Understanding the dispersibility enhancement of L-leucine in the spray drying of inhalable microparticles

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Introduction

The deaggregation of spray-dried therapeutical particles intended for lung delivery by dry powder inhalation is an important stage of the delivery that greatly affects the emitted and delivered doses. To help with particle deaggregation, a specific class of compounds known as dispersibility enhancers is commonly used to decrease the inter-particle adhesion or contact area between different particles. L-leucine is one of the most promising of these dispersibility enhancers currently in clinical development [1]. The dispersibility enhancement of leucine and its moisture protection capabilities are due mostly to its surface activity and low aqueous solubility, both of which induce early surface crystallization during droplet evaporation [2]. Here, both a monodisperse droplet

chain instrument and conventional spray drying were used to study the solidification behavior of leucine-containing microparticles in detail.

Methods

Different combinations of leucine, as a dispersibility enhancer, and trehalose, as a glass stabilizer, were dried in a custom-built monodisperse droplet chain instrument at a drying gas temperature of 20 °C [3] and a laboratory-scale spray dryer (B-191, Büchi Labortechnik AG, Flawil, Switzerland) at a gas temperature of 75 °C to produce microparticles in the respirable range with a variety of morphologies and solid phases. The droplet chain instrument produces monodisperse microparticles in a controlled environment, while lab-scale spray drying produces polydisperse powders in realistic environments similar to those encountered in industrial dryers.

The initial diameters of the generated solution droplets were measured via an imaging system in the droplet chain setup (GO-5000 M-USB, JAI, Shanghai, China). The diameters of the resulting monodisperse dried particles were approximated from SEM micrographs (Sigma FESEM, Zeiss, Jena, Germany), which allowed the estimation of the particle densities.

The surface morphologies of the spray-dried powders were also assessed using time-of-flight secondary ion mass spectrometry (TOF.SIMS^5, ION-TOF GmbH, Münster, Germany), and the percentage of crystalline leucine was measured using a custom-built dispersive Raman spectrometer.

Results and Discussions

The SEM micrographs of the monodisperse particles generated via the droplet chain setup are shown in figure 1. The pure leucine particles show relatively similar morphologies, becoming larger when the initial feed concentration is increased, because of earlier crystallization. The leucine/trehalose particles exhibit different morphologies at different compositions since trehalose interferes with the crystallization of leucine. The ultra-magnified insets show crystals formed near the surface of the leucine-containing particles that are absent in the pure trehalose particles. The normalized particle diameters and calculated particle densities of these monodisperse particles are shown in figure 2. The increase in particle diameters and the decrease in particle densities at higher leucine fractions are apparent.

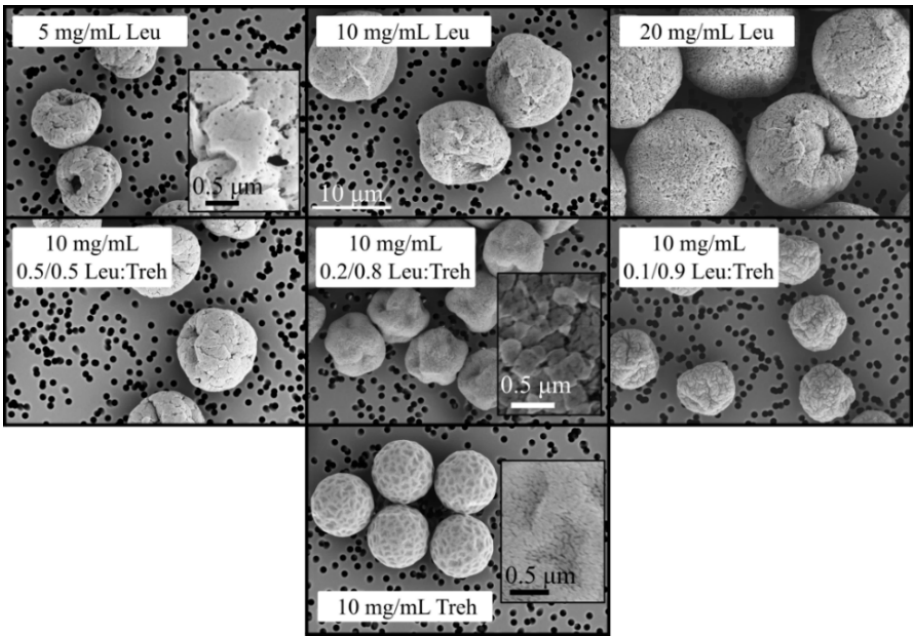

Figure 1 SEM micrographs of the monodisperse particles generated using the droplet chain setup at a drying temperature of 20 °C.

