Leucine Shells on Spray-Dried Medicinal Microparticles

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Outline

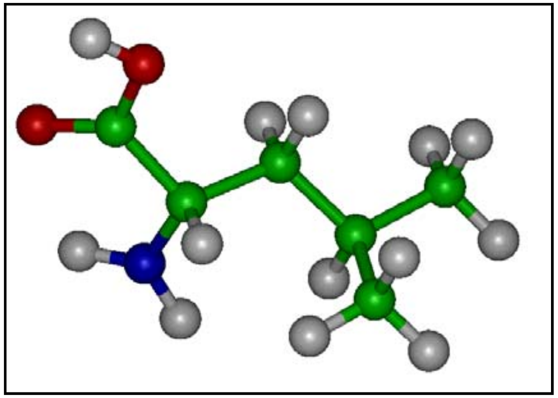
- Introduction
- Experimental
- Theoretical Description
- Particle Formation for Leucine Particles
- Particle Design Example

Key Attributes for Medicinal Particles

• Stability	- Glass stabilization, encapsulation
• Targeting	- Bioactive surfaces, carrier particles
• Pharmacokinetics	- Controlled release
• Bioavailability	- Transporter, tight junction modulation
• Adjuvanticity	- Solubility, bioadhesion
• Delivery	- Low density, surface modification

- Delivery
  - Particle diameter
  - Dispersibility

Leucine in Medicinal Particles



- Vectura, Inc.
  - Uses leucine as "force-control-agent" to improve dispersibility of carrier-based dry powder formulations

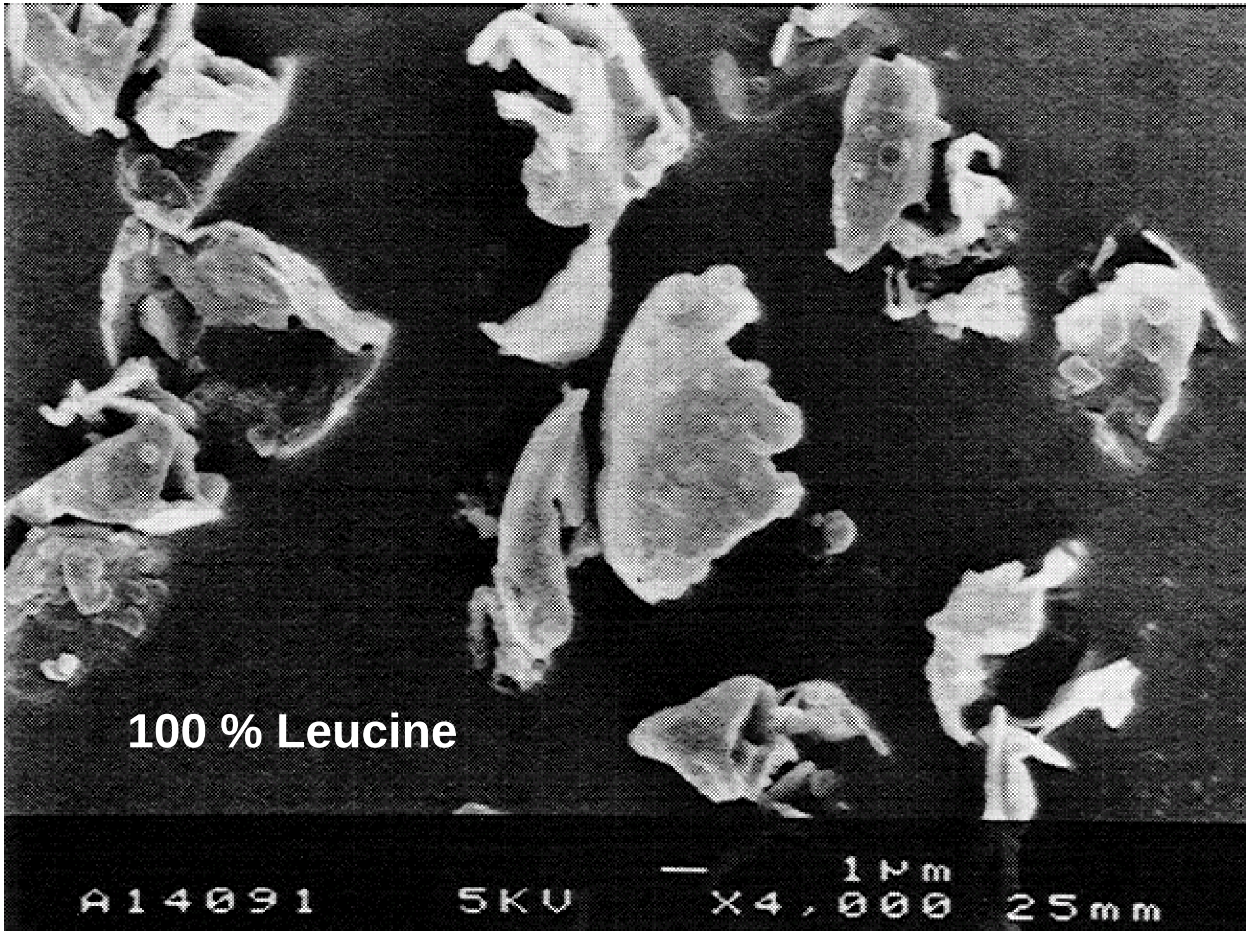
- Nektar Therapeutics, Inc.
  - Owns a series of patents covering amino acids, di- and tripeptides, specifically leucine and trileucine as dispersibility enhancers,

