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

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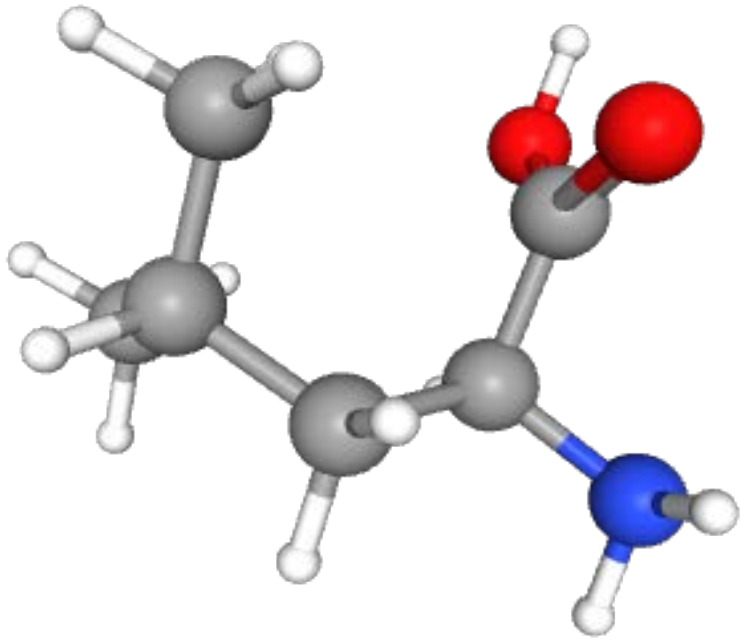
MECHANICAL ENGINEERING

# Introduction

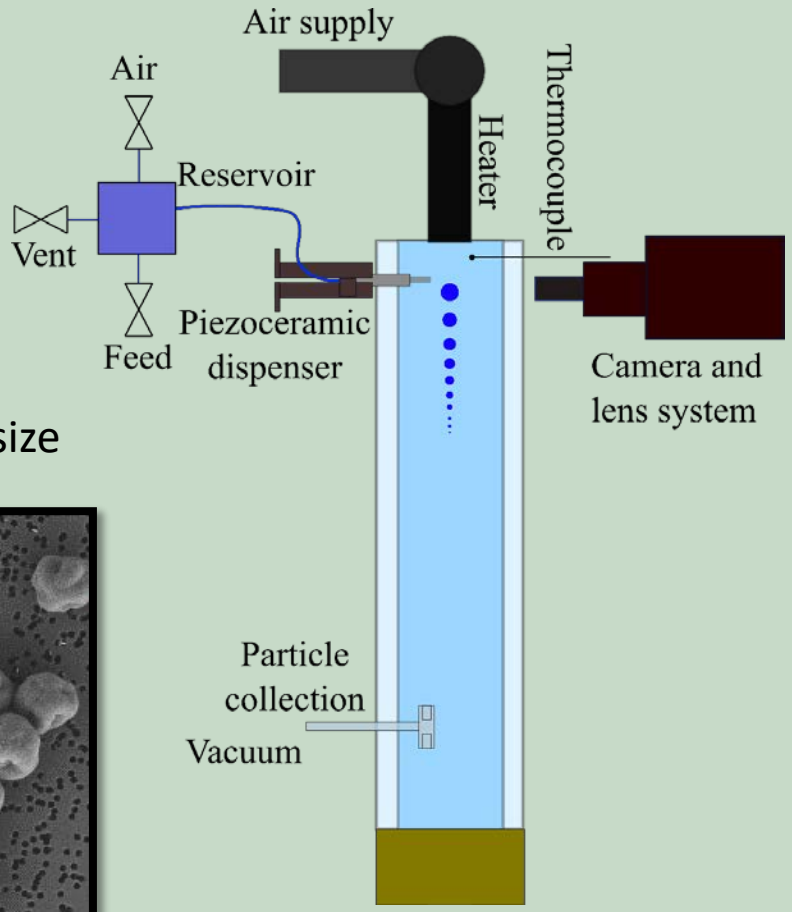
- Dispersibility enhancers are used during spray drying to decrease interparticle cohesion and adhesion with the device components.
- L-leucine is one of the dispersibility enhancers currently in clinical development[1].
- It is surface-active and crystallizes during spray drying[2].
- The underlying mechanisms of shell formation of leucine during spray drying is not understood fully.
- These facts complicate the use of conventional particle formation theories in predicting the surface enrichment of leucine-containing particles and their solid phase.



