Particle Design via Spray Drying

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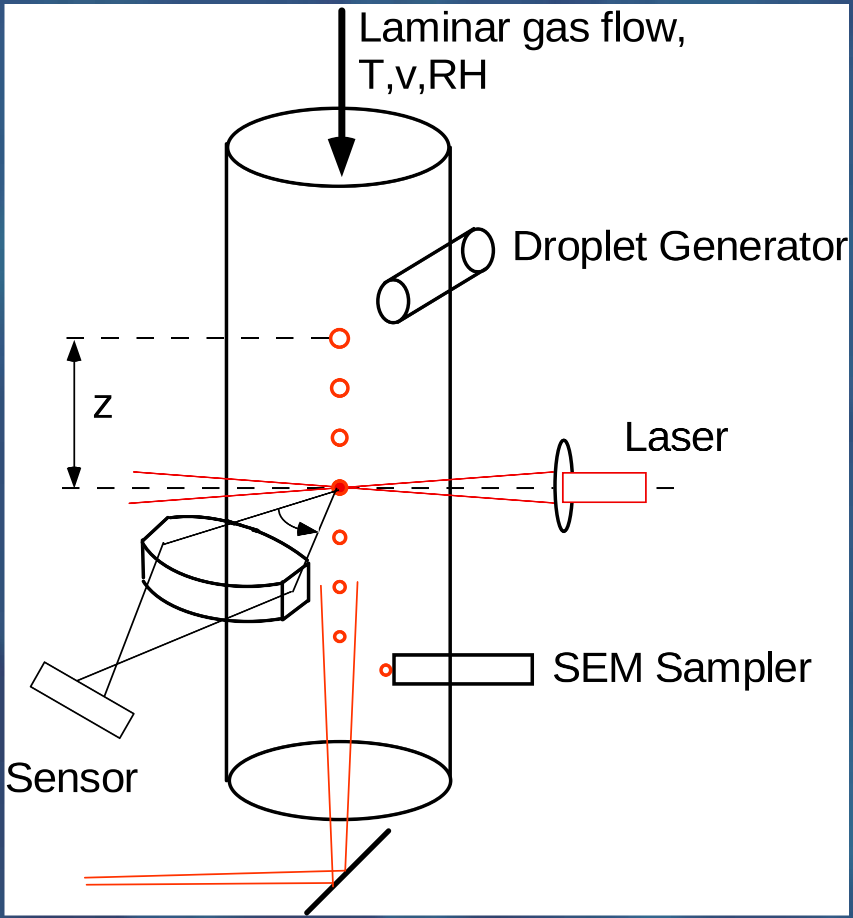
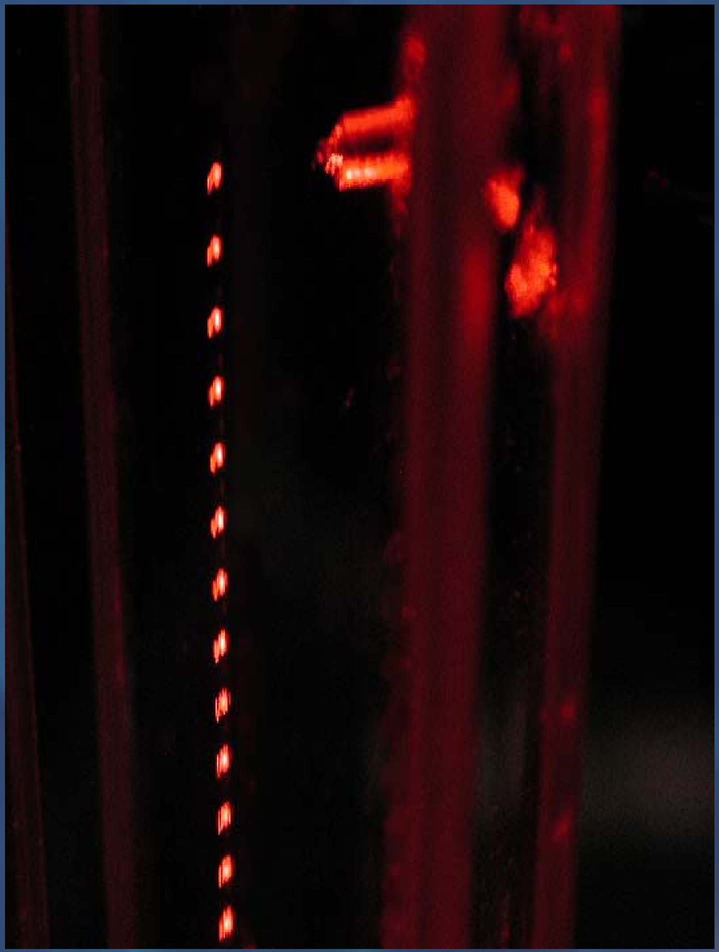
Outline

- **Study of Particle Formation Mechanism**
  - Experimental Methods
    - Droplet Chain
    - Monodisperse Spray Dryer
  - Theoretical Approach
  - Results
- **Particle Design Examples**
- **Summary and Outlook**

Droplet Chain Technique





- Droplets do not influence gas phase
- Allows measurement of evaporation rates

Vehring, et al., AAAR Annual Conf., Atlanta, GA, 2004

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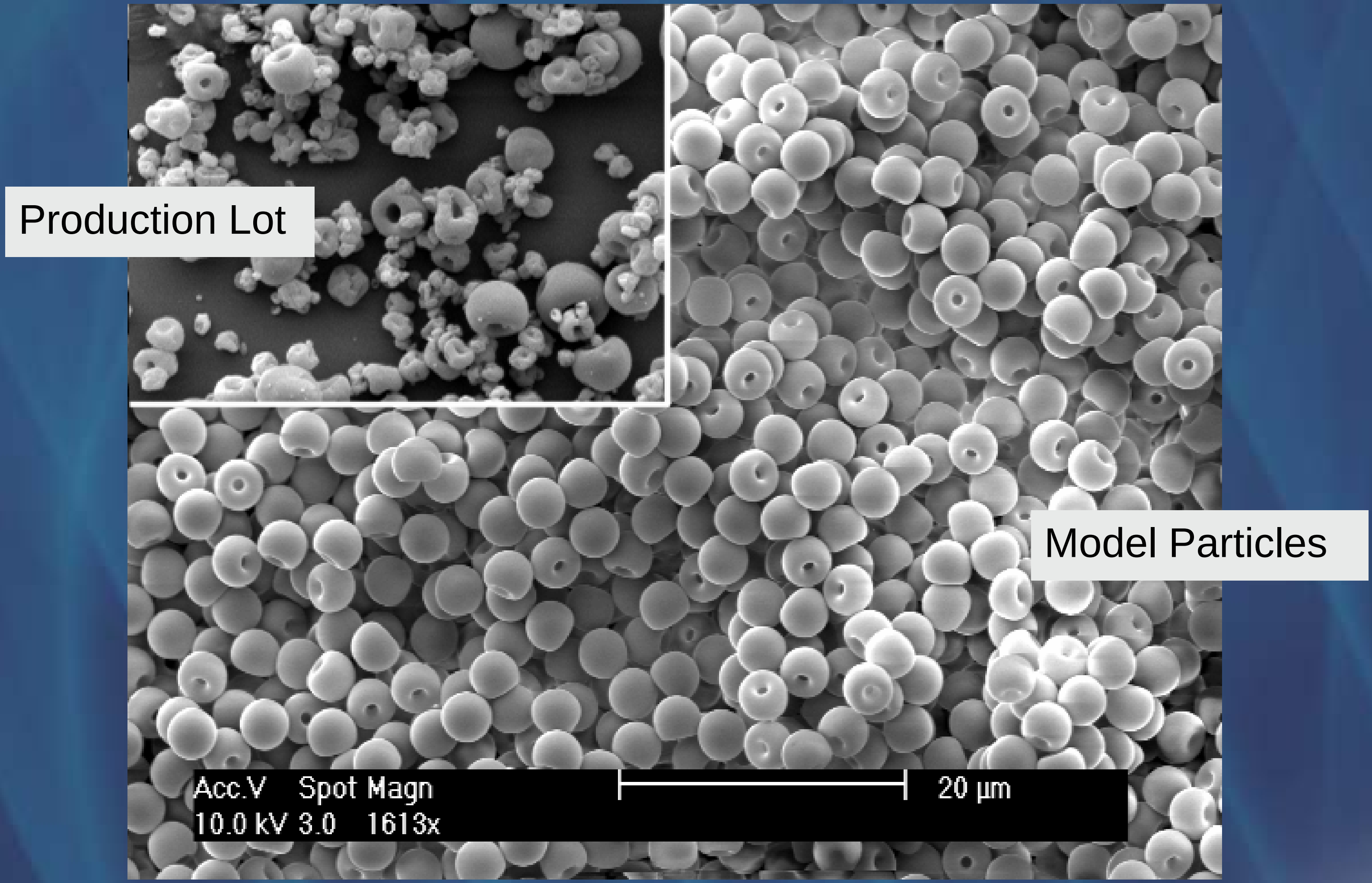
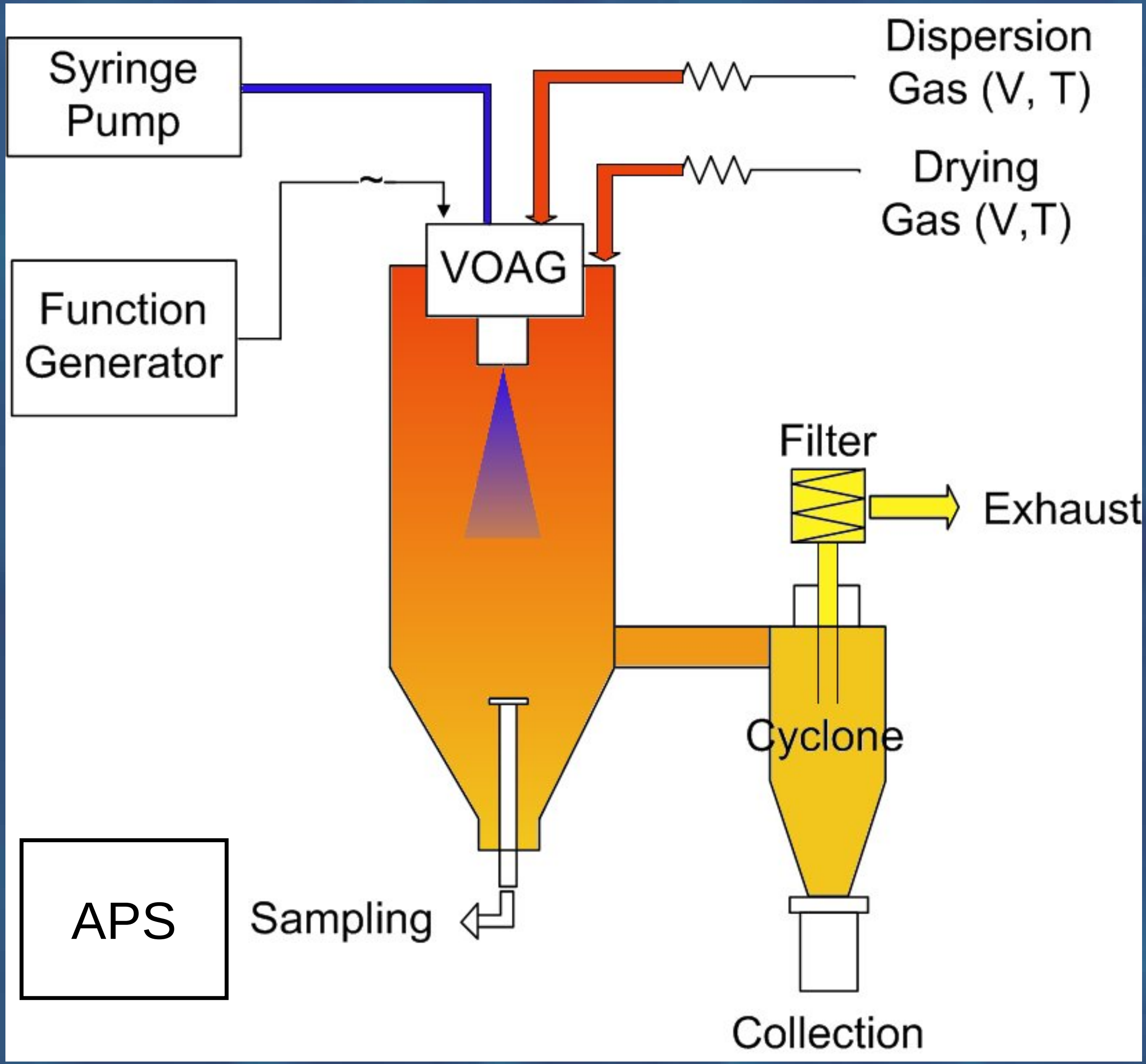
Monodisperse, Monomorph Particles