- Gene Delivery Research Group at Cardiff University
  - Found significant increase in dispersibility for a lactose-based plasmid DNA formulation
  - Also found that leucine affected the integrity of the gene therapy vector

- Edwards / Caponetti at Harvard & Aeras Foundation
  - Suggest drying BCG vaccine without desicco- or cryoprotectants in a leucine particle

S. Nagarajan, et al., Nektar Therapeutics, Inc., USA Patent 7,112,341 (2006); H.-Y. Li, et al. *J. Drug Target.* ***11***, 425 (2003).
Y.-L. Wong, et al., *Proc. Nat. Acad. Sci.* ***104***, 2591 (2007).
P. Lucas, K. Anderson, U. J. Potter, and J. N. Staniforth. *Pharm. Res.* ***16***, 1643 (1999).

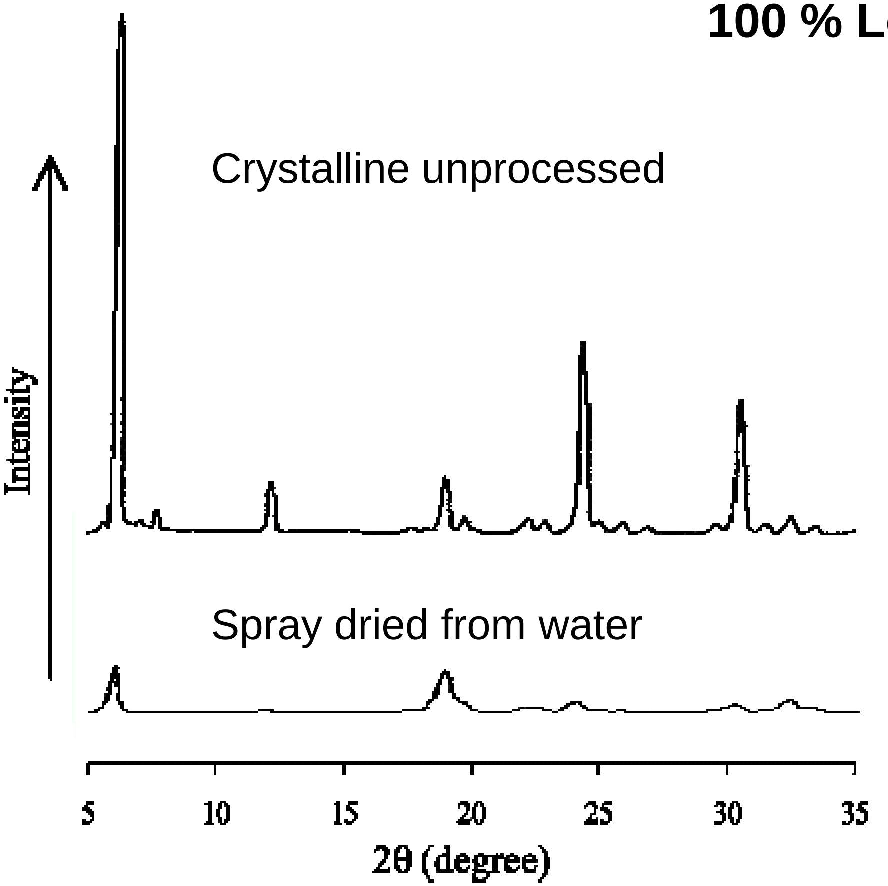
What is Known:
Spray Dried Leucine Produces Hollow Particles

