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

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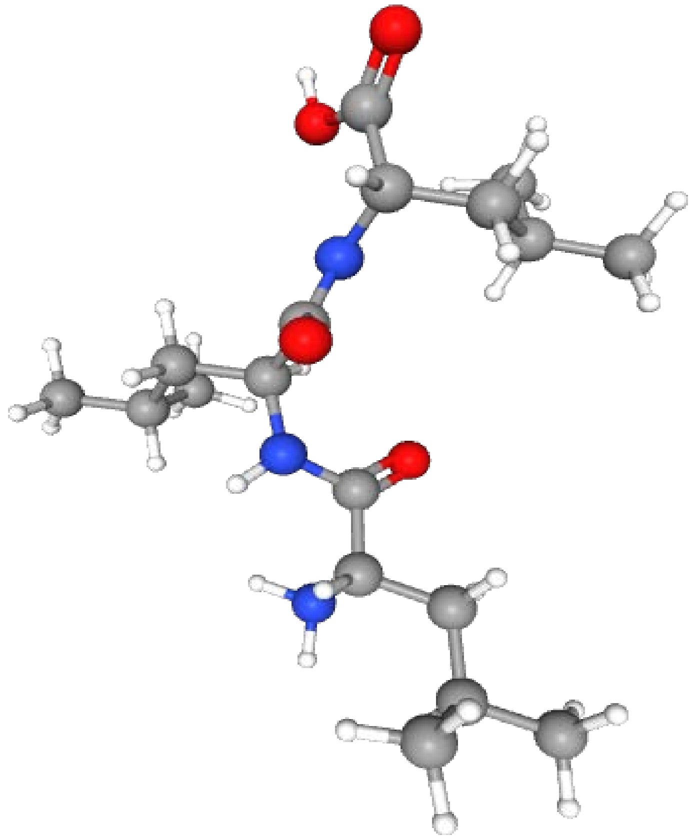
MECHANICAL ENGINEERING

Introduction

- Trileucine
  - is a strong surface-active material,
  - has low aqueous solubility ($\sim 6.8\ \mathrm{mg/mL}$),
  - and makes an amorphous solid upon spray drying [1].
- These conditions make it a strong dispersibility enhancer of spray-dried inhaled microparticles.
- Even small quantities of trileucine can significantly improve aerosol performance of microparticles[2].
- It is a relatively expensive excipient and it would be beneficial to design the formulation in a manner to include the smallest quantities of trileucine.
- Current particle formation models cannot predict the drying behavior of surface-active and low-soluble glass formers[3].

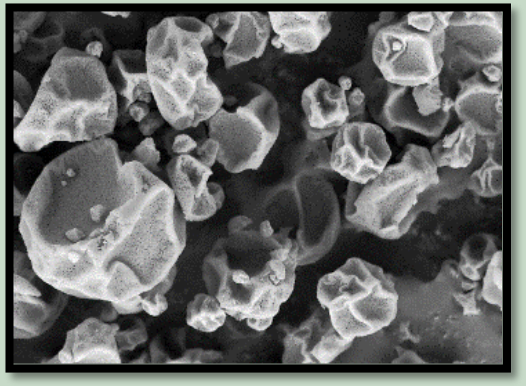


Methods – Drying of Trileucine and Trehalose Particles

Lab-Scale Spray Dryer (B-191)

$T_{in} = 75\ °C$
$d_0 \cong 8\ \mu m$

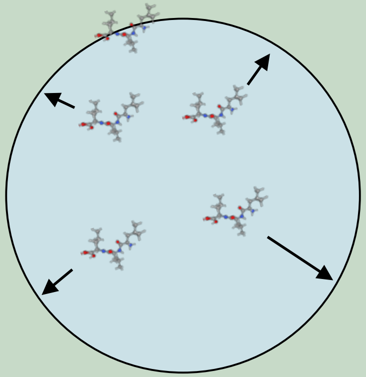
- SEM
- ToF-SIMS
- Raman spectroscopy



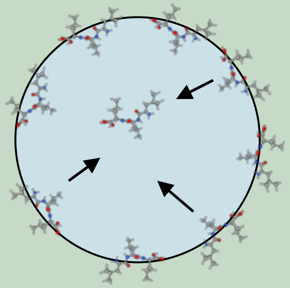
Theoretical Estimation of Surface Adsorption and Phase Separation