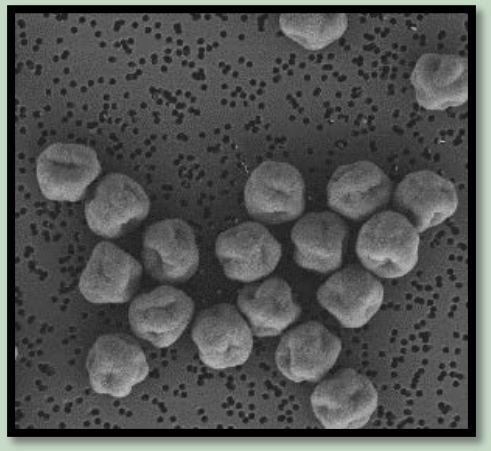
# Methods – Drying of Leucine and Trehalose Particles

## Monodisperse Droplet Chain Instrument

$T_{in} = 20\ °C$
$d_0 \cong 40\ \mu m$



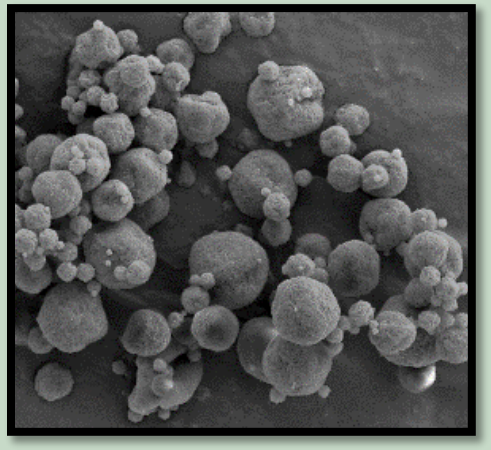

- SEM
- Initial droplet size



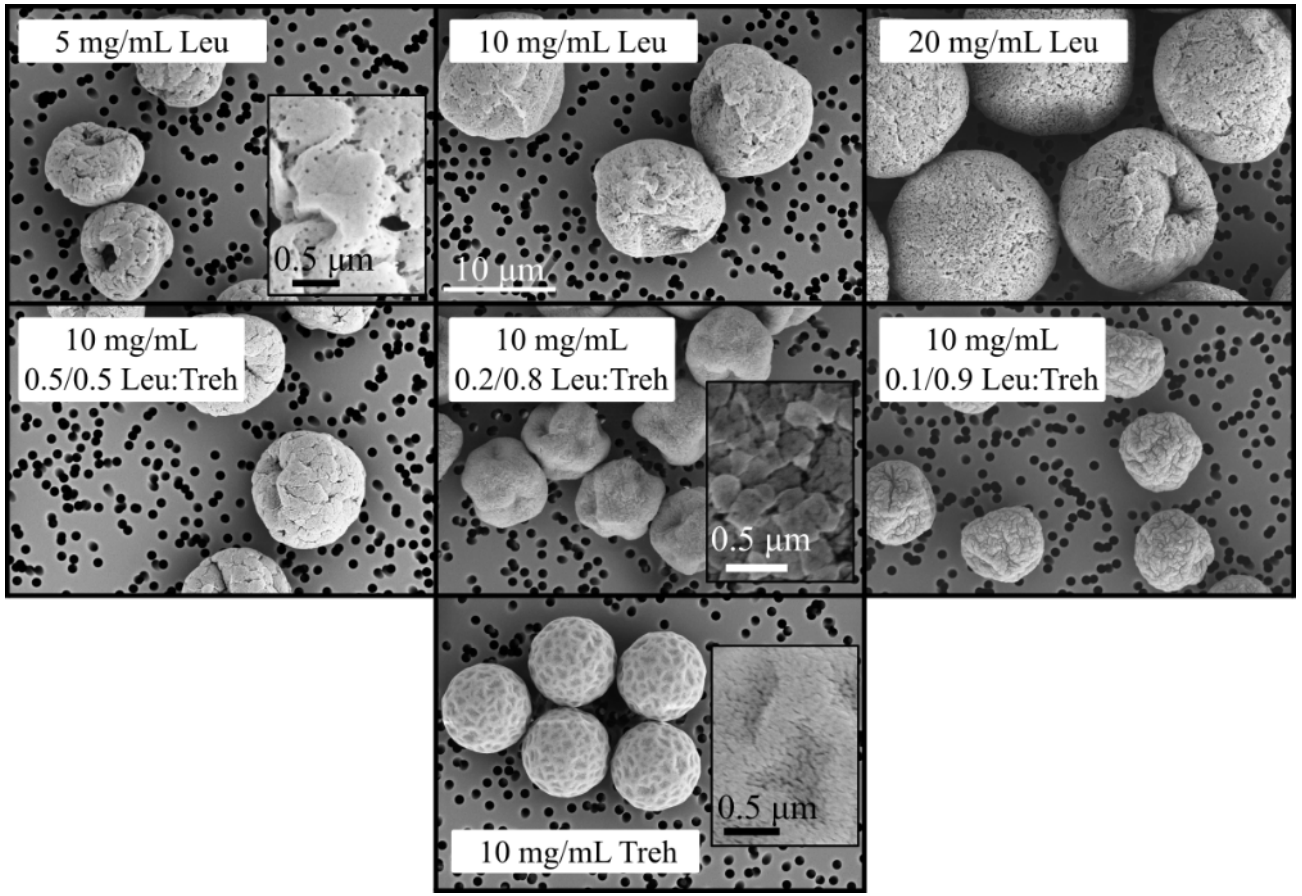
## Lab-Scale Spray Dryer (B-191)