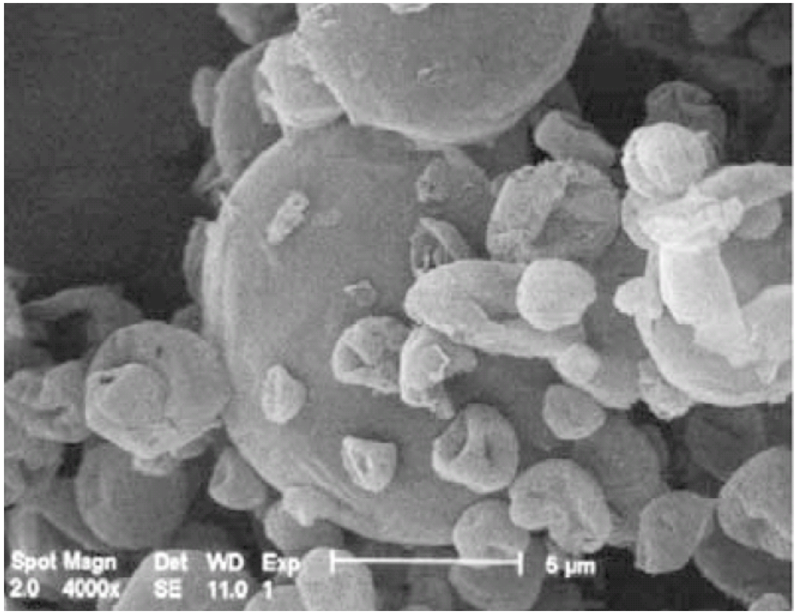


P. Lucas, K. Anderson, U. J. Potter, and J. N. Staniforth. *Pharm. Res.* ***16***, 1643 (1999).

Spray Dried Pure Leucine is Crystalline

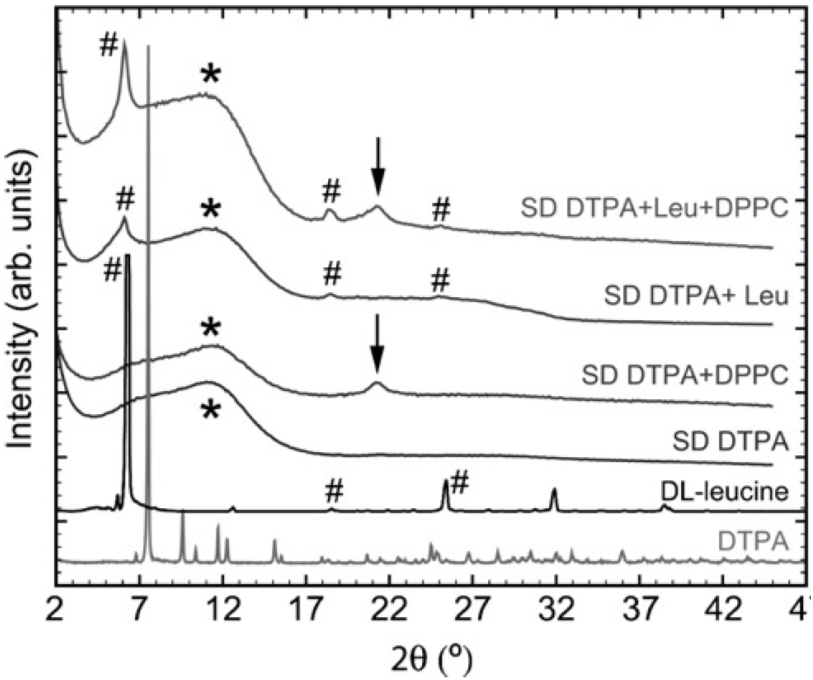
100 % Leucine

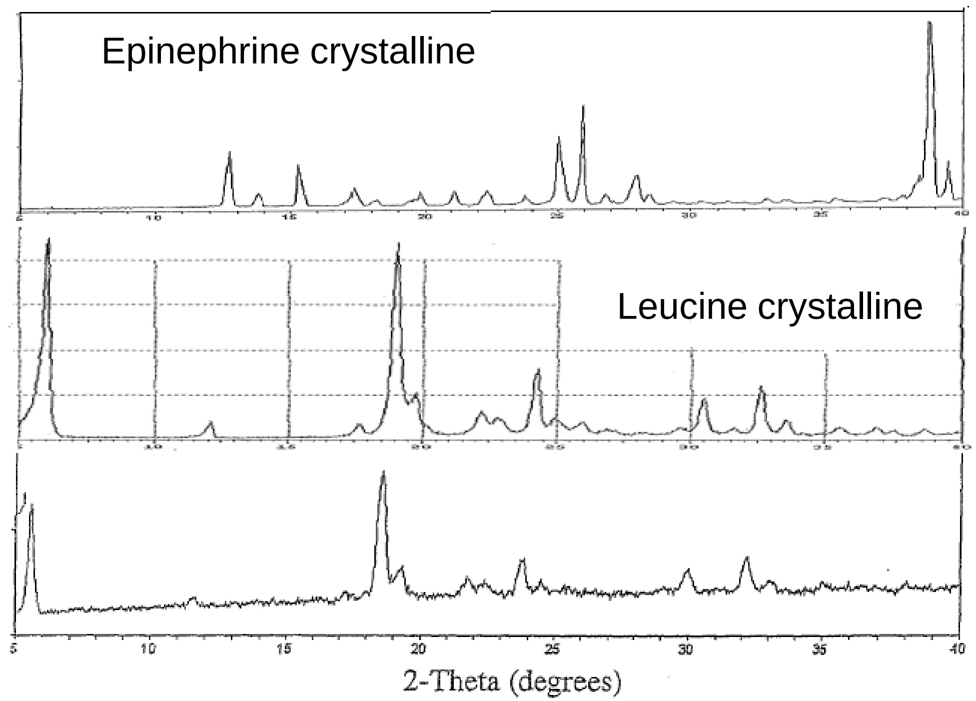




A. R. Najafabadi et al. *Int. J. Pharm.* ***285***, 97 (2004)

Leucine is also Crystalline in Spray Dried Formulations