- Surface adsorption of trileucine on the surface:

$\Gamma < \Gamma_{max}$



$\Gamma = \Gamma_{max}$



- The Flory-Huggins theory was used to give an estimate of when trileucine would phase separate in an aqueous solution due to spinodal decomposition:

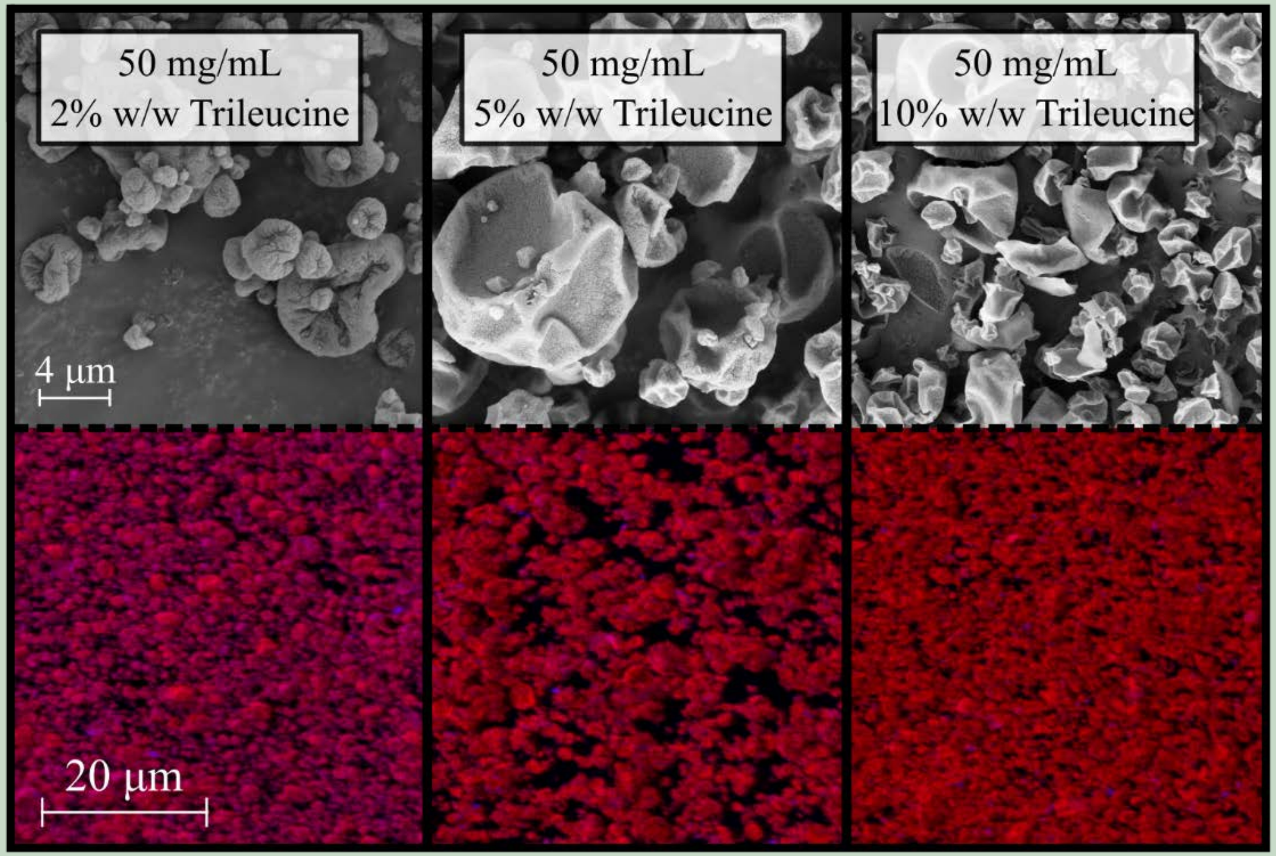
$$c_{sp,leu3} \cong 18\ \mathrm{mg/mL} \text{ at } 20\ °C$$