Geometric diameter and density can be correlated with drying rate

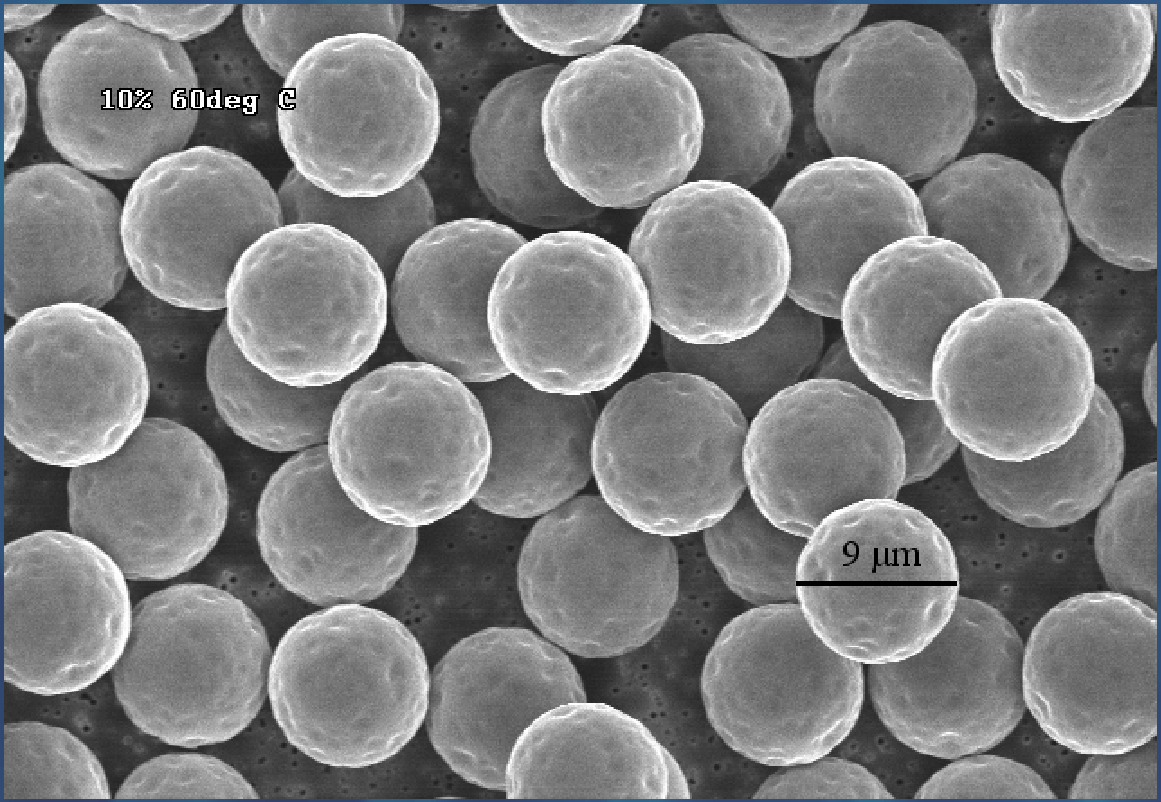
Only small quantities can be produced (< 1mg/h)

Monodisperse Spray Dryer



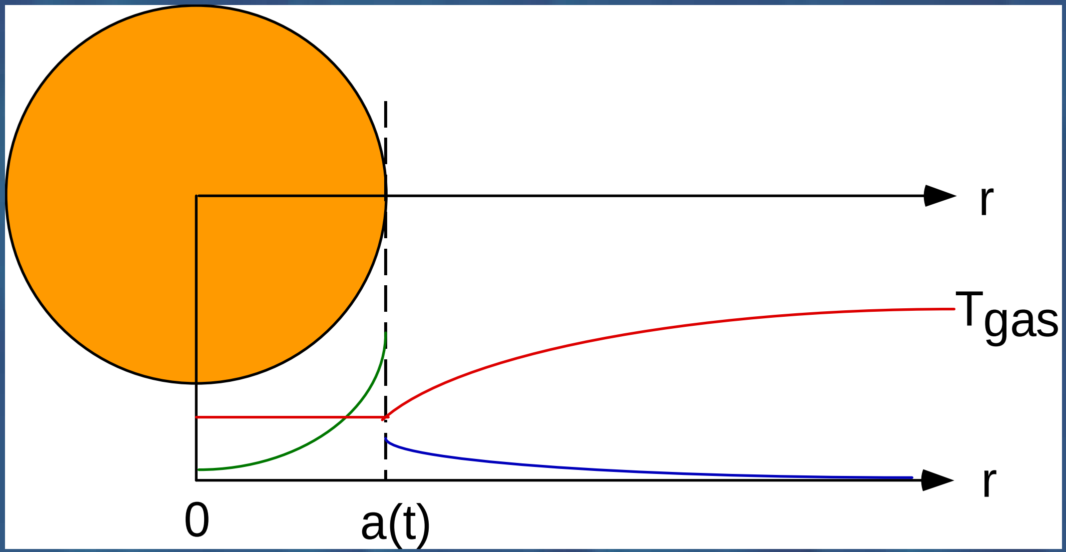
- 1000 x higher production rates
- Gas phase conditions not constant
- No direct observation of evaporation process
- Online measurement of aerodynamic dry particle diameter

Particles from Monodisperse Spray Dryer



- Consistent morphology
- Density of main population can be determined

Numerical Model of Droplet Evaporation



- Transient evaporation of a radially symmetric droplet
- Finite difference mesh moves with interface
- Concentration and temperature profiles in liquid and gas
- Temperature and concentration dependent material properties
- Multiple solutes and solvents
- Accounts for surface activity

Analytical Description

Analytical model provides dimensionless numbers

Diffusion equation for normalized radial coordinate, $R=r/r_s$,

$$\frac{\partial c}{\partial t} = \frac{D}{r_s^2}\left(\frac{\partial^2 c}{\partial R^2} + \frac{2\partial c}{R\partial R}\right) + \frac{R\partial c\partial r_s}{r_s\partial R\partial t} \quad , \qquad d^2(t) = d_0^2 - \kappa t$$

D: Diffusion coefficient, c: concentration, r_s: droplet radius, *d*: droplet diameter, κ: evaporationon rate.

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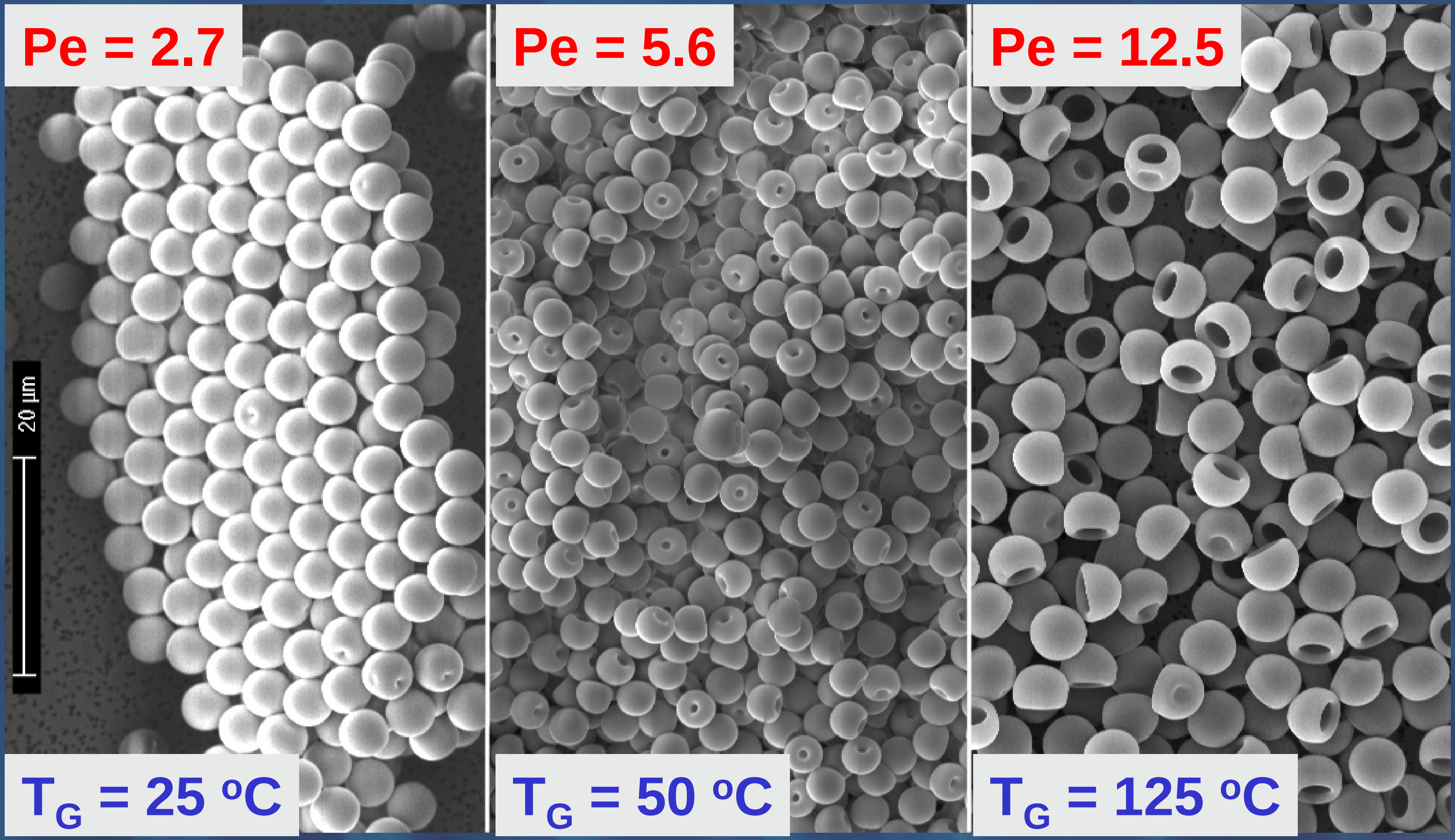
Solution

$$c = c_m \frac{\exp\left(-0.5\mathrm{Pe}R^2\right)}{3\int_0^1 R^2 \exp\left(-0.5\mathrm{Pe}R^2\right)\mathrm{d}R} \quad , \qquad \mathrm{Pe} = -\frac{r_s\partial r_s}{D\partial t} = \frac{\kappa}{8D}$$

where the concentration is expressed as a function of the average concentration in the droplet, c_m. Pe is the Peclet number.