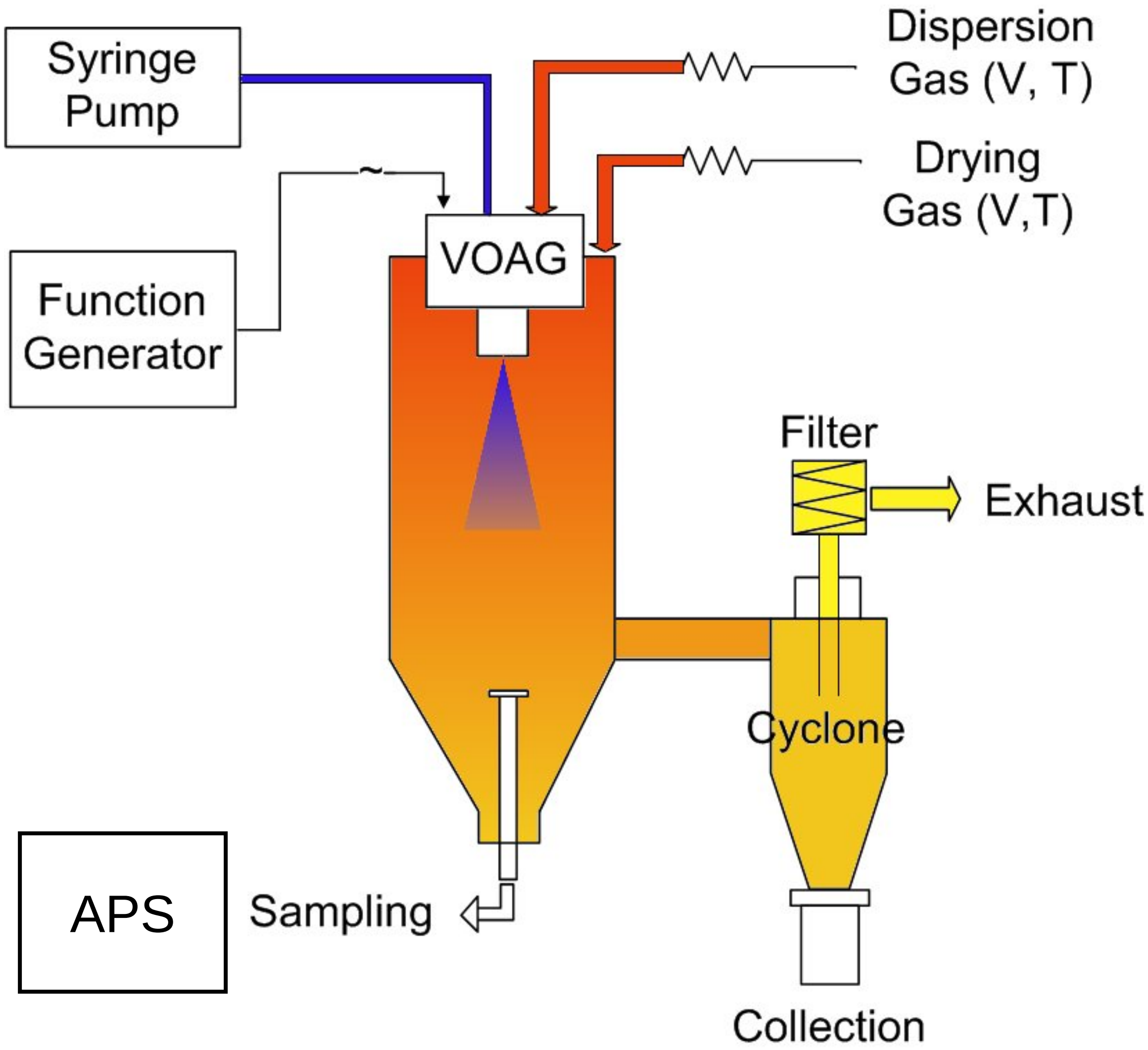




Leucine + Epinephrine spray dried

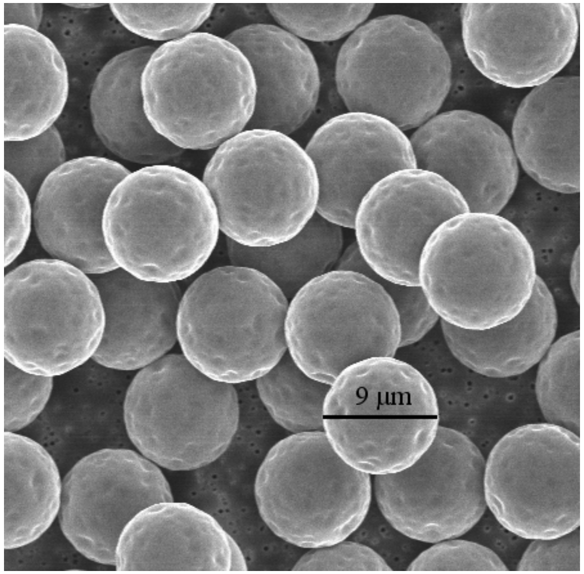
C. Gervelas et al. *J.Contr.Release* ***118***, 78 (2007); R. P. Batycky et al., Adv. Inhalation Research, Int. Pat. WO 2004/002551

Experimental: Monodisperse Spray Dryer

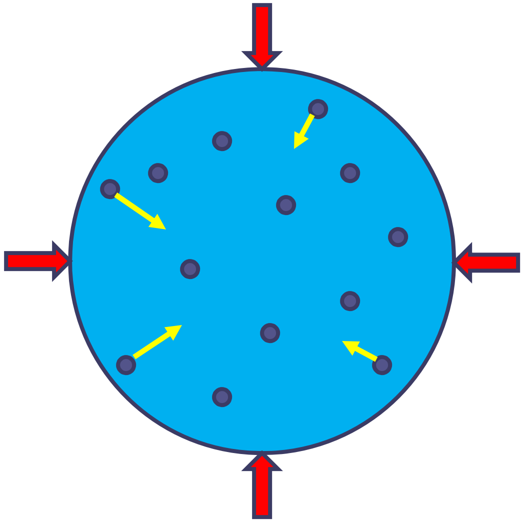


Nearly monodisperse and monomorph.

Density of main population can be determined



Dimensionless Numbers



Peclet Number: $\mathrm{Pe}_i = \dfrac{\kappa}{8D_i}$

Describes balance between velocity of surface recession and diffusion. High Pe leads to

Surface Enrichment: $E_i = \dfrac{c_{s,i}}{c_{m,i}}$

Ratio of surface concentration to average concentration

$$E_i \approx 1 + \frac{\mathrm{Pe_i}}{5} + \frac{\mathrm{Pe_i^2}}{100} - \frac{\mathrm{Pe_i^3}}{4000}$$