Spray-Dried Powders – Minimal Amount of Size-Dependency of Surface Coverage Observed

SEM

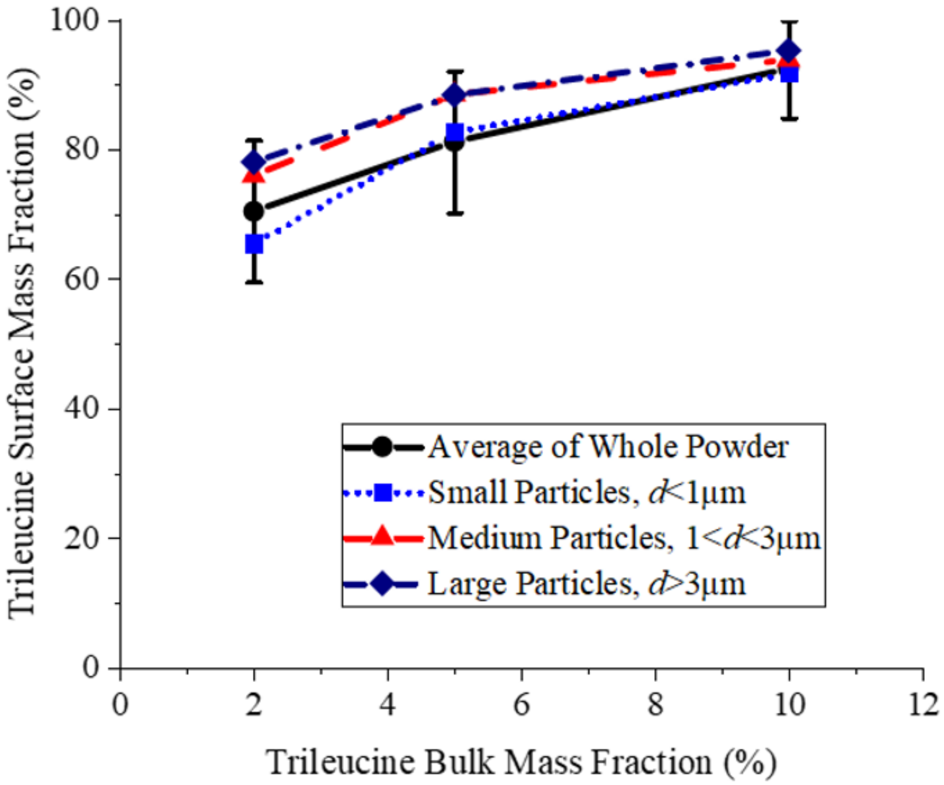
ToF-SIMS

Red: trileucine
Blue: trehalose



Raman Spectroscopy

Completely amorphous trileucine and trehalose for all cases.



