologies were observed at experimental points marked with a cross in Fig. 1. Lactose dendritic morphology have previously been reported by dehydrating ethanolic lactose suspensions [4]. However, those dendritic structures reported were contrastingly different from the current spiky ball-like and 'weaved' dendritic morphologies. Although varying the absolute and relative humidity of the ethanolic stream did not result in any consistent trend, two distinct dendritic structures can be randomly observed. The first type consisted of relatively long straight dendrites which pointed outwards from the centre of the particle giving a spiky ball-like structure (Fig. 2). There was no apparent entwine of the individual dendrits. On the other hand, the second type consisted of shorter less distinct dendrites which tend to 'weave' slightly to form a sponge like structure. It is unclear at the moment if the shorter dendritic structure is the precursor for the longer more distinct structures or if the two morphologies undergo different formation mechanisms.

In view of this unexpected morphology, the next question was: Are these dendrites crystals or amorphous? XRD analysis typically used to determine distinct crystalline structures were not undertaken due to the small size and the random orientation of the structures. From the distinct sharp and edgy feature, particularly the long straight dendrite ones, it might appear that these dendrites are of crystalline structure growing outwards away from the centre of the particle. Such formation of outwards growing crystals was reported for various materials [11]. For lactose particles, clusters of outwards growing precipitated lactose have been observed in some industrial based research [12]. The clusters were attributed to the lack of nuclei formation leading to multiple crystals growing outwards from a single point. However, the crystal clusters are large bulky crystals unlike the spiky one observed here. Therefore, to our best knowledge, this is the first report of such spiky ball lactose morphology. More work is required to ascertain the applicability of the nuclei formation mechanism mentioned or if coagulation of the nuclei [5] contributes to the current morphology observed.

Along that line, an interesting feature observed, regardless of the spiky ball or entwined dendrite morphology, is that solid bridges can form between the dendrites in the agglomerated particles (Supplementary Fig. 2). Formation of such solid bridges is typical behaviour of soft rubbery amorphous materials [13]. However, this is speculative at the moment. Therefore, further work is required to gauge if this type of structure is a new type of amorphous structure induced by material self assembly or perhaps such solid bridges are due to the crystal growth phenomenon. Nevertheless, the unexpected spiky lactose might offer an advantage compared to conventional lactose particles in terms of aerosolization for dry particle inhalation applications [11]. Pollen-like particles have been shown to exhibit larger diameters but yet retain lower bulk density, due to the outwards grown dendritic structure which improves the aerolization of the particles.

Coming back to the initially expected smooth microspheres, these precipitated particles were also observed primarily at the