After: Leong, K. H., *J. Aerosol Sci* **18**, 511, (1987)

Case 1: Large Molecules



Morphology and density change with drying rate

Glycoprotein, MW: 51 kDa, D: $6 \cdot 10^{-11}$ m^2/s (estimate)

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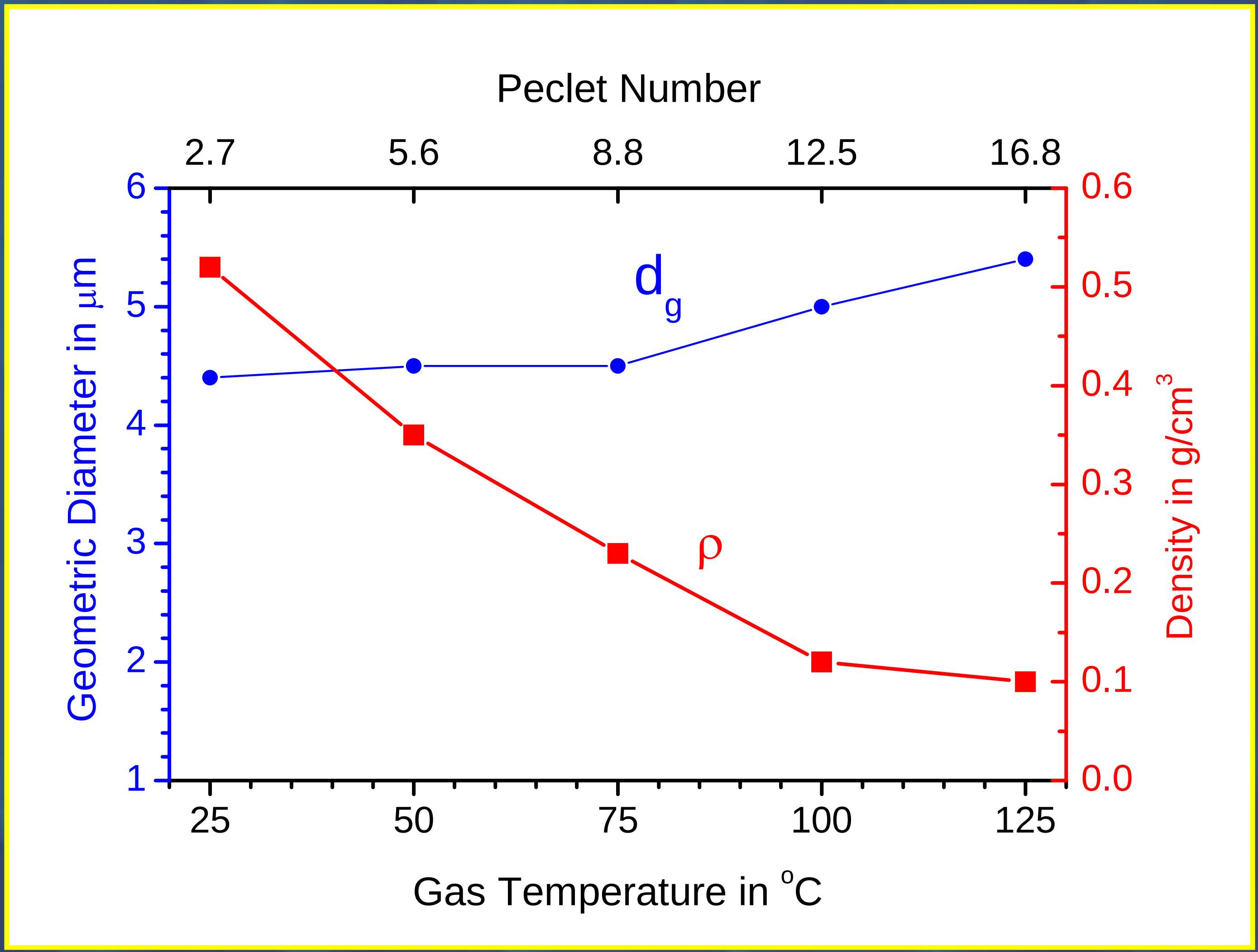
Density Decreases with Increasing Pe-Number



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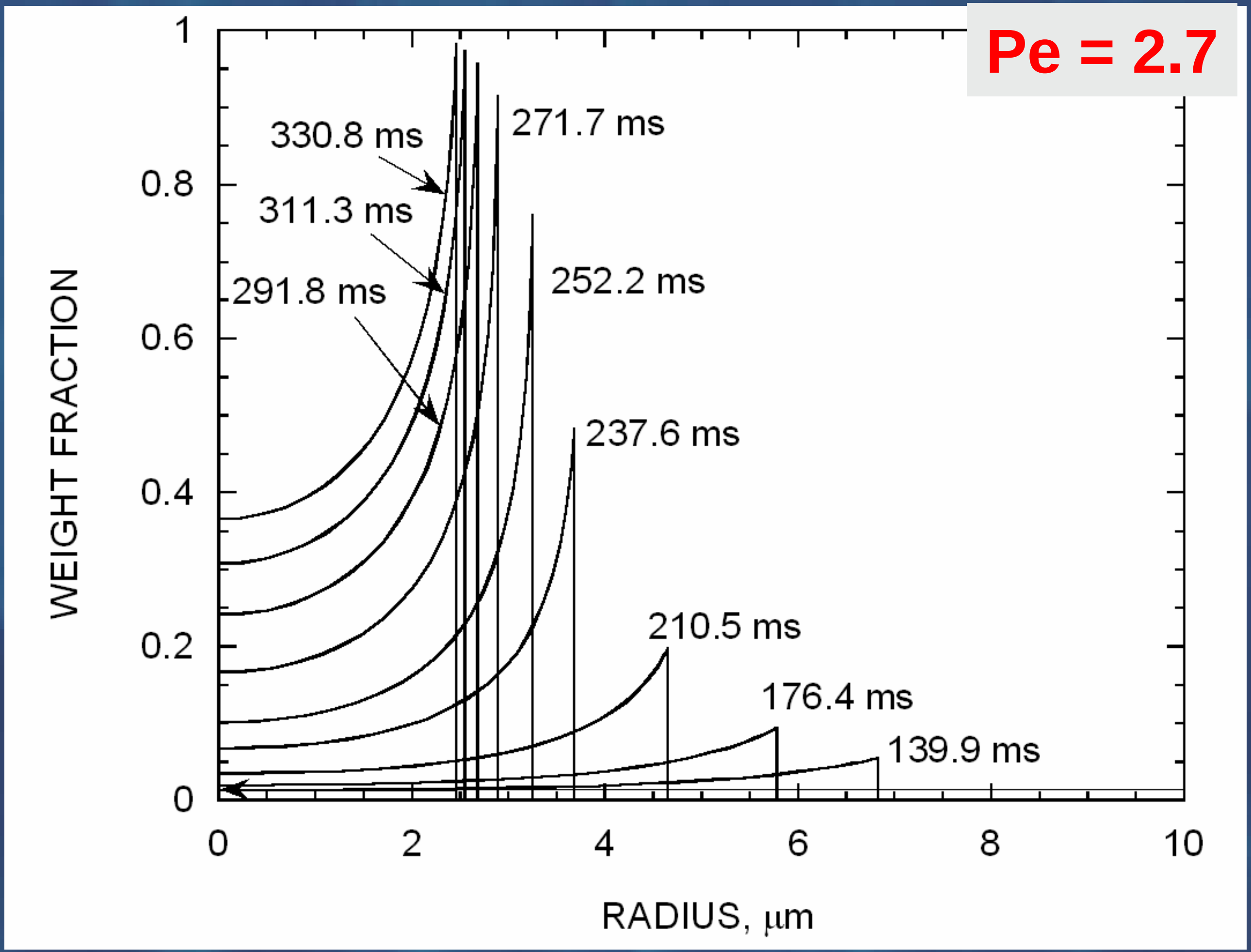
Model Predicts Surface Enrichment of Protein



