How does trileucine act as a dispersibility enhancer in the spray drying of microparticles?

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Introduction

Among the different excipients used as dispersibility enhancers, trileucine is one of the most promising and effective candidates, minute quantities of which can significantly improve the delivery efficiency from a dry powder inhaler [1]. Trileucine is a strong surface-active material with low aqueous solubility (~6.8 mg/mL). Upon atomization, such a component is expected to adsorb at the air-water interface and induce liquid-liquid phase separation, after the concentration near the surface exceeds the stability limit [2]. The combination of these effects contributes to the increase in powder dispersibility. The adsorbed monolayer with hydrophobic tails pointing outwards is believed to reduce the surface energy of the particles and hence to decrease the interparticle cohesion with minimal changes in particle morphology, even when very

small quantities of trileucine are present in the system [3]. Given sufficient quantities of trileucine, the early phase separation near the surface causes a thin shell to be formed early on which results in a wrinkled and rugose particle.

In this study, the effects of surface adsorption and early phase separation were modeled theoretically, and the results were used to explain the morphology and surface composition of spray-dried particles containing trileucine and trehalose.

Methods

A laboratory-scale spray dryer was used to produce three batches of powder with different compositions of trileucine and trehalose dried at a gas temperature of 75 °C. Scanning electron microscopy (Sigma FESEM, Zeiss, Jena, Germany) was used to compare the morphologies of the resulting particles, while time-of-flight secondary ion mass spectrometry (TOF.SIMS^5, ION-TOF GmbH, Münster, Germany) was used to quantify their surface compositions. Raman spectroscopy was also performed using a custom-built dispersive Raman spectrometer to confirm the amorphous nature of the spray-dried powders.

A new theoretical model was used to estimate the trileucine surface adsorption during droplet evaporation. Using the Flory-Huggins solution theory, it was also estimated that trileucine and water undergo spinodal decomposition (spontaneous phase separation) upon surpassing a trileucine concentration of about 18 mg/mL during drying. The concentration at which trehalose was expected to affect the viscosity of the liquid droplet and interfere with the evaporation was previously measured to be about 830

mg/mL [4]. These values were used to compare different time-scales of interest during the drying of an aqueous solution droplet, including trileucine and trehalose.

Results and Discussions

The SEM micrographs of the spray-dried trileucine and trehalose particles accompanied by the ToF-SIMS results are shown in figure 1. In the ToF-SIMS images, the red and blue colors indicate the trileucine and trehalose molecules, respectively. When the trileucine feed fraction was increased the particles became less dense with a thinner shell. It was also observed that even at only 2% w/w trileucine, the surface of the particles was mostly packed with trileucine, possibly due to the adsorbed monolayer. Some small surface-composition size dependency was observed for the 2% w/w trileucine powder due to incomplete surface adsorption in smaller droplets at this low concentration. The quantified trileucine surface coverages obtained from the ToF-SIMS measurements are also shown in figure 2. These data were obtained for the whole powder, small, medium, and large particles, as shown in the figure. The size dependency was seen to decrease in effect at higher trileucine fractions.

The normalized time (time divided by the drying time of each droplet) expected for trileucine to form a packed monolayer on the droplet surface, τ_{Γ}; the normalized time at which the trileucine surface concentration surpassed the instability limit of 18 mg/mL, $\tau_{\mathrm{sp,Leu3}}$; and the normalized time at which trehalose was expected to affect the evaporation of the droplet upon reaching a bulk concentration of 830 mg/mL, $\tau_{\mathrm{c,Treh}}$, were calculated numerically and are shown in figure 3. These timescales were calculated for the three different spray-dried feed compositions dried at 75 °C and are shown as a function of the initial atomized droplet diameter, d_0. It was observed that for

the 2% trileucine case, which had size-dependent surface compositions, the time to a fully packed trileucine monolayer was comparable to the other timescales for smaller droplet diameters. This means that at smaller trileucine fractions in the system, trehalose would solidify before trileucine could form a monolayer on the surface. This interference is expected to be even stronger with lower trileucine content. For the 2% trileucine case, it was also observed that the point of spinodal decomposition coincided with the trehalose solidification, which explains the less wrinkled morphologies of these particles.

