Spray Drying of Protein Particles for Pulmonary Delivery

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Outline

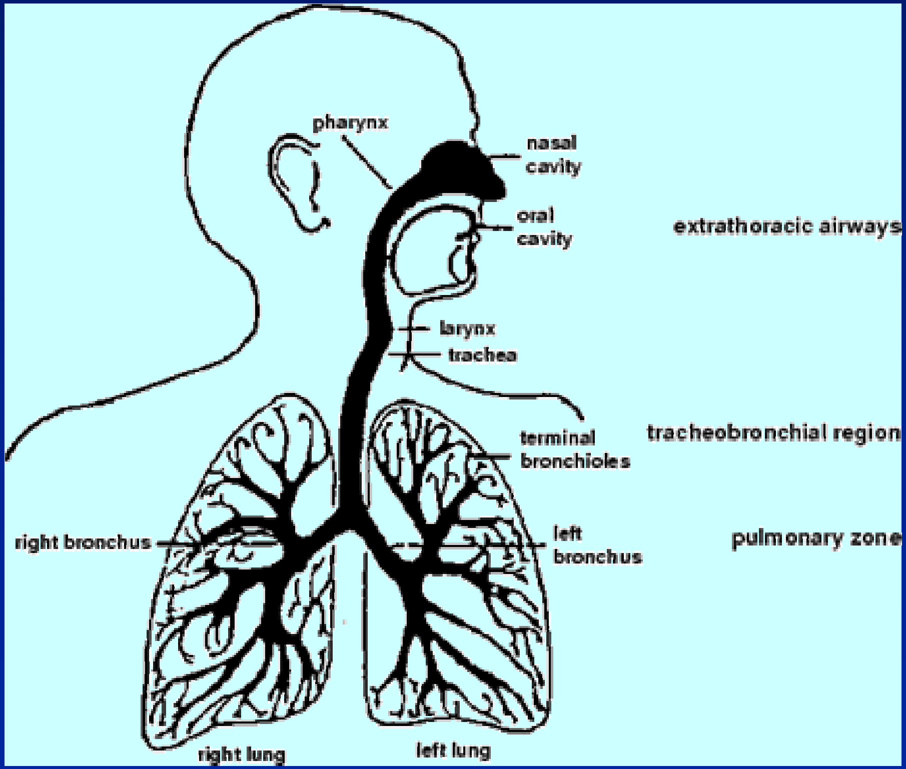
- **Introduction:**

  Pulmonary delivery of pharmaceutical particles.

- **The spray drying process and how to control it.**
  - CFD model and characterization of the atomization step
  - CFD model of the drying chamber
  - Numerical and experimental studies on particle formation
  - Raman spectroscopy as a particle design tool

Goal: Pulmonary Delivery

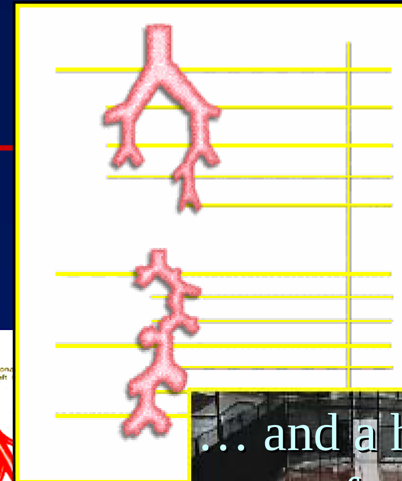
- **Non-invasive delivery of macromolecules to the deep lung via inhalation of aerosolized drug**



…in addition to the classic application of treating locally.

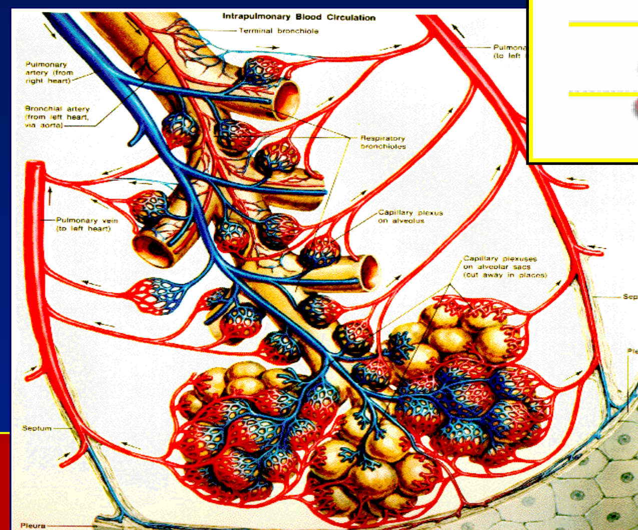
- Asthma
- COPD, CF
- Infections

Biology: How does it work?