Glycoprotein, T_G: 25 °C

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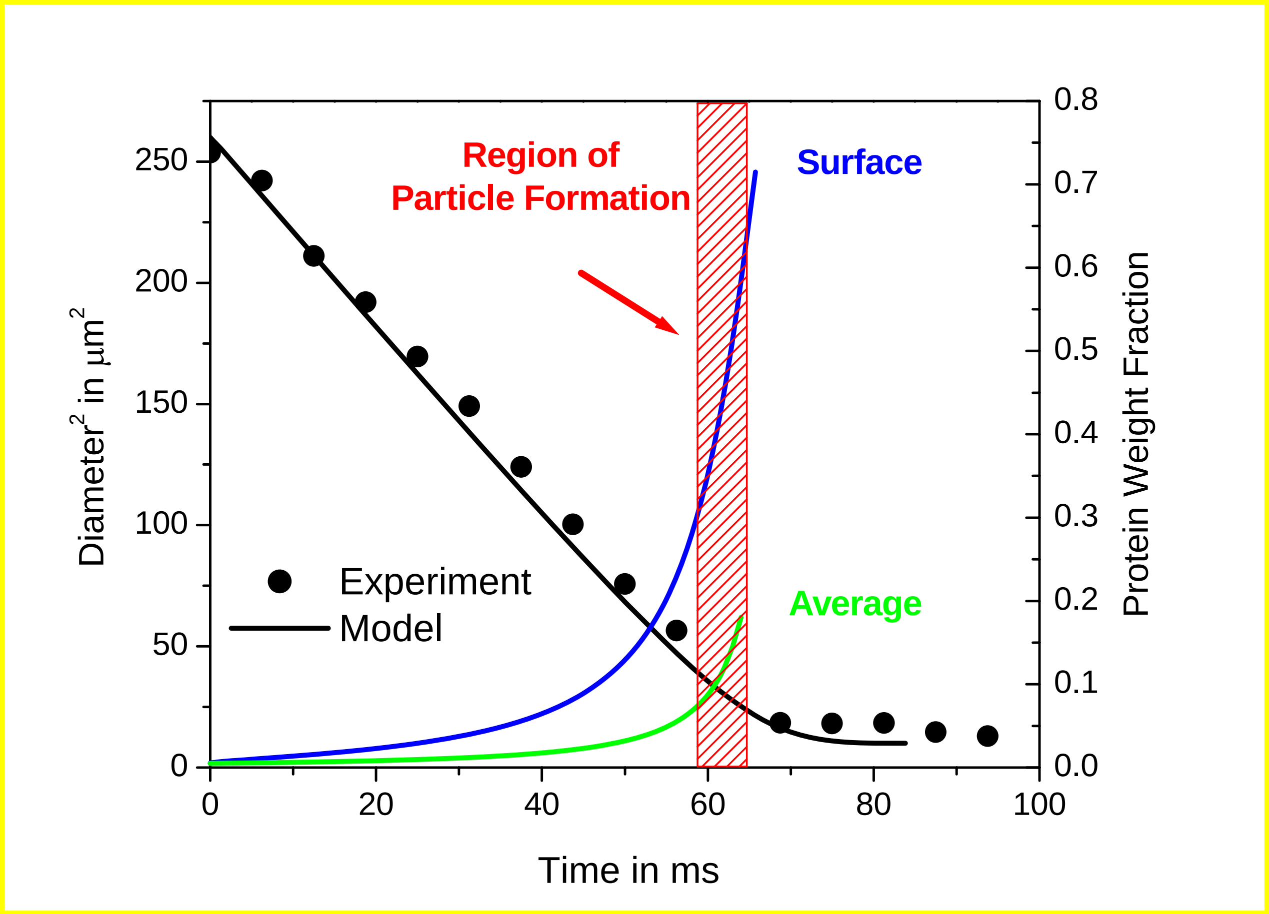
Comparison with Experiment Verifies Mechanism



Dry particle formation coincides with predicted high surface concentration of the protein.

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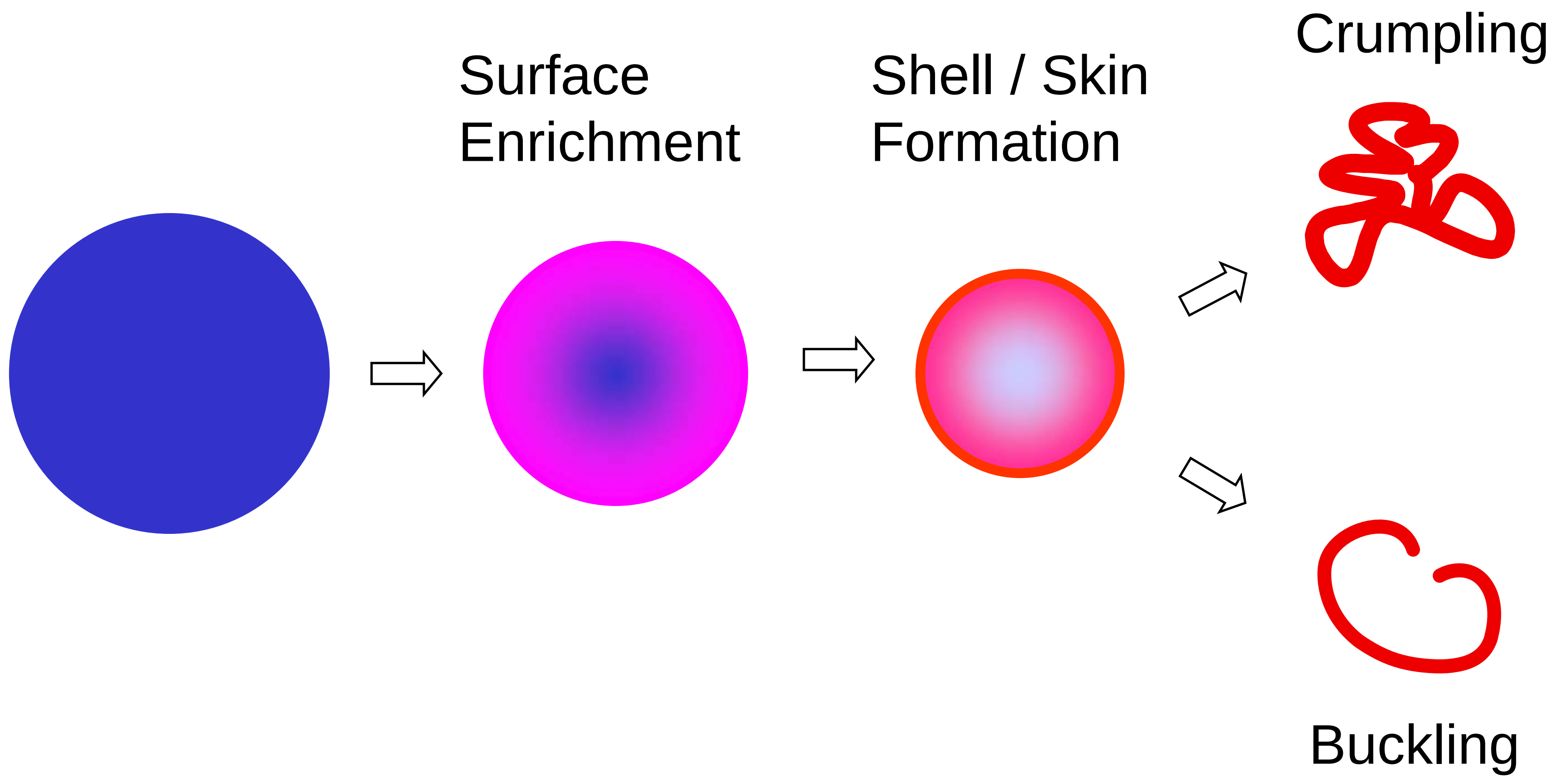
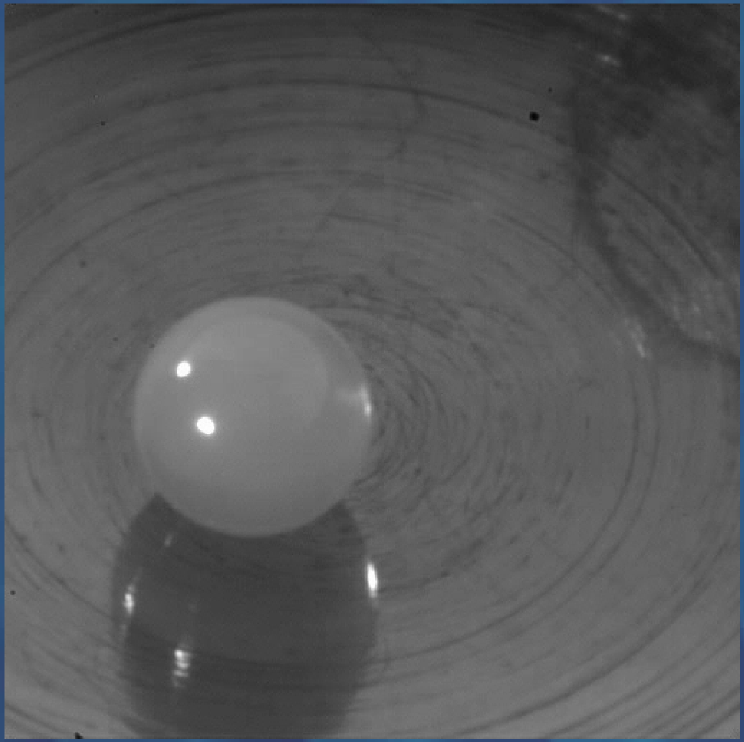
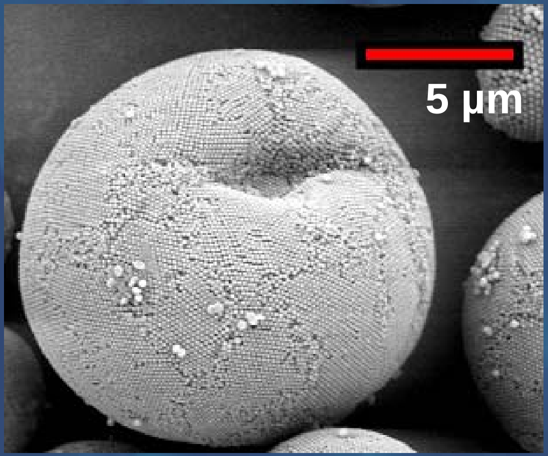
Diffusion Controlled Particle Formation

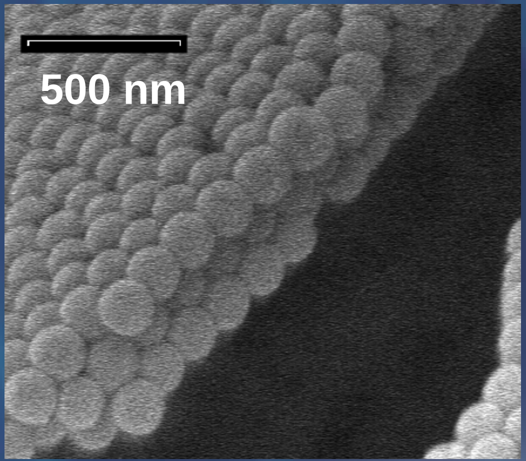


Buckling of Shells Made of Nanoparticles



- Millimeter sized droplet levitated by Leidenfrost phenomenon
- 2 mg/ml polystyrene nanoparticle (170 nm) suspension





Courtesy of Nicolas Tsapis
Faculté de Pharmacie
Châtenay-Malabry

Tsapis et al. PRL 94, 018302 (2005);
Sugiyama et al. Langmuir, 22, 6024 (2006)