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

- SEM
- ToF-SIMS
- Raman spectroscopy

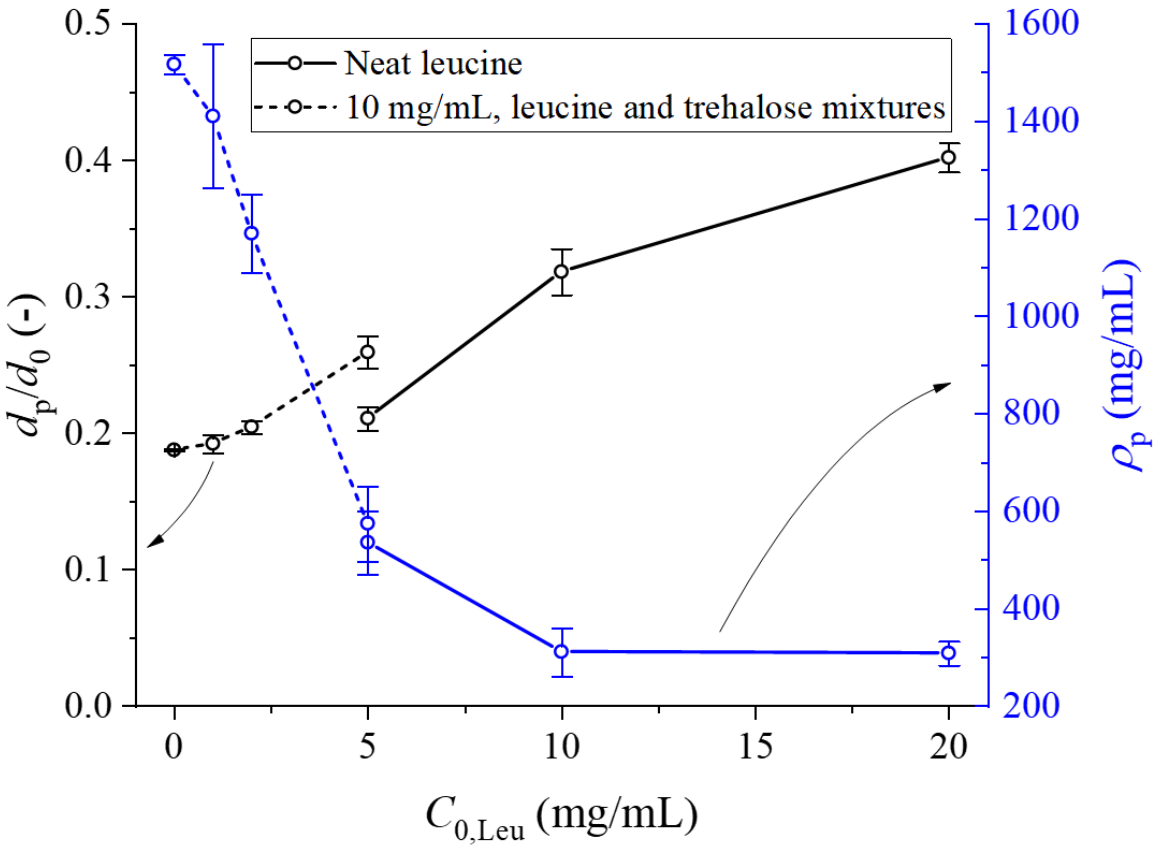


# Monodisperse Particles – Increase in Leucine Fraction Results in Lower Density Particles Due to Earlier Shell Formation