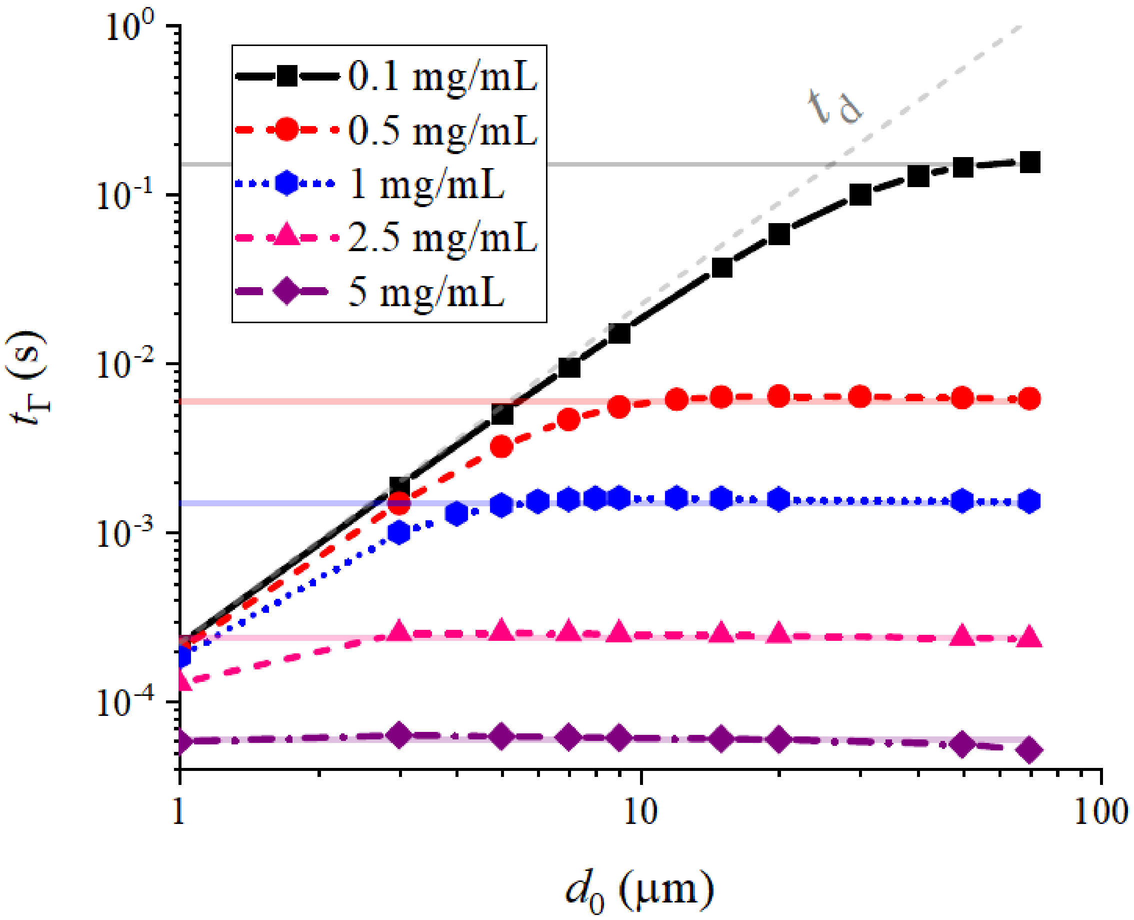
More than 30-fold increase in trileucine surface coverage compared to the bulk.

Probably due to:

- surface activity,
- early phase separation at 18 mg/mL.

Prediction of the Surface Adsorption of Trileucine – At High Feed Concentrations Trileucine Can Always Make a Fully Packed Monolayer