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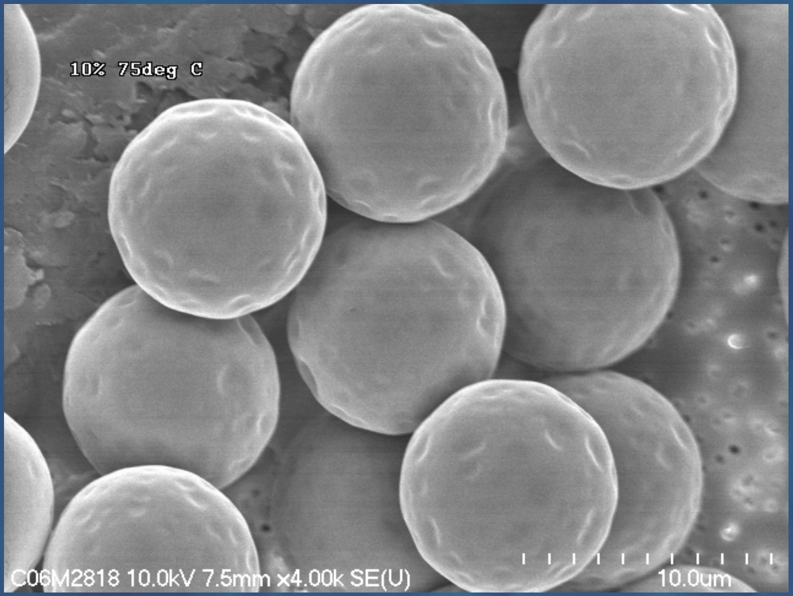
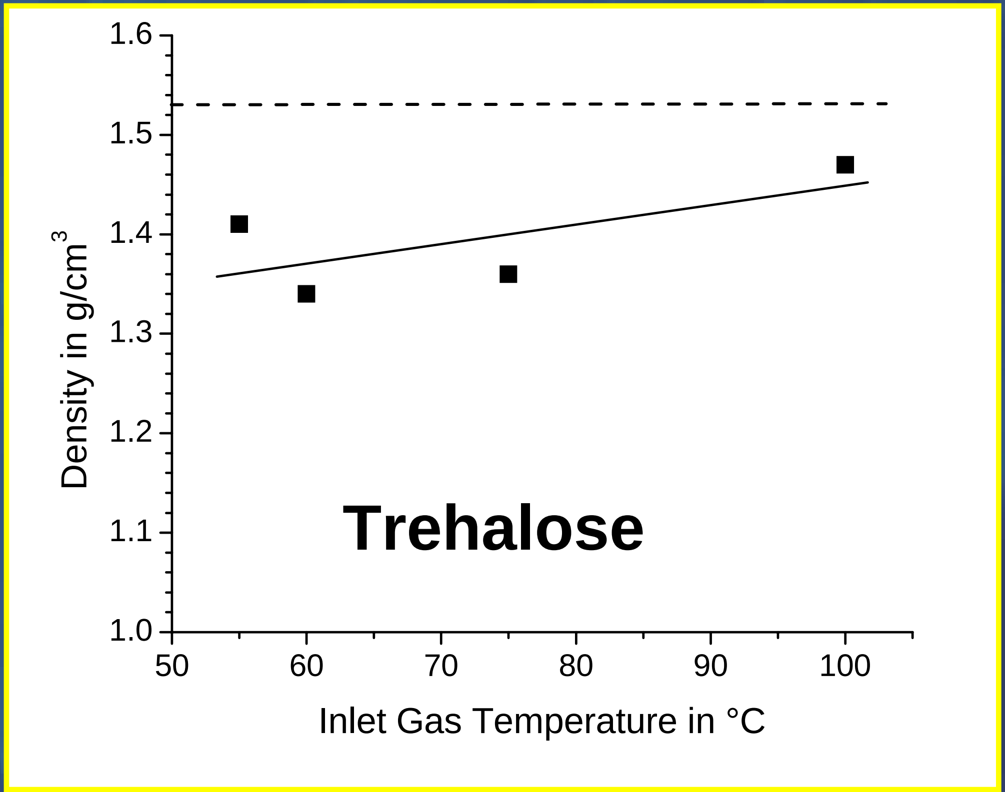
Case 2: Small Molecules





Low Peclet Number (<2) and high solubility leads to solid particles with a density close to the pycnometer density (1.53 g/cm^3)

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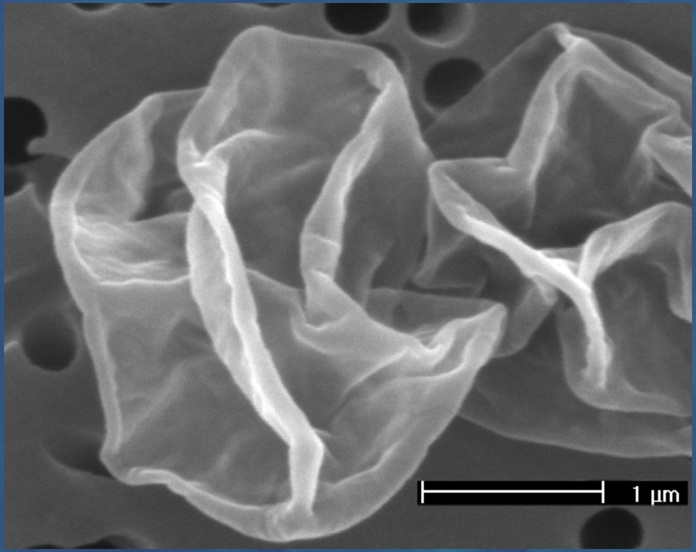
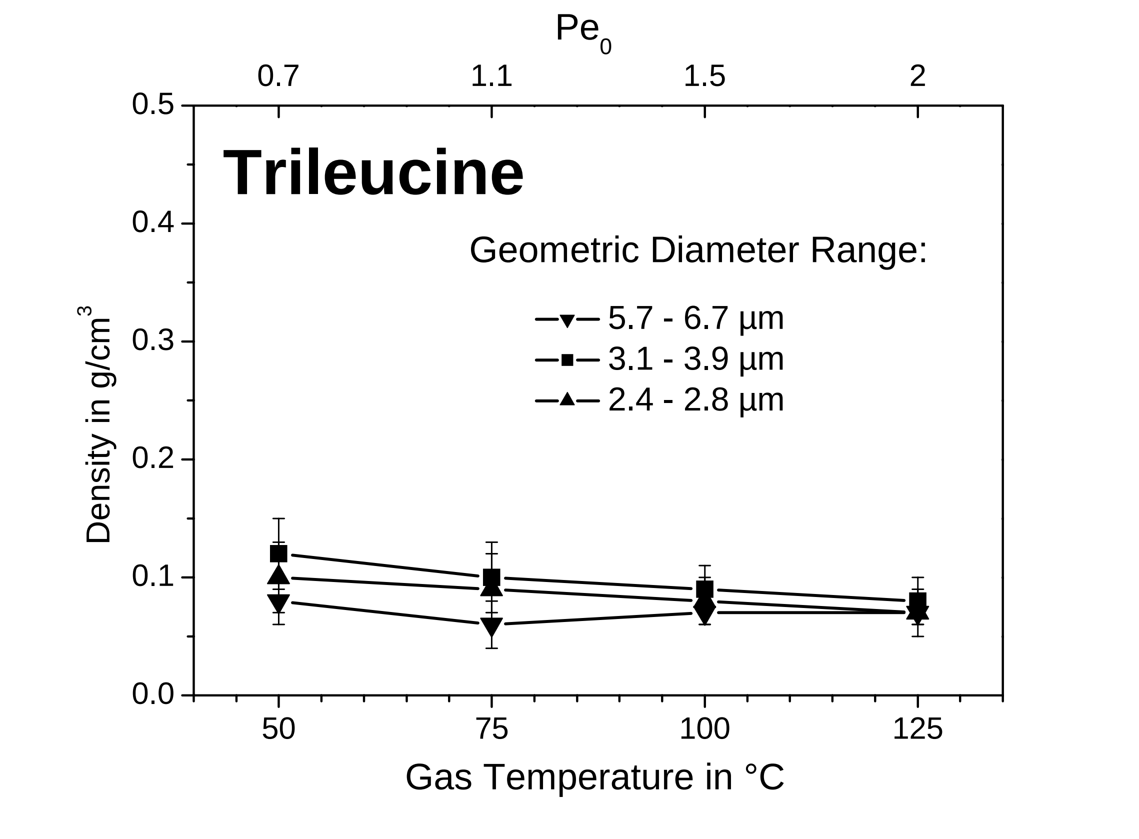
Small Molecules

Low Solubility – High Surface Activity





Solubility: 8 mg/ml (25°C, pH7)

Surface Activity: 42 mN/m (sat, 25°C)

MW: 357.5 Da

Particles with very low density can be formed from small molecules

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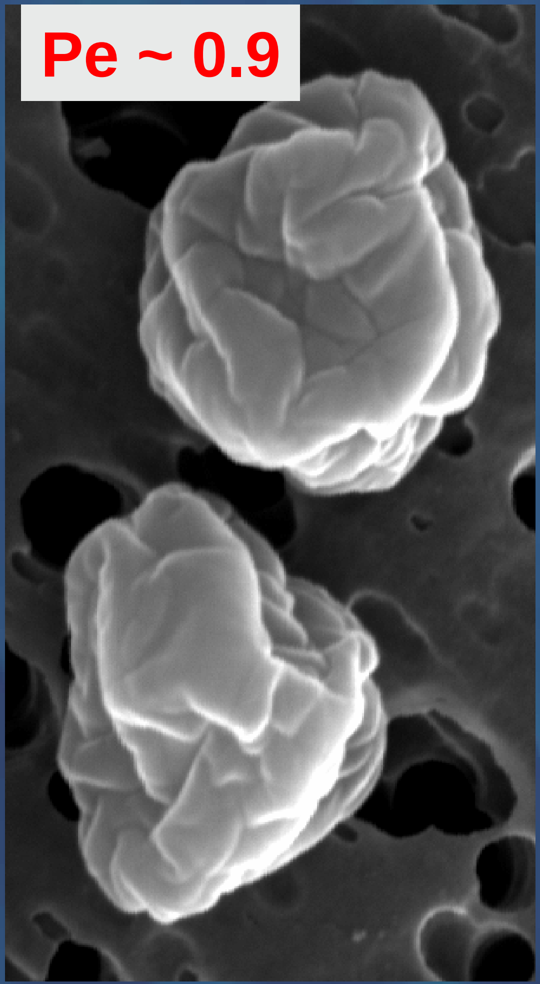
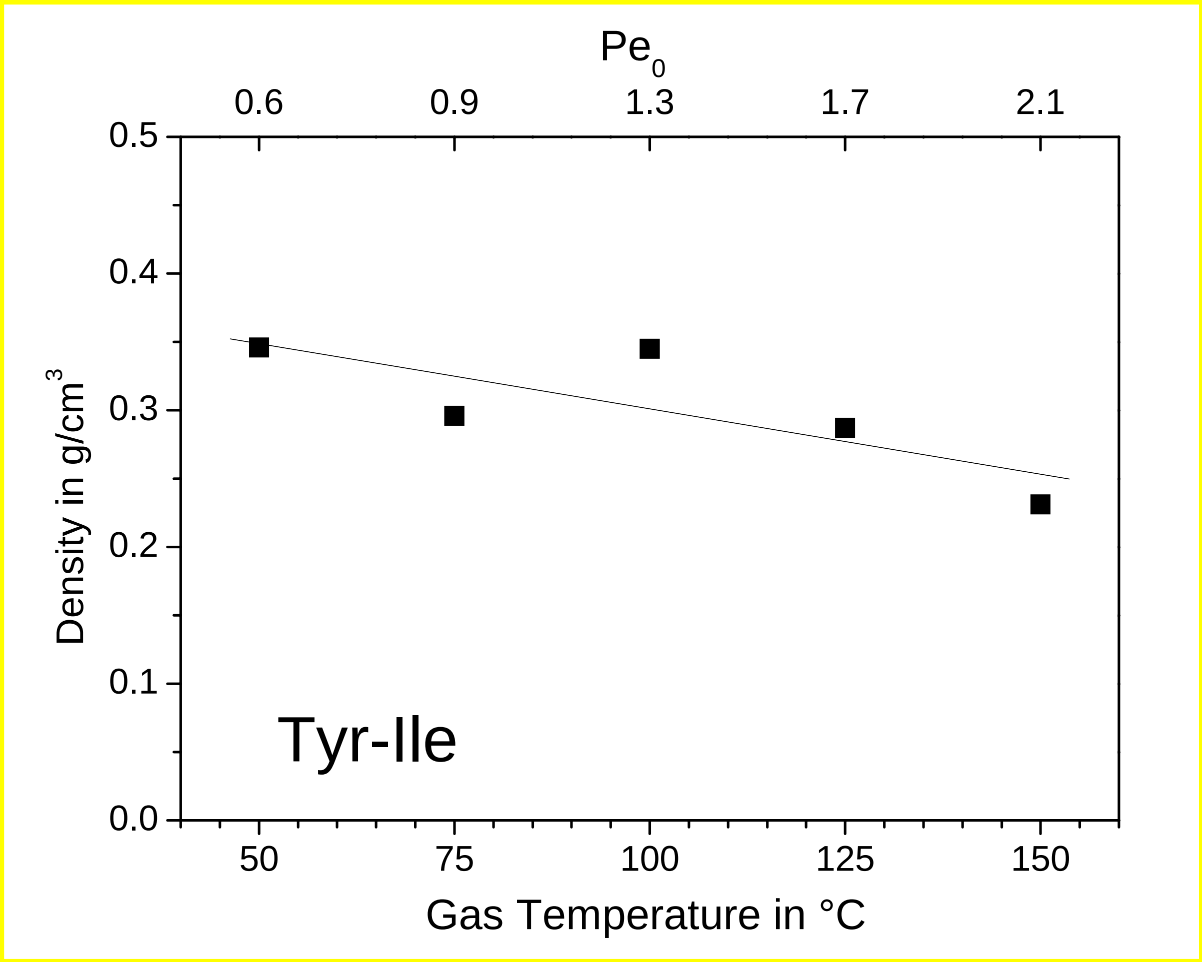
Small Molecules