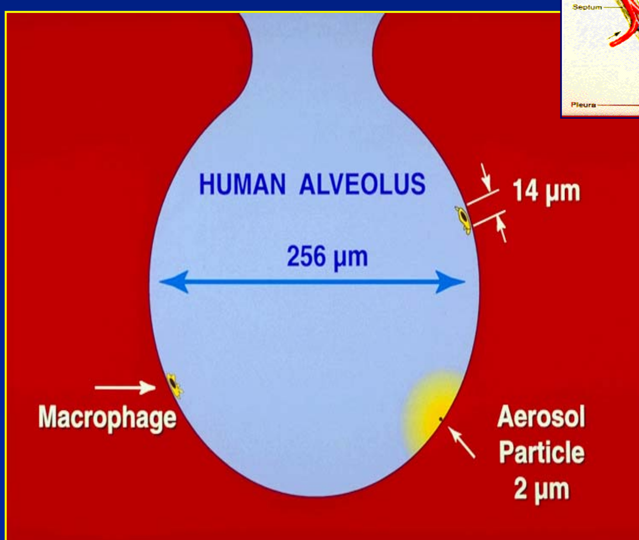
A branching structure leading to …

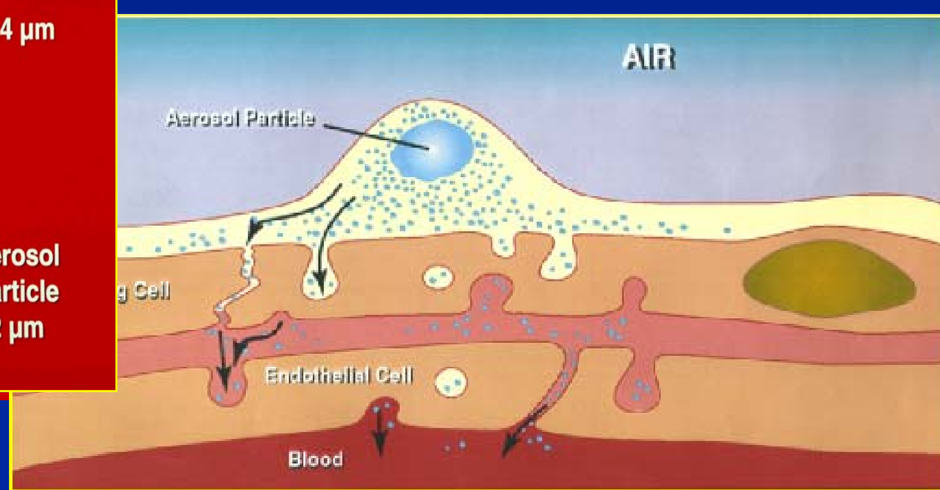
… a tight contact with vasculature …



… and a huge transport surface.