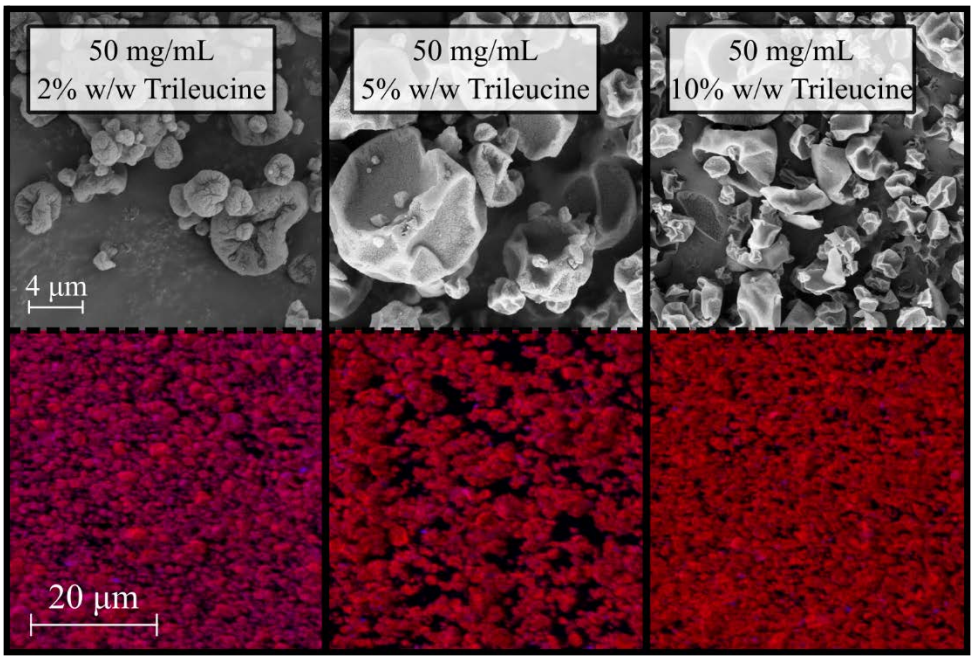

Figure 1 SEM micrographs showing the spray-dried particles at the top and their corresponding ToF-SIMS data at the bottom. In the bottom row, red and blue colors correspond to the trileucine and trehalose molecules, respectively.

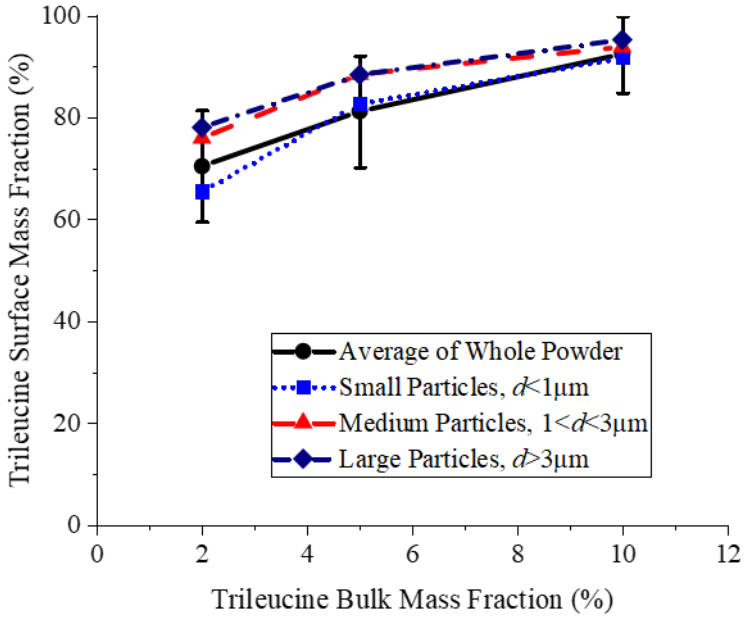

Figure 2 Trileucine surface coverages of the spray-dried trileucine and trehalose particles.