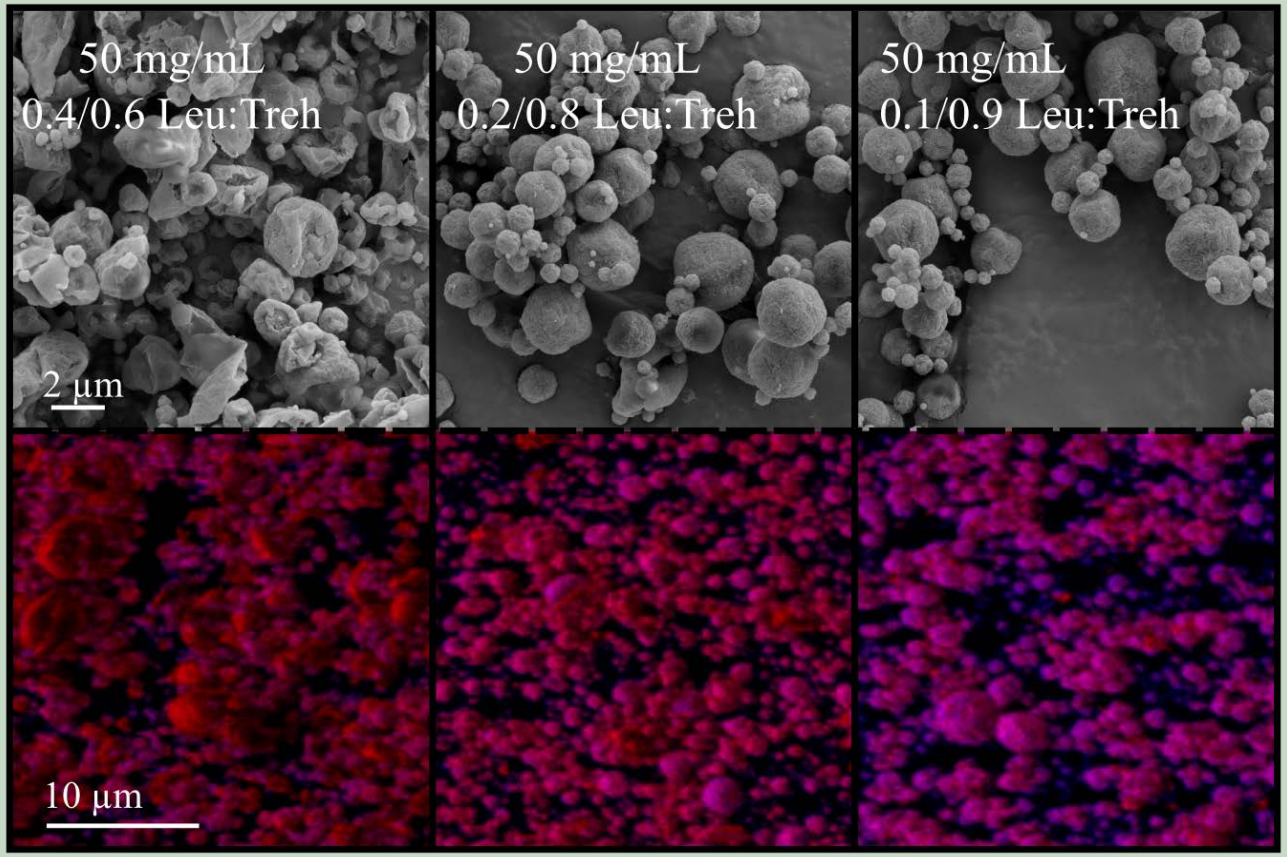


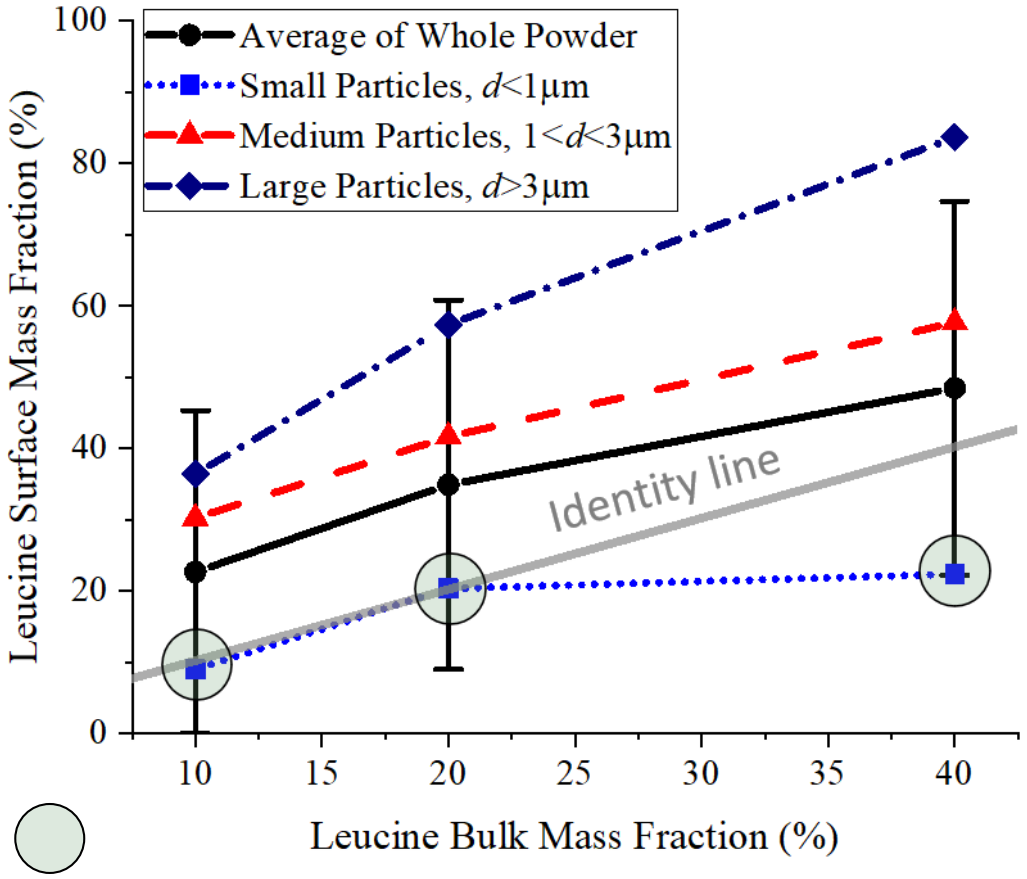

The 10 µm scale bar corresponds to all figures but the insets for which separate scale bars are provided.