Initial Saturation: $S_{0,i} = \dfrac{c_{0,i}}{c_{sol,i}}$

Ratio of initial concentration of the solutes to their solubility

R. Vehring, W. R. Foss, and D. Lechuga-Ballesteros. *J. Aerosol Sci.* **38**, 728 (2007)

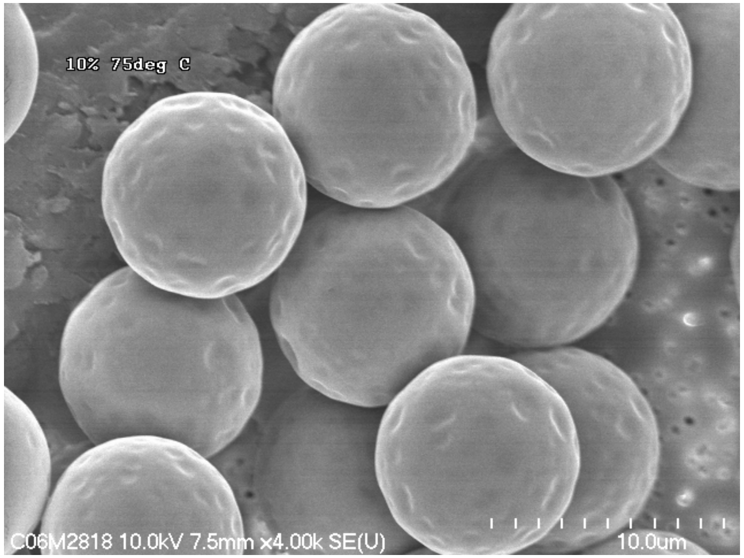
Characteristic Times

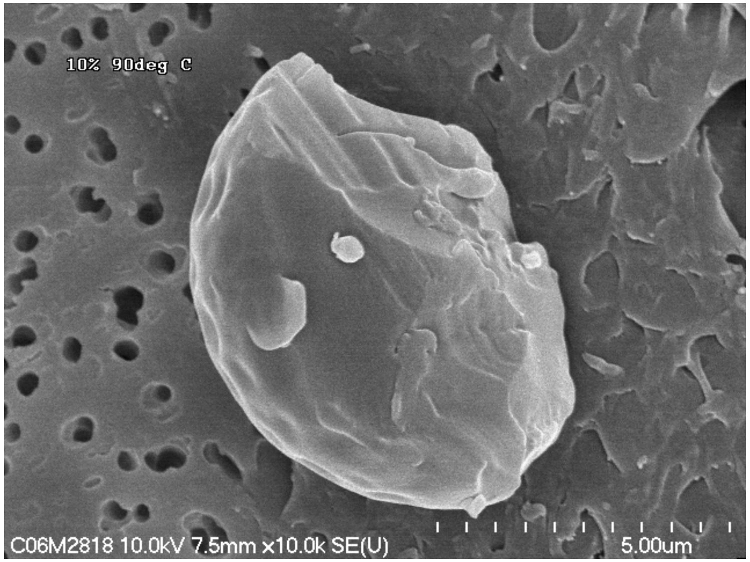
Droplet drying time: $$\tau_{\mathrm{D}} = \frac{d_0^2}{\kappa}$$

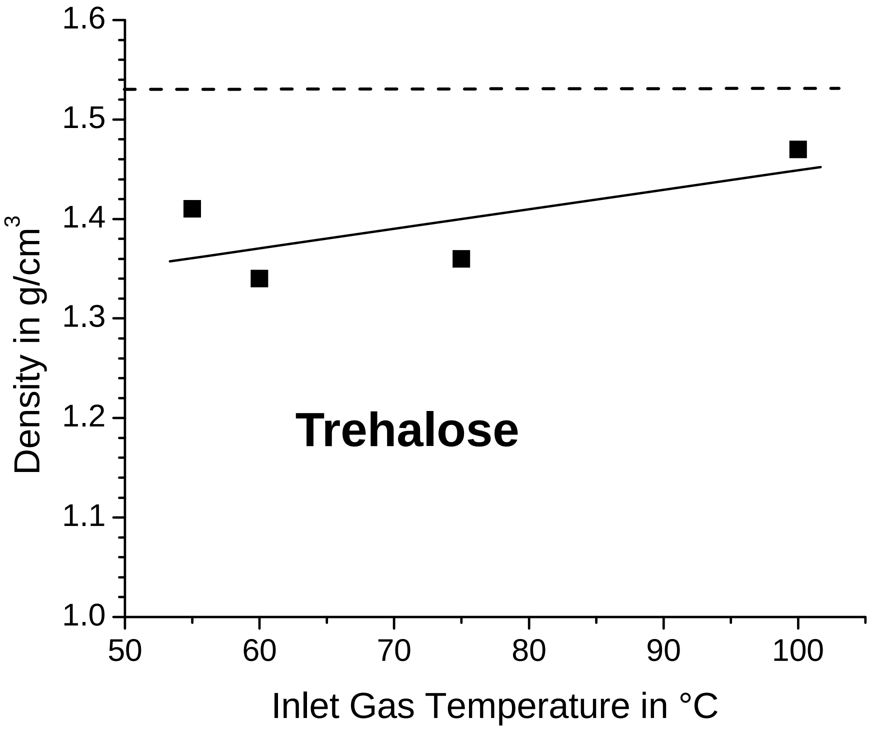
Time to saturation: $$\tau_{sat,i} = \tau_D \left(1 - \left(S_{0,i} \cdot E_i \right)^{\frac{2}{3}} \right)$$

Precipitation Window: $$\tau_{p,i} = \tau_D - \tau_{sat,i} = \frac{d_0^2}{\kappa} \left(S_{0,i} E_i \right)^{\frac{2}{3}}$$