Deep lung deposition …





… leads to effective transport into the bloodstream

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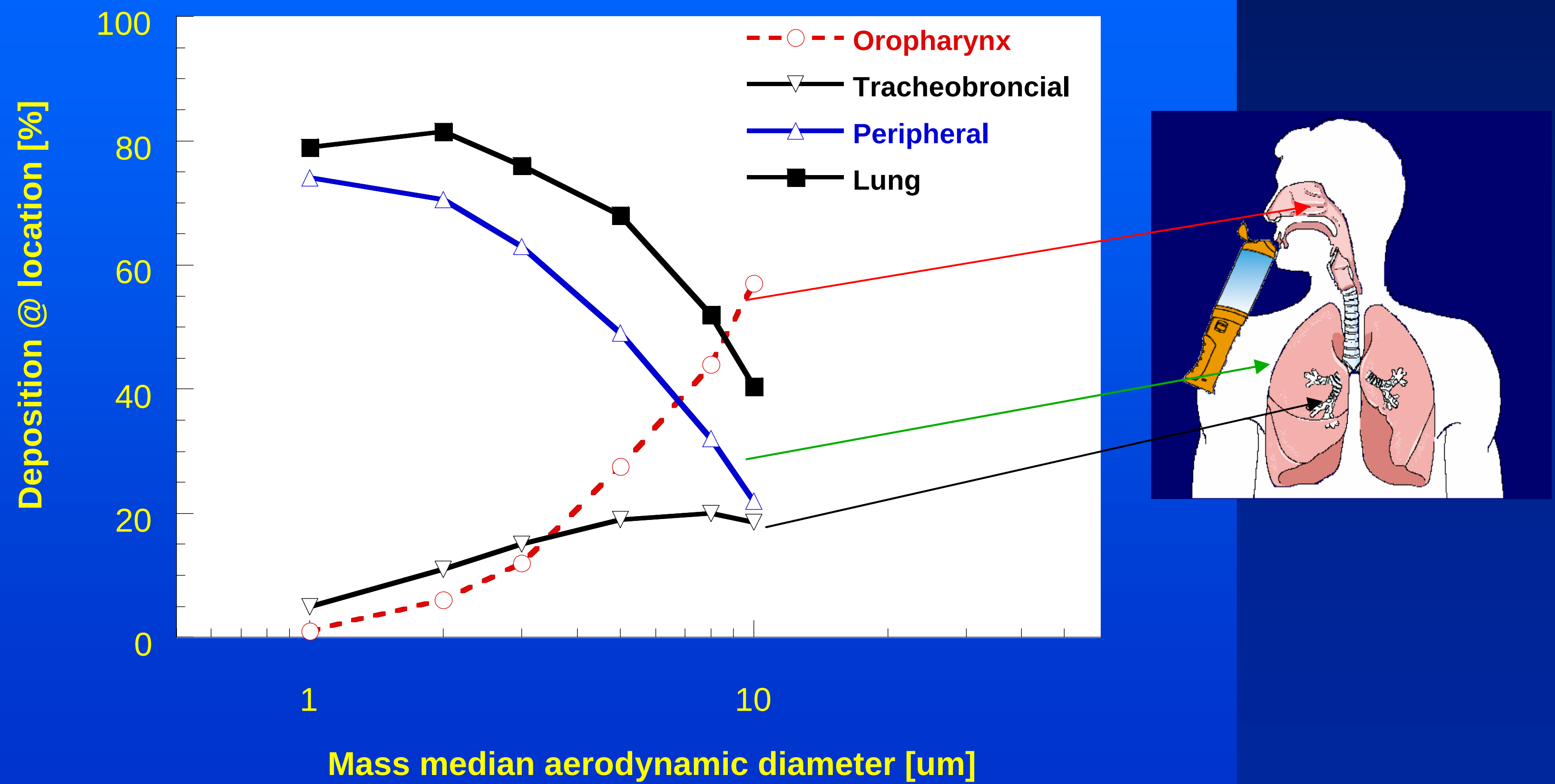
Lung Deposition for Polydispersed Aerosols

Inhaled volume 4 l
Inhaled flow rate 30 l/min
Breath hold 10secs
GSD 2.2



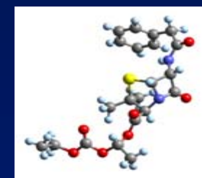
After Clark & Egan (1994) J Aerosol Sci., Vol25, #1, 175-186

What's the Ideal Particle

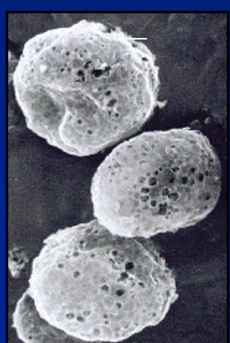
- Consistent properties independent of drug chemistry
  - Size and morphology optimized for lung delivery
  - Physical chemistry ensuring long shelf-life
  - Chemical stability of active
  - Non-toxic
- Manufacturable
  - In low and high quantities
  - Economical
  - With good yields