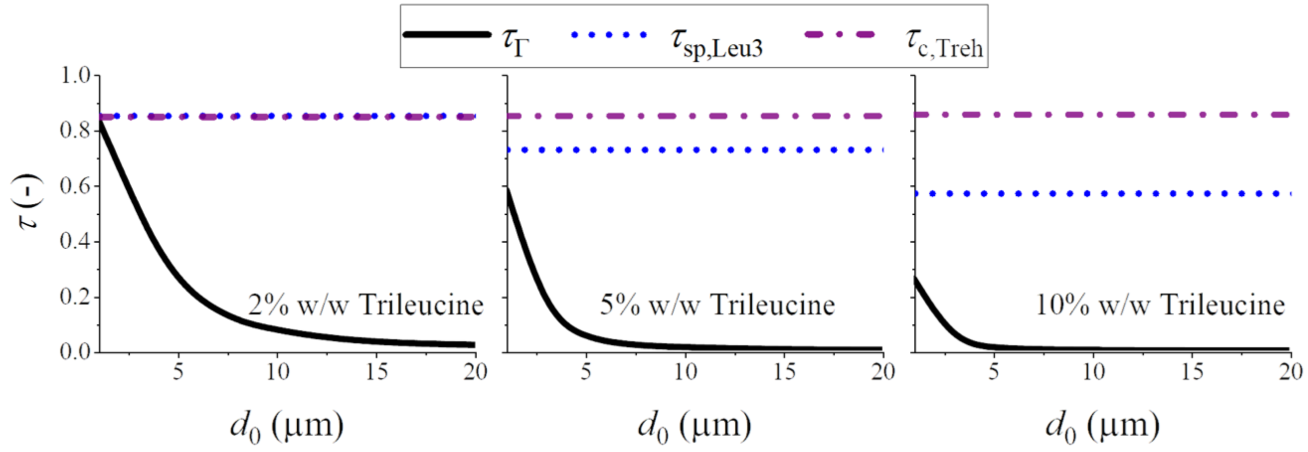
Drying temperature of 75 °C



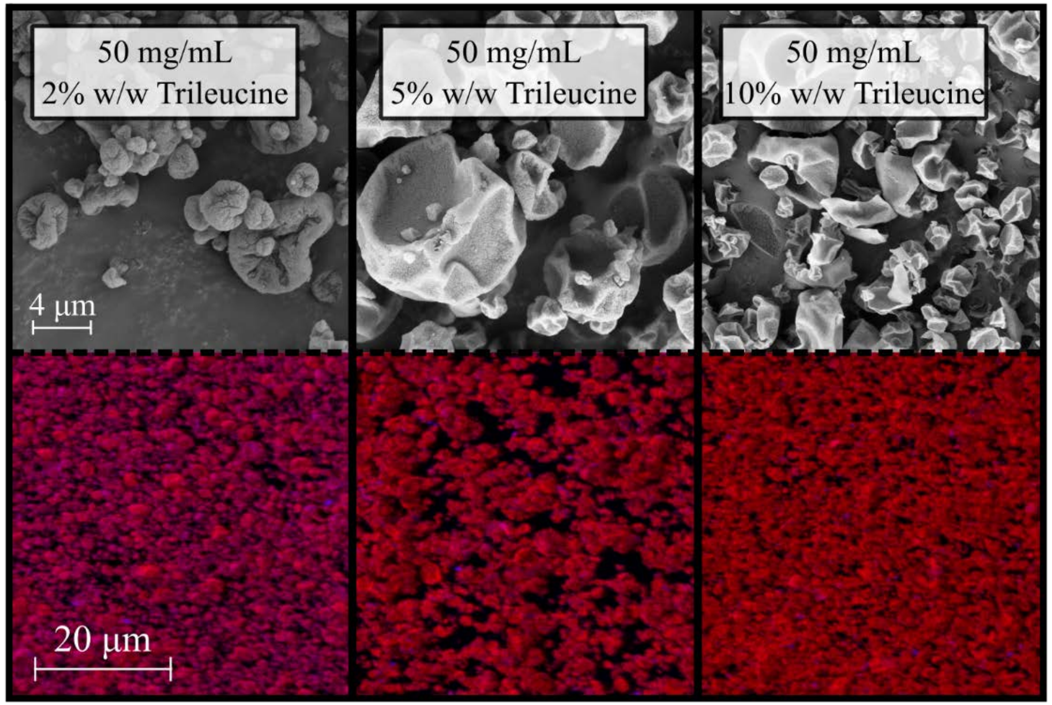
- t_Γ is the time at which the maximum surface excess of Γ is reached.
- t_d is the droplet drying time.
- The maximum surface excess is a measure of the packing of molecules on the air-water interface.
- It was estimated to be $\sim 0.17\ \mathrm{mg/m^2}$ for trileucine from tensiometry data.

Trileucine should have enough time to make a saturated monolayer to act as an efficient dispersibility enhancer.