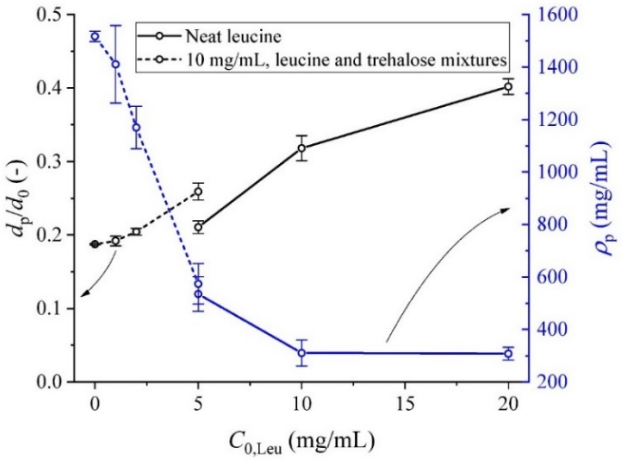

Figure 2 The measured normalized particle diameters and calculated particle densities obtained from the monodisperse droplet chain setup at a drying temperature of 20 °C. The error bars represent one standard deviation of about two hundred measurements.

The SEM micrographs accompanied by the ToF-SIMS results of the spray-dried leucine/trehalose particles are shown in figure 3. In the ToF-SIMS images, leucine and trehalose are represented by the red and blue colors, respectively. It was observed that the particle surface compositions were size-dependent, with smaller particles having less leucine on the surface than the larger particles. This observation confirms that nucleation and crystal growth kinetics control the surface enrichment of leucine. The percentages of leucine crystallinity in the resulting bulk powders were also measured using Raman spectroscopy and were found to be 100%, 100% and 23%, respectively, for the spray-dried powders in figure 3 from left to right.

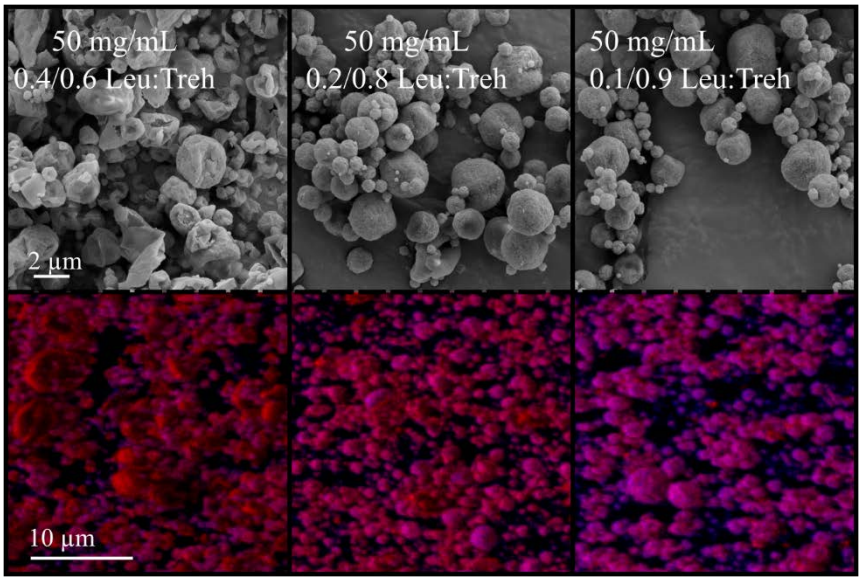

Figure 3 The SEM micrographs and ToF-SIMS images of the spray-dried leucine/trehalose particles with different excipient mass fractions. In the ToF-SIMS images, the red and blue colors represent leucine and trehalose molecules, respectively.

Conclusions

It was concluded that the surface accumulation of leucine during spray drying is due mostly to nucleation and crystal growth near the droplet surface. In the presence of other excipients or active pharmaceutical ingredients, the surface coverage of leucine and possibly its crystallinity are size-dependent in a polydisperse spray-dried powder. Smaller particles are expected to have lower leucine coverage than larger particles and may be partially amorphous. These results show that leucine-containing particles cannot be designed according to a simple formulation composition rule. Particle size, evaporation rate and the concentration and characteristics of other excipients and actives must also be considered using a proper particle formation model to maximize dispersibility, control particle density, and ensure the long-term physical stability of leucine-containing powders.

References

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