Low Solubility – Low Surface Activity





Surface activity is not necessary for low particle density

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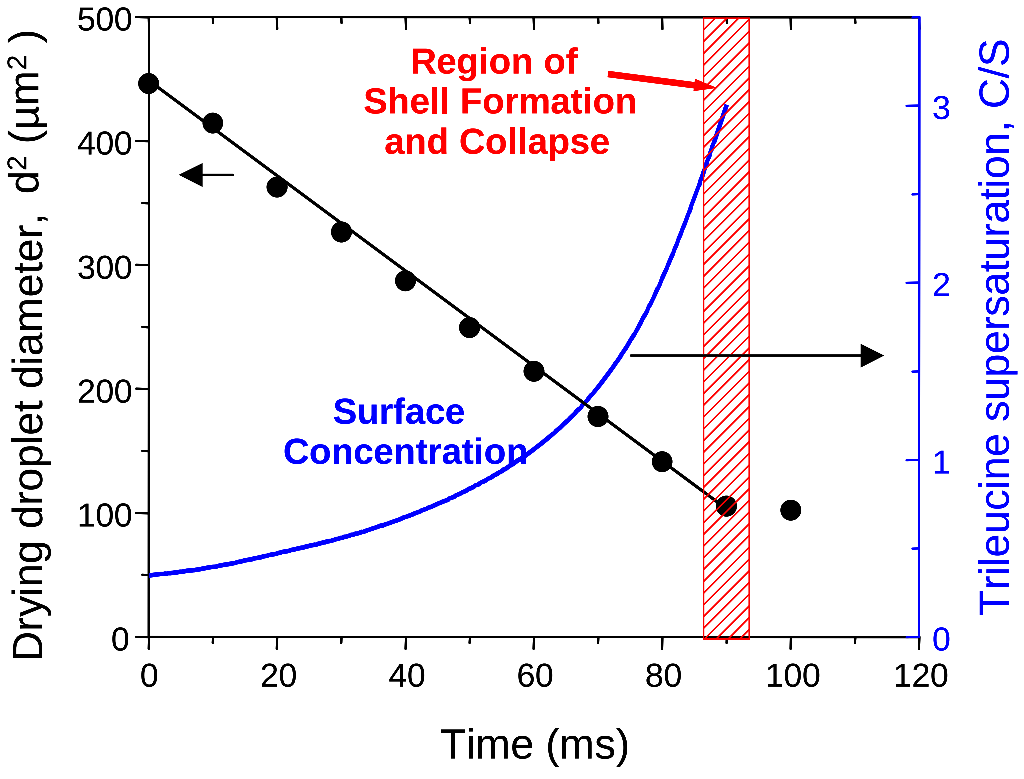
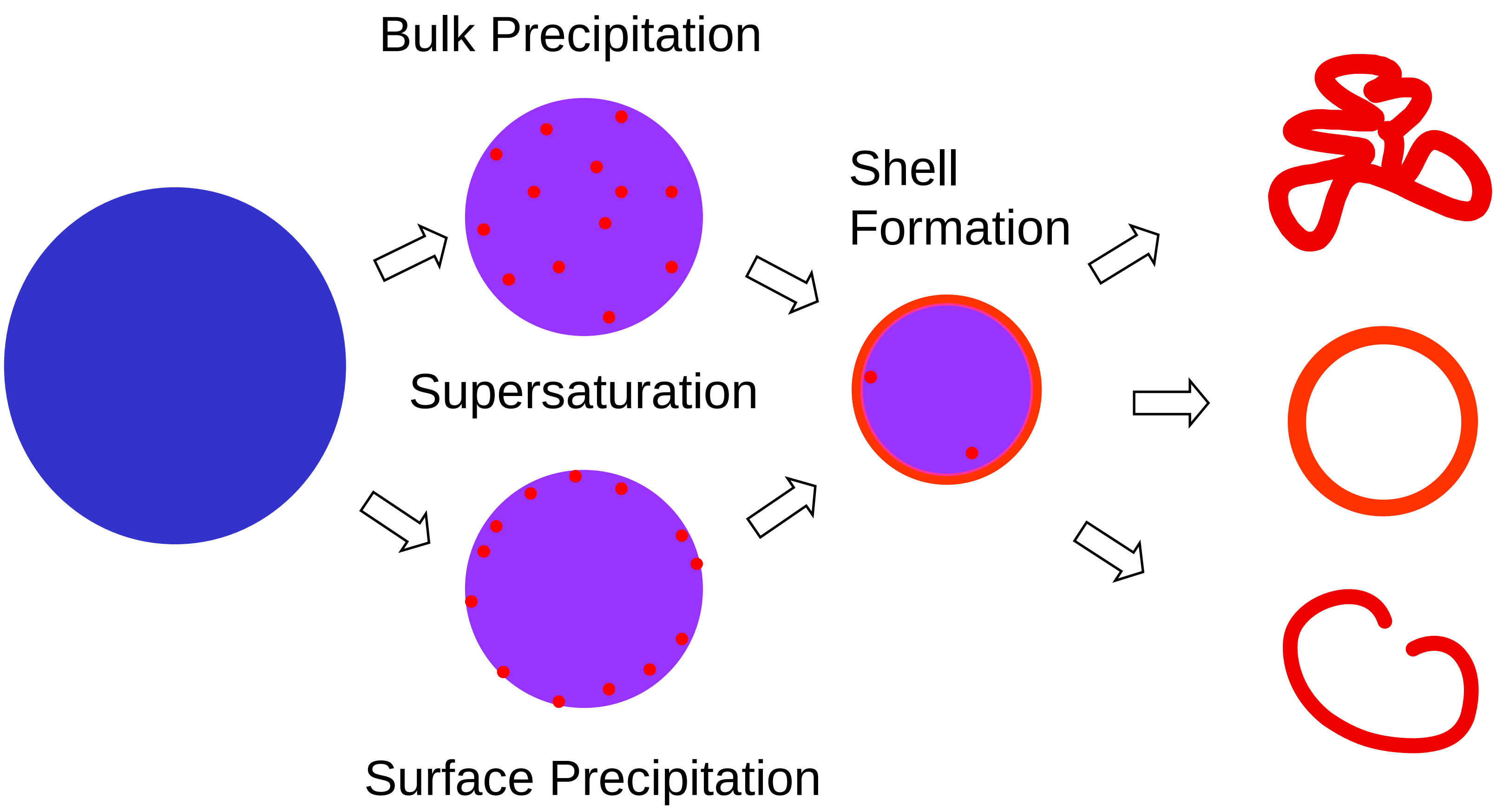
Particle Formation Coincides with Supersaturation



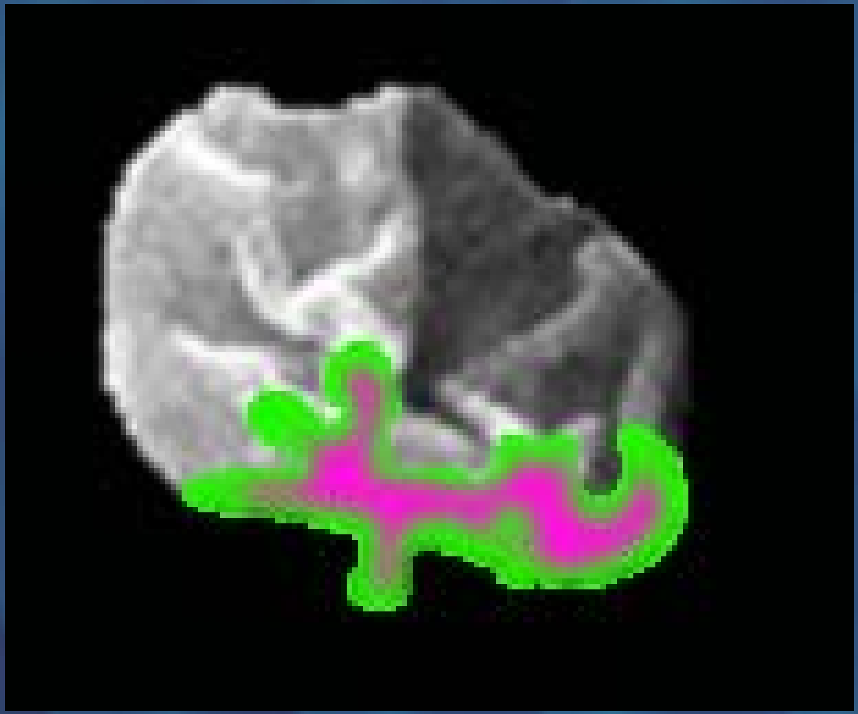
Precipitation leads to sharp increase in Pe - number

Lechuga-Ballesteros, D., C. L. M. Stults, et al. Control Release Society, Glasgow, 2003

Particle Formation with Early Phase Separation



Designing Structured Particles - Applications



- **Encapsulation**
- **Structural layers**

- **Improving physical stability**
- **Improving biological / chemical stability**
- **Improving powder / aerosol properties**
  - Flowability
  - Dispersibility
  - Density / Aerodynamic diameter
- **Improving delivery**
  - Solubility
  - Bioadhesion
  - Release