Solid Saccharide Particles

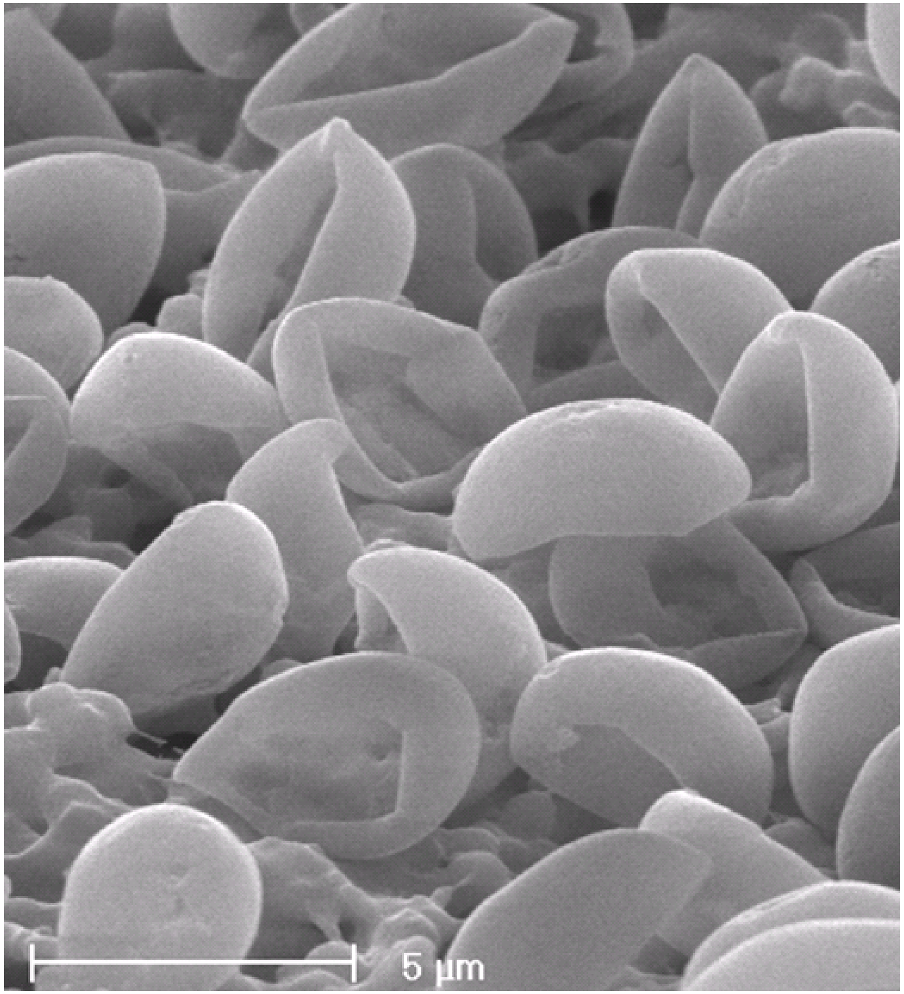






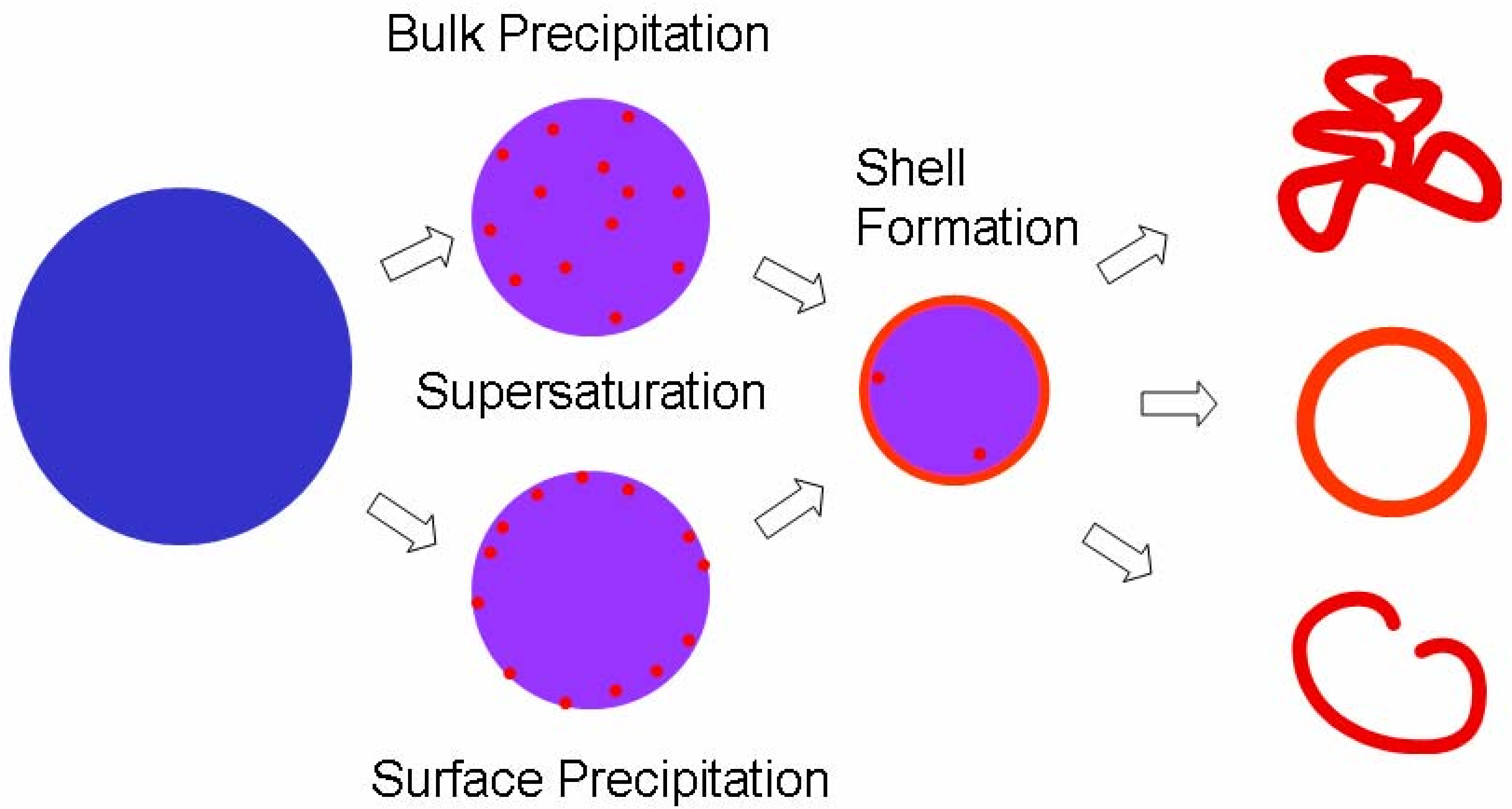
Low Peclet Number (<2), high solubility and a low propensity to crystallize leads to solid particles with a density close to the true density (1.53 g/cm³)