Particle Formation Theory for Trileucine/Trehalose Systems – At Very Small Feed Fractions the Shell Formation of Trileucine Can Be Hindered by Other Components



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



For the 2% w/w trileucine system:

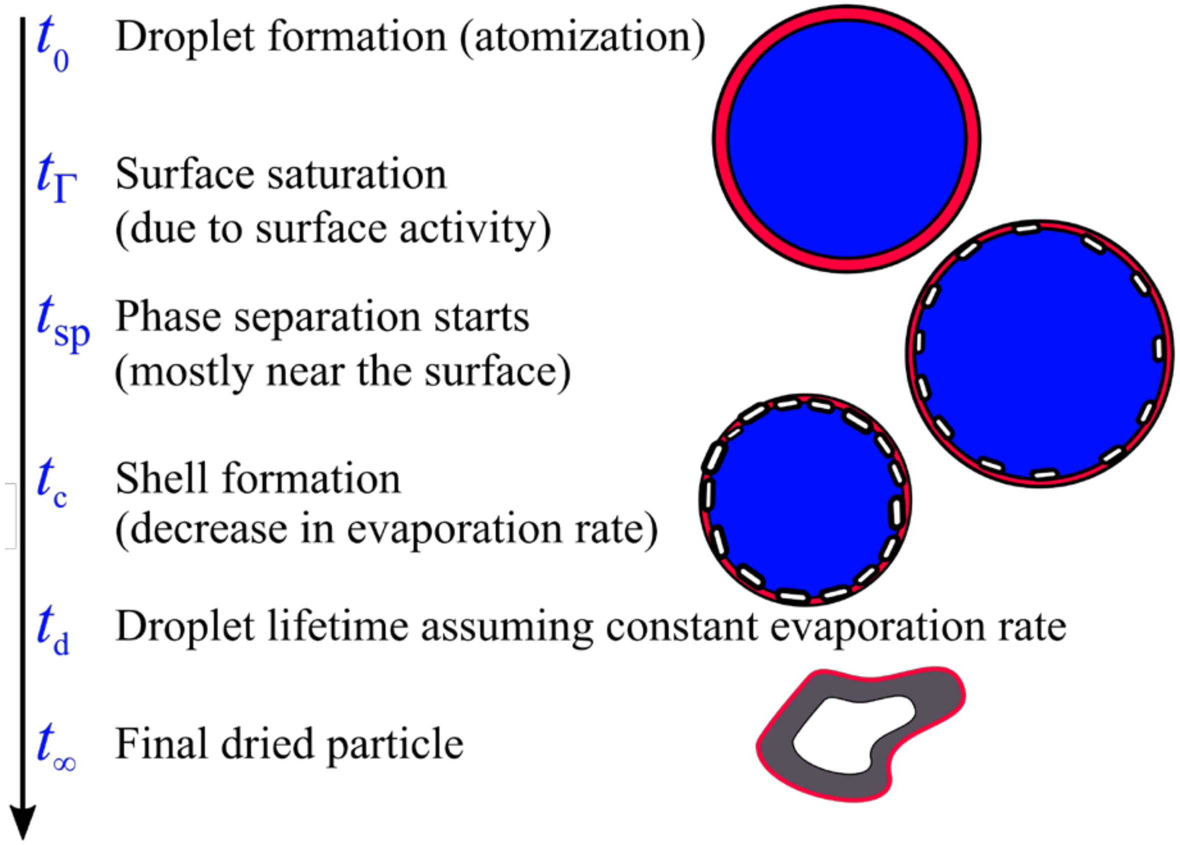
- Trileucine and trehalose are expected to solidify together.
- The smaller particles probably won't have a saturated monolayer of trileucine on the surface.

For the other two cases:

- A saturated trileucine monolayer is formed regardless of the droplet diameter.
- Trileucine is expected to solidify first followed by trehalose.

Conclusions

- The dispersibility enhancement of trileucine is caused by:
  - The adsorption of the surface-active molecules on the air-water interface.
  - Early phase separation and shell formation resulting in low-density and rugose particles.
- The proposed particle formation method can be used in the early stages of product development for a combination of excipients and actives to meet the design criteria.



References

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[2] H. Wang, D.S. Nobes, R. Vehring, Particle Surface Roughness Improves Colloidal Stability of Pressurized Pharmaceutical Suspensions, Pharm. Res. 36 (2019) 43.

[3] R. Vehring, Pharmaceutical Particle Engineering via Spray Drying, Pharm. Res. 25 (2008) 999–1022.