$$\rho_p = C_0 \left(\frac{d_0}{d_p}\right)^3$$



# Spray-Dried Powders – Smaller Particles Have Less Leucine on the Surface

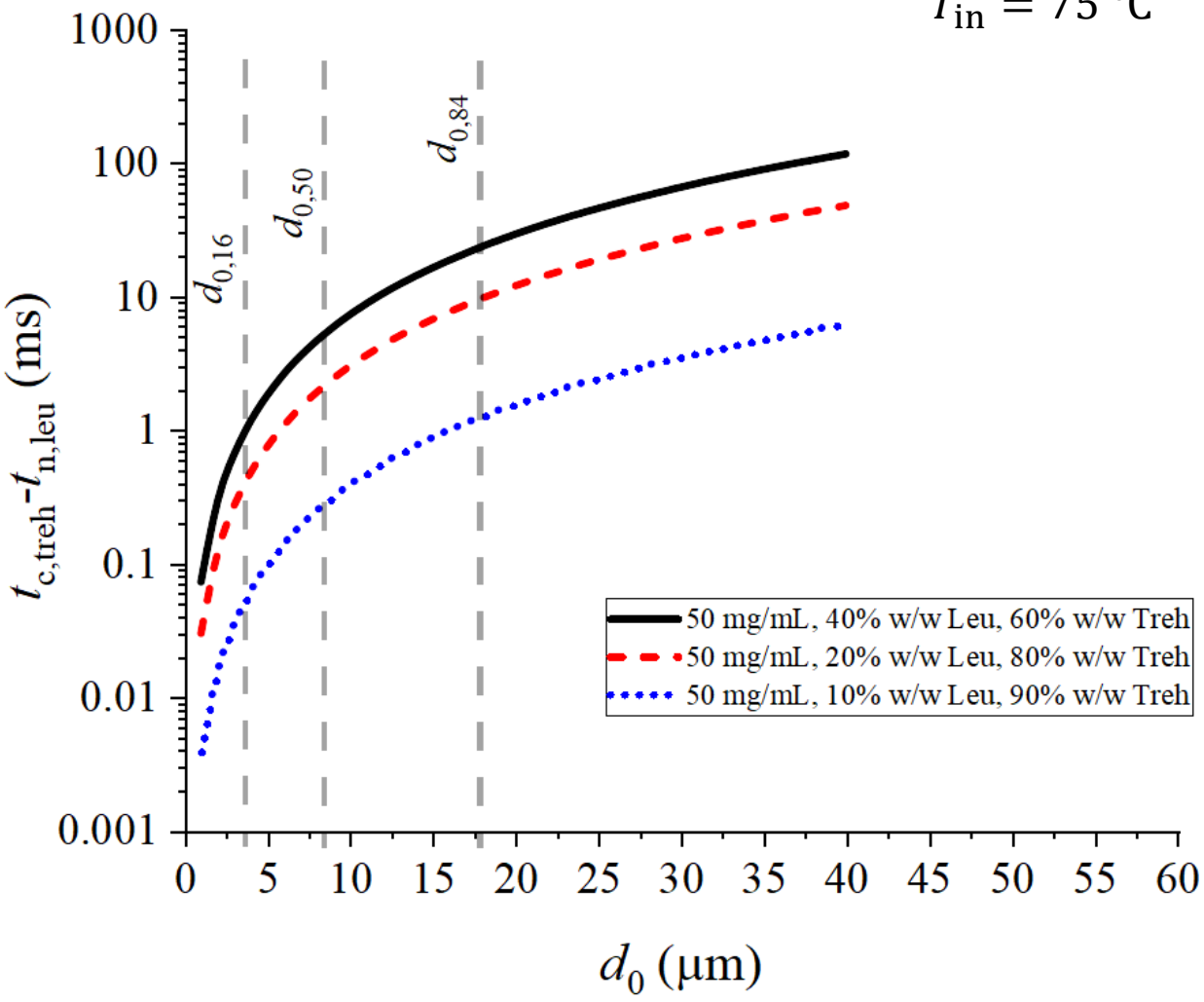



Hypothesis:
Small particles are amorphous with minimum surface enrichment of leucine.