Hollow Leucine Particles



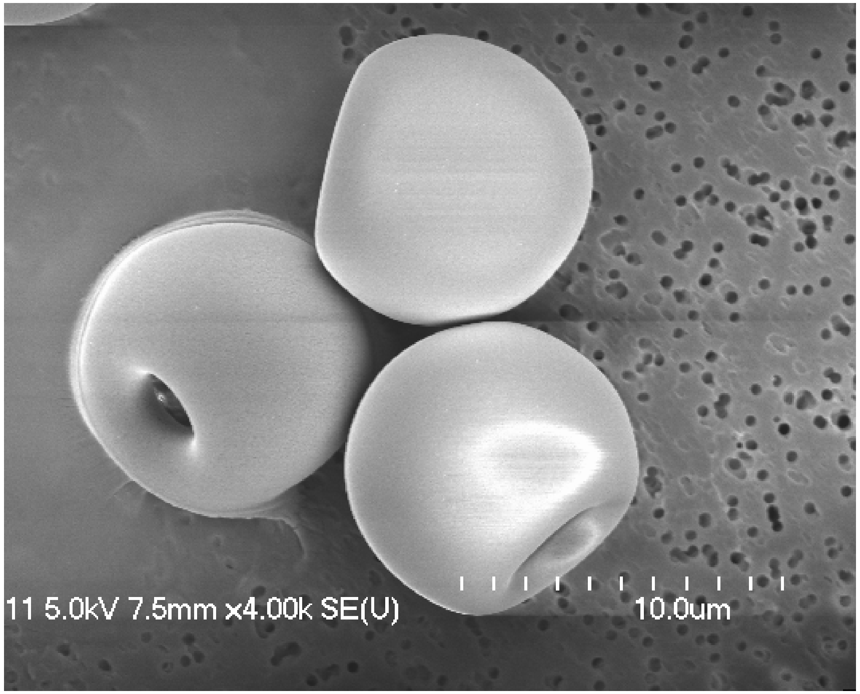
Low Peclet Number (<2) , low solubility and a propensity to crystallize leads to hollow particles with a density much lower than the true density.

Proposed Formation Mechanism for Leucine Particles



Application: Encapsulation of an Antibody

IgG1 + Leucine at $S_o = 0.09$



Unchanged form pure IgG1

IgG1 + Leucine at $S_o = 0.25$

Successful surface modification

Leucine Particle Design Guidelines

- Ways to increase the effectiveness of leucine:
  - Increase fraction of leucine in formulation
    - Reduces capacity of particles for active pharmaceutical ingredient
  - Increase feed solution concentration
    - Increases aerodynamic particle size (~ proportional to the cube-root of the feed solution concentration)
  - Reduce solubility of leucine in solvent system
    - Co-solvent system may not be compatible with active pharmaceutical ingredient
  - Reduce concentration of competing shell-formers or inhibitors

Scale-Up for Leucine Particle

Don't change the precipitation window !

$$\tau_{p,i} = \frac{d_0^2}{\kappa}\left(S_{0,i}E_i\right)^{\frac{2}{3}}$$

Things to keep unchanged:

- Atomizer droplet size distribution
- Drying gas temperature
- Ratio of feed rates for drying gas and liquid
- Formulation composition
- Feed solution concentration