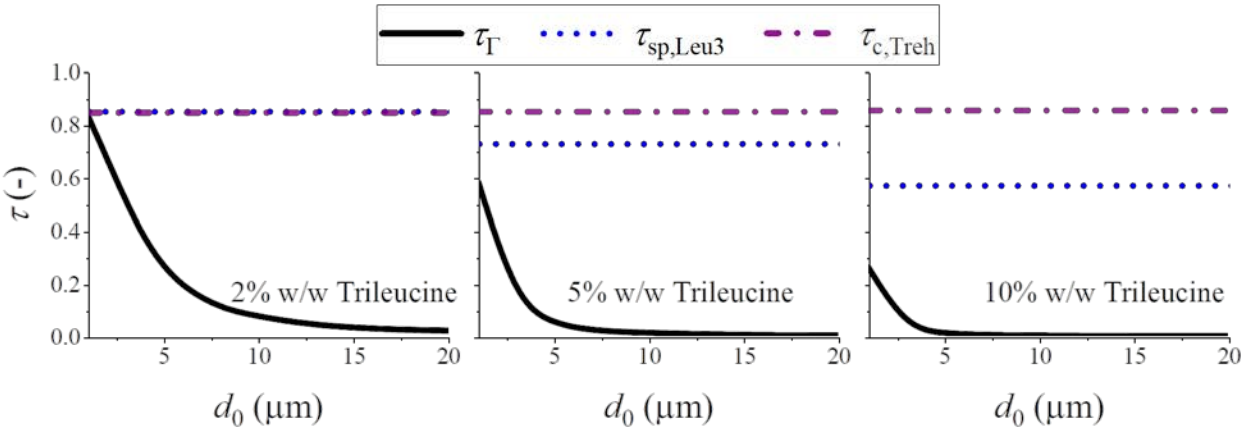

Figure 3 The normalized time to a fully packed trileucine monolayer, τ_{Γ}, the start of trileucine spinodal decomposition, $\tau_{\mathrm{sp,Leu3}}$, and the start of trehalose solidification, $\tau_{\mathrm{c,Treh}}$.

Conclusions

It can be concluded that trileucine phase-separates by spinodal decomposition, not by crystallization, forming a high-T_g amorphous shell. This characteristic is advantageous for the formulation of biologics requiring glass stabilization. Moreover, trileucine is

effective even at very low mass fractions, thus offsetting its higher cost compared to that of other dispersibility enhancers.

It was also determined that the dispersibility enhancement of trileucine as an excipient in the spray drying of inhalable microparticles is caused by a combination of its high surface activity and low aqueous solubility. During the drying of the solution droplet, trileucine molecules need to have ample time to form a monomolecular layer on the droplet surface to efficiently decrease the surface energy of the resulting dried particles. If a highly rugose and low-density morphology is required, other excipients and APIs in the system should not interfere with the phase separation of trileucine. Both of these aspects can be theoretically predicted for a successful formulation design with minimal experimental iterations.

References

[1] D. Lechuga-Ballesteros *et al.*, “Trileucine Improves Aerosol Performance and Stability of Spray-Dried Powders for Inhalation,” *J. Pharm. Sci.*, vol. 97, no. 1, pp. 287–302, Jan. 2008.

[2] M. A. Freedman, “Phase separation in organic aerosol,” *Chem. Soc. Rev.*, vol. 46, no. 24, pp. 7694–7705, Dec. 2017.

[3] H. Wang, D. S. Nobes, and R. Vehring, “Particle Surface Roughness Improves Colloidal Stability of Pressurized Pharmaceutical Suspensions,” *Pharm. Res.*, vol. 36, no. 3, p. 43, Mar. 2019.

[4] M. Ordoubadi *et al.*, “On the particle formation of leucine in spray drying of inhalable microparticles,” *Int. J. Pharm.*, vol. 592, p. 120102, Jan. 2021.