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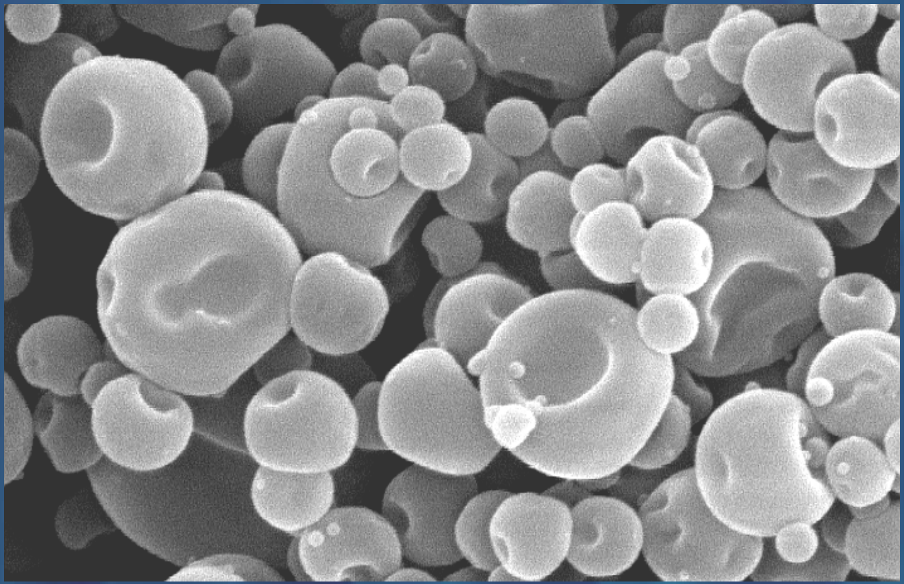
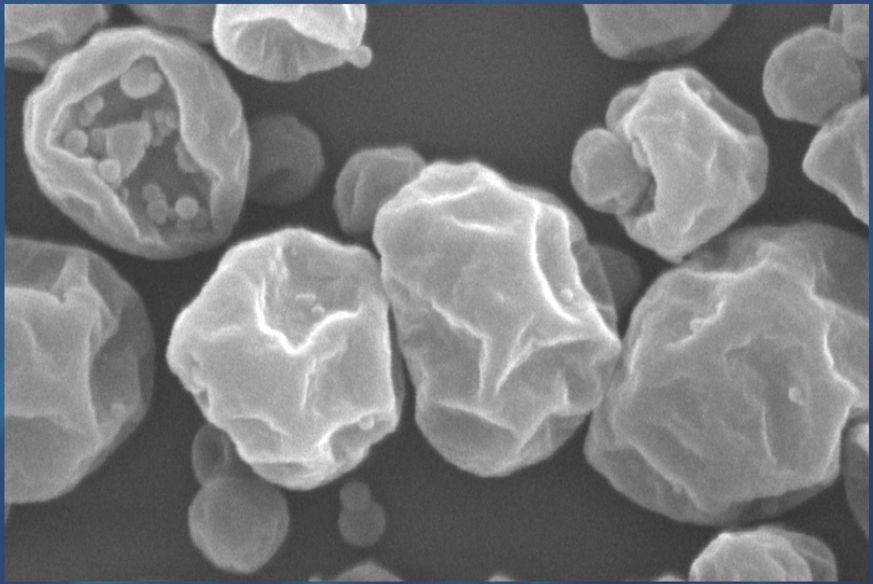
Encapsulation of a Model Molecule

100 % PVP K17



90 % PVP, 10 % Amino Acid



Amino acid solubility intentionally reduced by a co-solvent to achieve encapsulation

Vehring, et al., US 20050003004, WO/2005/000267

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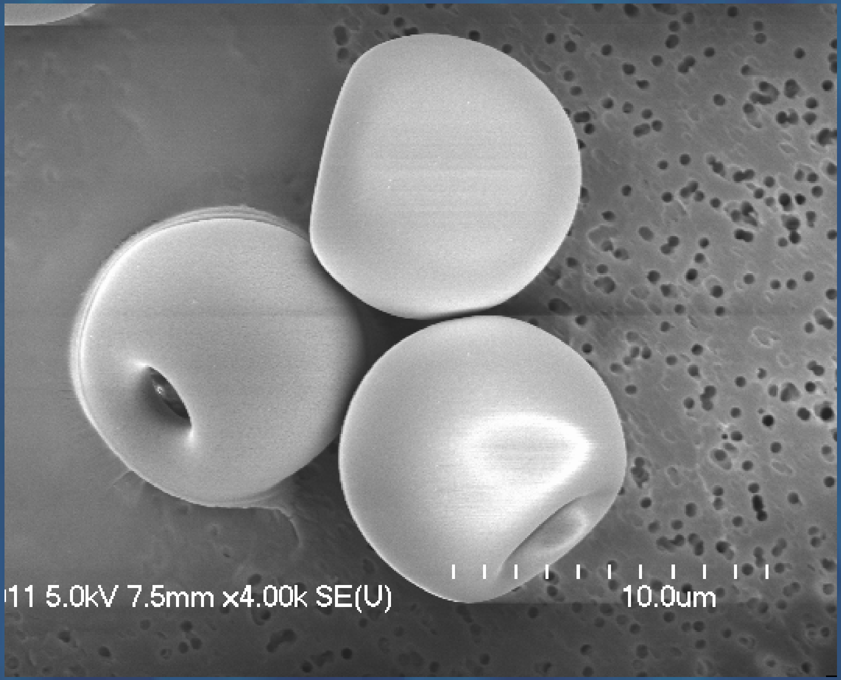
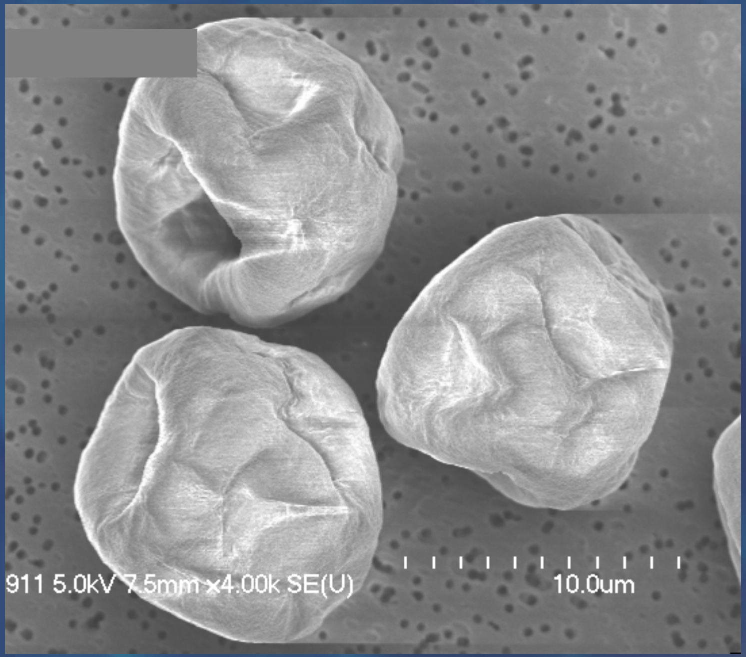
Surface Modification of an Antibody Therapeutic

IgG1 - Antibody



Encapsulated
with 37.5 % amino acid



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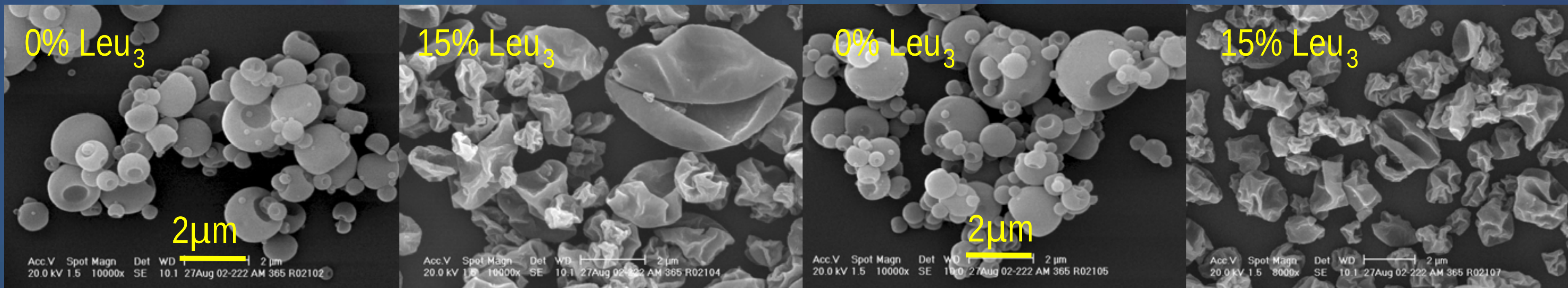
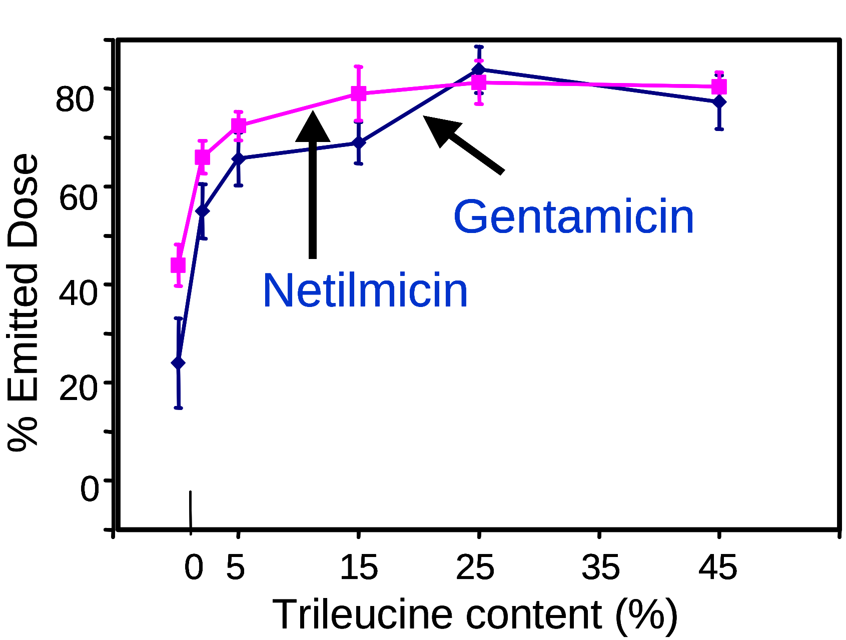
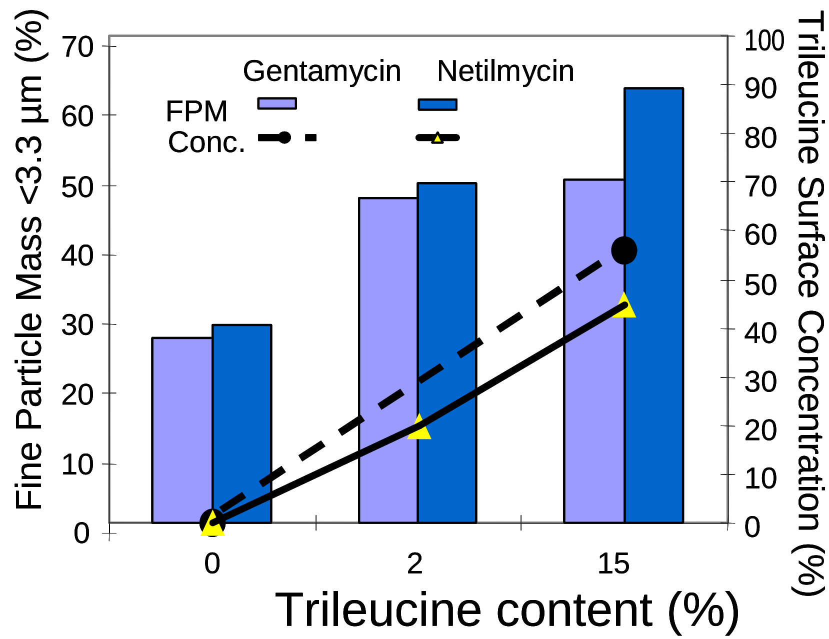
Encapsulation Improves Aerosol Performance