# Model – The Particle Formation Model Can Predict the Size-Dependency

$T_{in} = 75$ °C

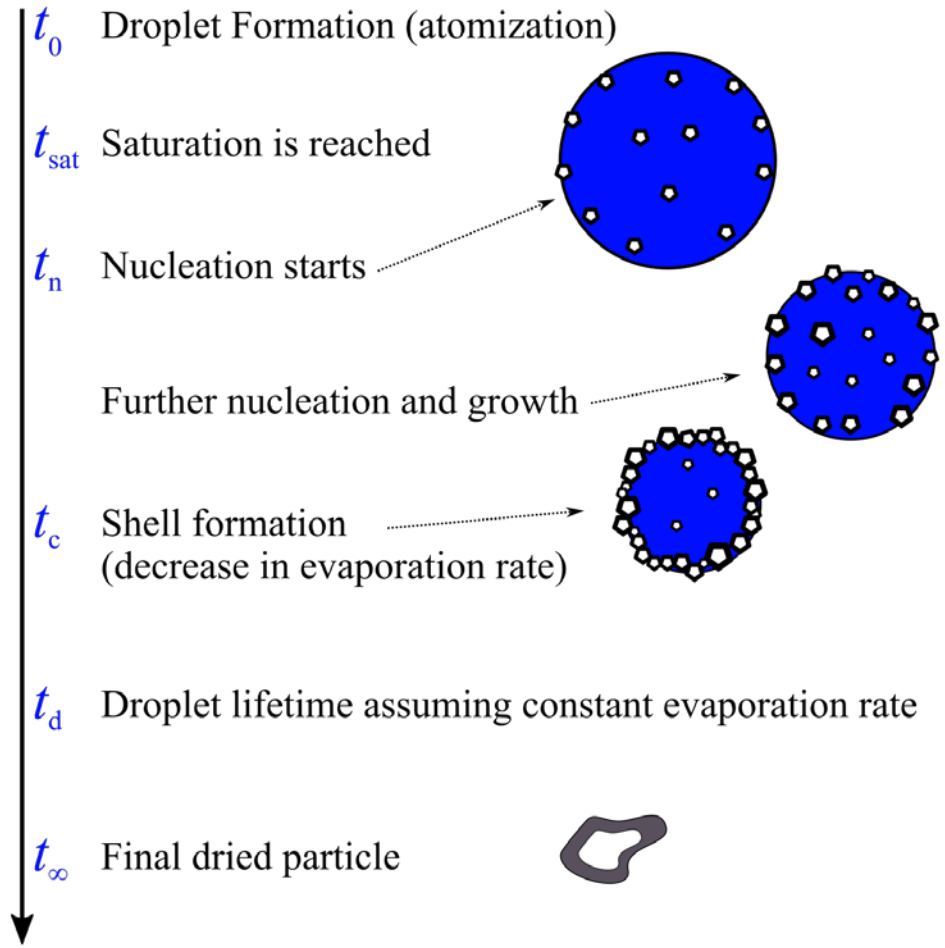



- Leucine is expected to undergo instantaneous nucleation upon reaching a supersaturation ratio of ~3.5[3].
- Trehalose is expected to begin its glass formation process upon reaching a concentration of ~830 mg/mL[2].

Larger $t_{c,treh} - t_{n,leu}$ → more leucine on the surface, higher leucine crystallinity
Smaller $t_{c,treh} - t_{n,leu}$ → less leucine on the surface, lower leucine crystallinity

# Conclusions

- Leucine acts as a dispersibility enhancer mostly by making a rugose crystalline shell on the particle surface*.
- Leucine-containing particles cannot be designed according to a simple formulation composition rule.
- Not given enough time for crystallization, some of the leucine molecules in the particles would make a co-amorphous mixture with the other glass formers.
- This can be predicted with the proposed particle formation model.




Suspected shell formation mechanism for leucine

* Low quantities of leucine in amorphous phase can still lower the surface energy, hence increase the dispersibility, of particles due to its surface-activity (not studied here).

# References


[1] D. Lechuga-Ballesteros, S. Hoe, and B. W. Maynor, “Particle Engineering Technology for Inhaled Therapies,” in *Pharmaceutical Inhalation Aerosol Technology*, 3rd ed., A. J. Hickey and S. R. P. da Rocha, Eds. Boca Raton, Florida: CRC Press, 2019, pp. 349–361.

[2] M. Ordoubadi, F.K.A. Gregson, H. Wang, M. Nicholas, S. Gracin, D. Lechuga-Ballesteros, J.P. Reid, W.H. Finlay, R. Vehring, On the particle formation of leucine in spray drying of inhalable microparticles, Int. J. Pharm. 592 (2021) 120102.

[3] G. He, V. Bhamidi, R.B.H. Tan, P.J.A. Kenis, C.F. Zukoski, Determination of Critical Supersaturation from Microdroplet Evaporation Experiments, Cryst. Growth Des. 6 (2006)

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Thank you!