Gentamicin Sulfate **Netilmicin Sulfate**







Lechuga-Ballesteros, D., C. L. M. Stults, et al. Control Release Society, Glasgow, 2003

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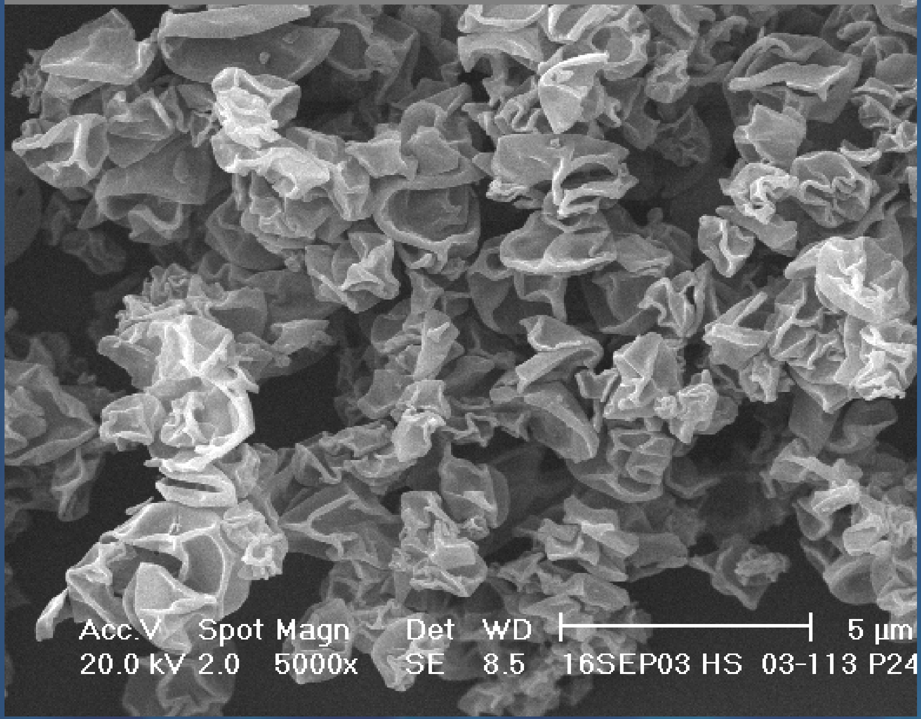
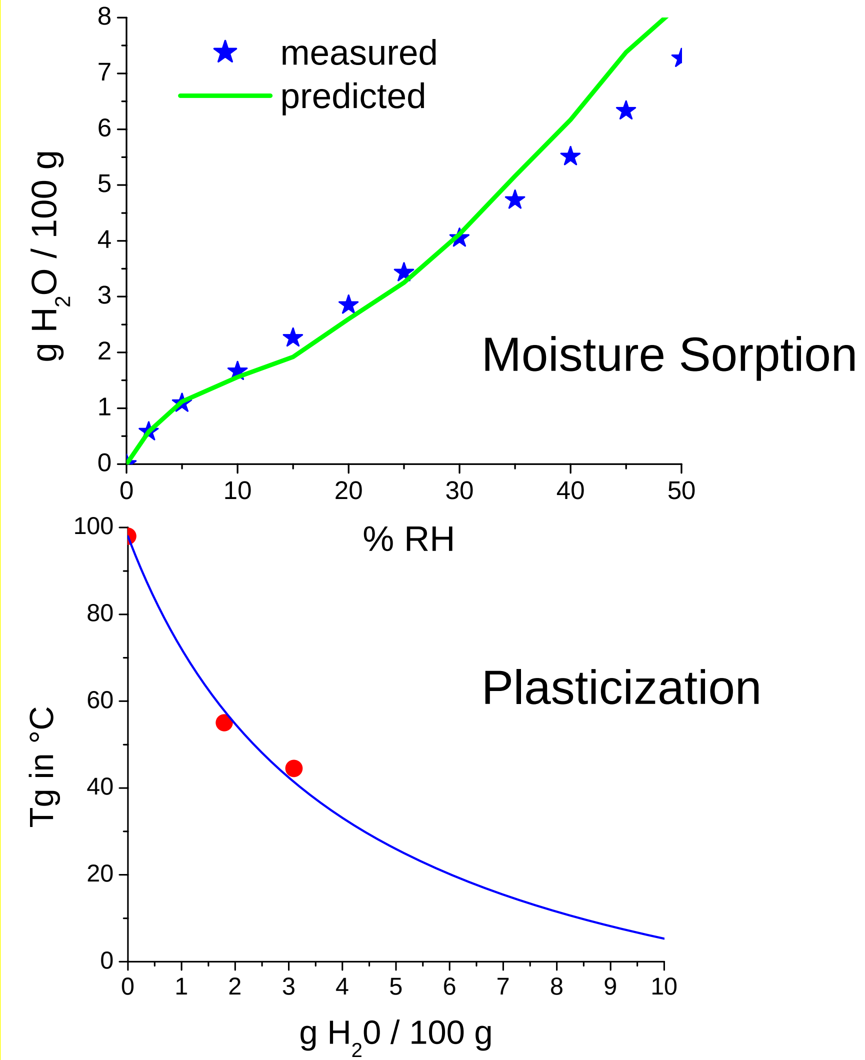
Encapsulation Improves Physical Stability

56 % encapsulation excipient, 20 % saccharide, 20 % low Tg API, 4 % organic salt





Low Tg core protected by a high Tg shell

Vehring, R. IBC 4th Annual Conf., Deliv. Strat. Proteins & Peptides, Boston, 2004

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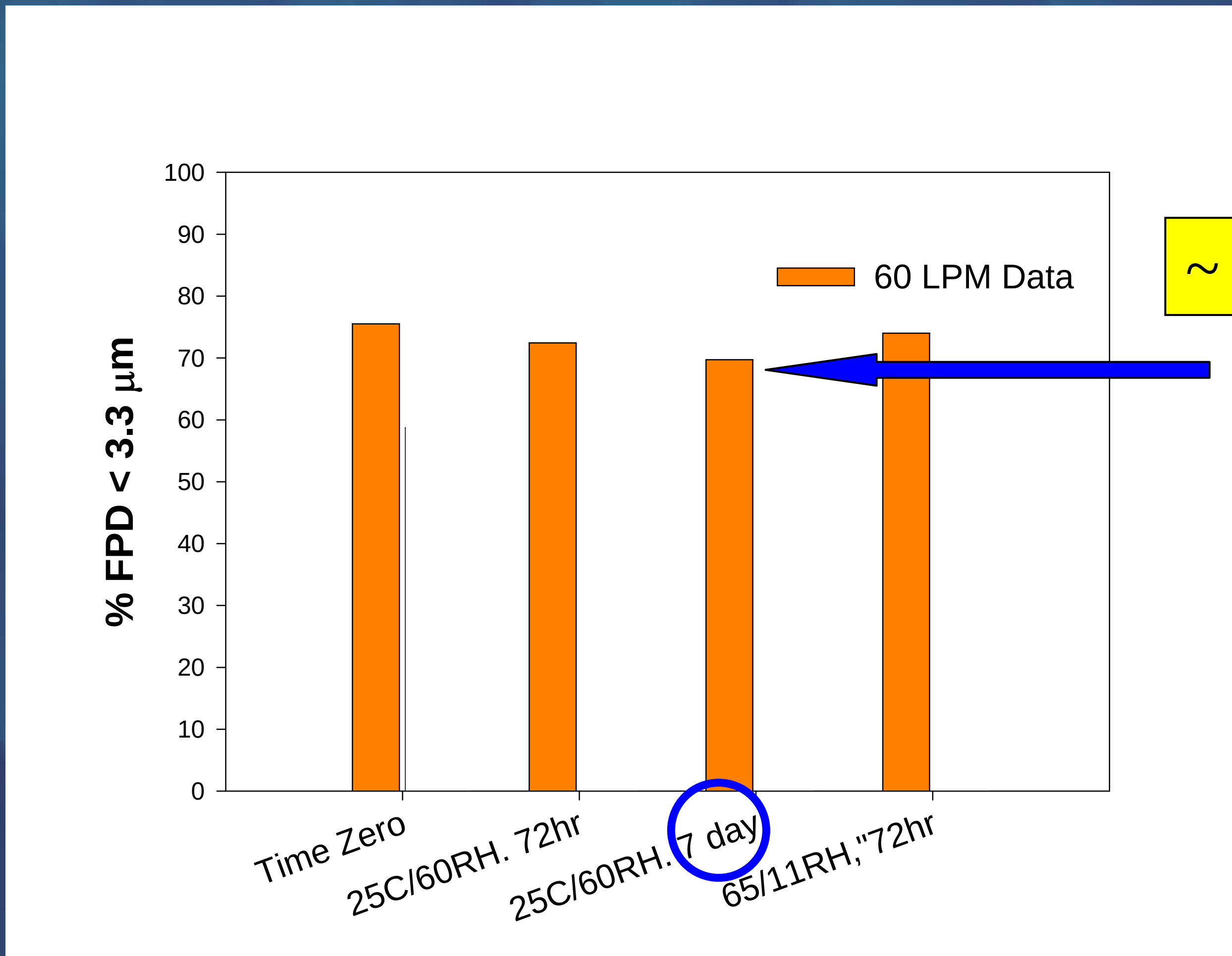
Structured Particle with Excellent Environmental Robustness



~ **20 °C above Tg !**

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Summary and Outlook

- Particle formation can be understood in the context of component saturation and Peclet number
- Surface activity and other material properties may influence particle morphology
- Analysis of particle formation enables rational particle design of structured particles through formulation and process design
- Particle engineering achieves much improved particle properties, enabling new products and improving product performance
- More work is necessary to understand and control nanostructures and multiple functional layers
- Process technology and formulation science must work together

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