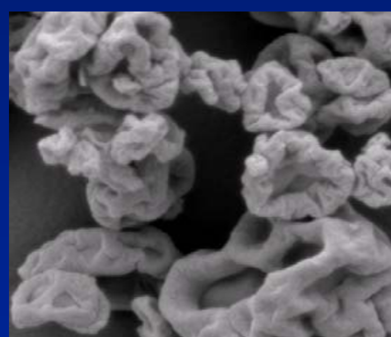
Methods to Produce a Fine Dry Powder

Molecule

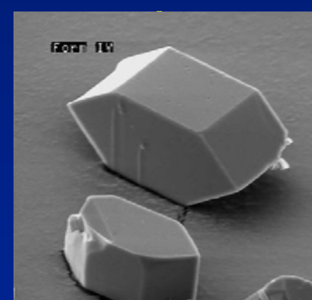


Spray Drying | ***SCF*** | ***Lyophilization*** | ***Crystallization***





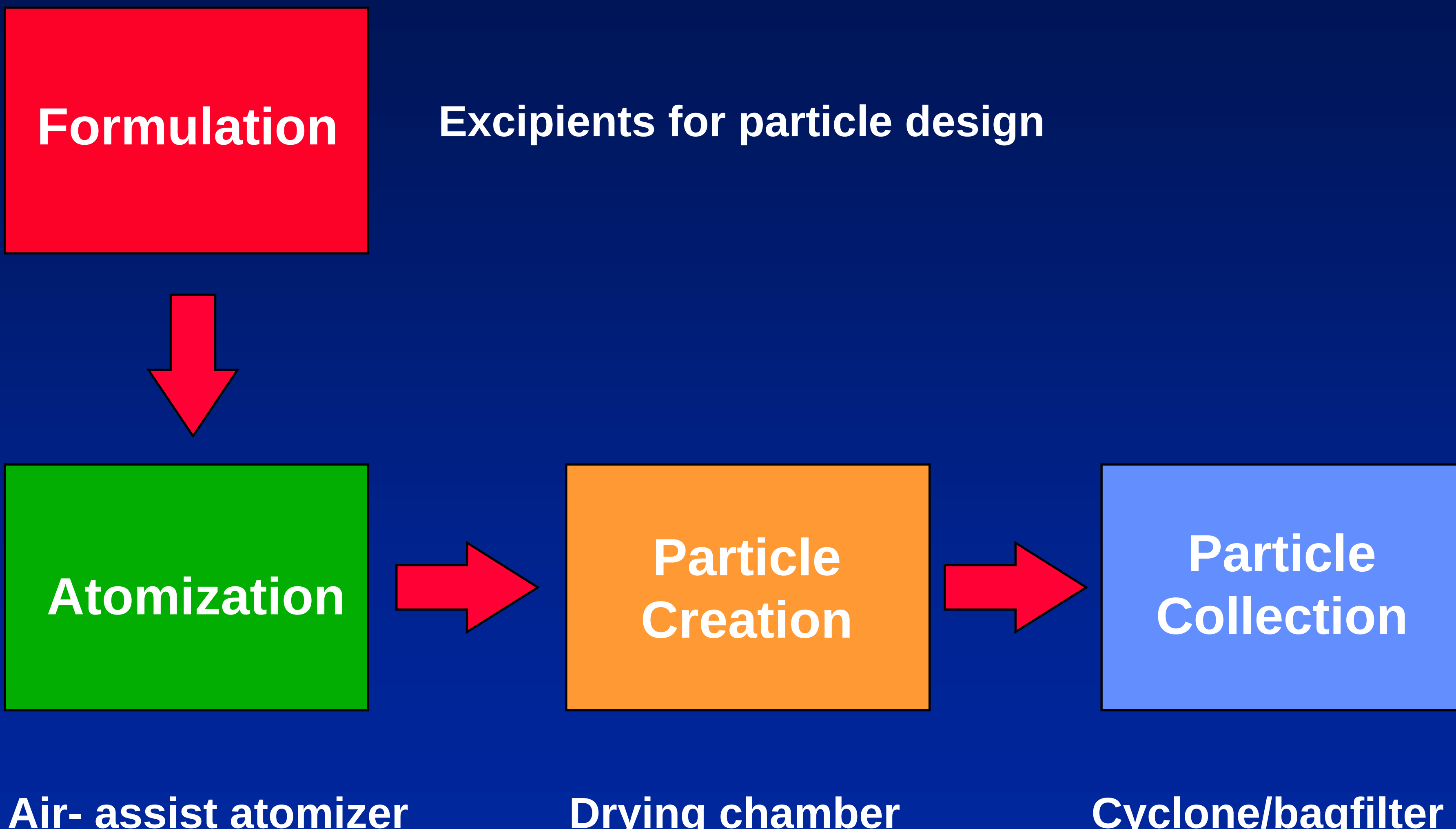
Pulmosphere™ **Pulmosol™**



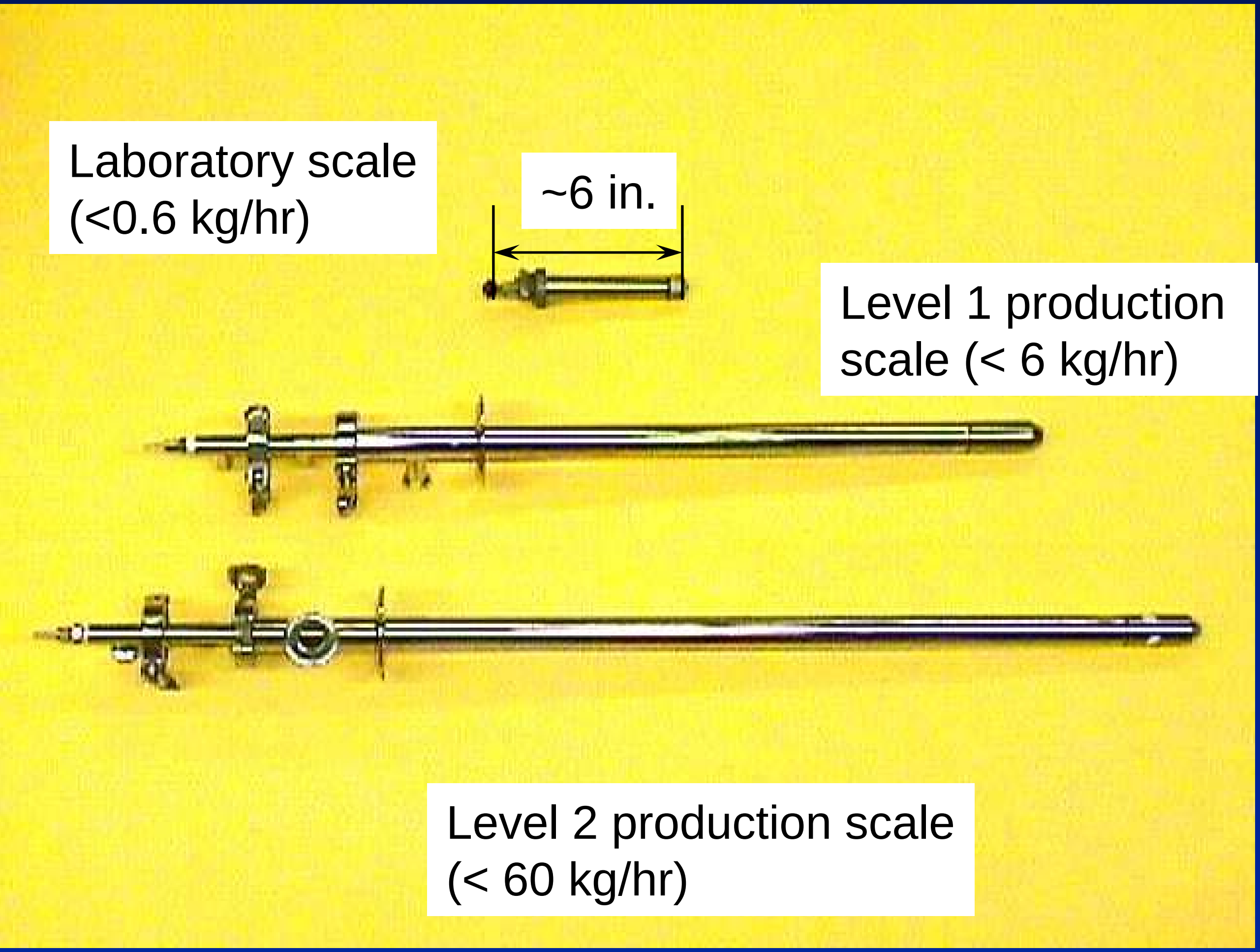
Hammer / Jet Milling

Fine Powder
(MMAD ~ 1-3 µm)

Functional Elements of the Spray Drying Process



Atomizers: From Laboratory to Production



Air-assisted atomization.

Center liquid jet enshrouded by high speed gas annulus.

Repeatable performance.

Drug contact material compliant.

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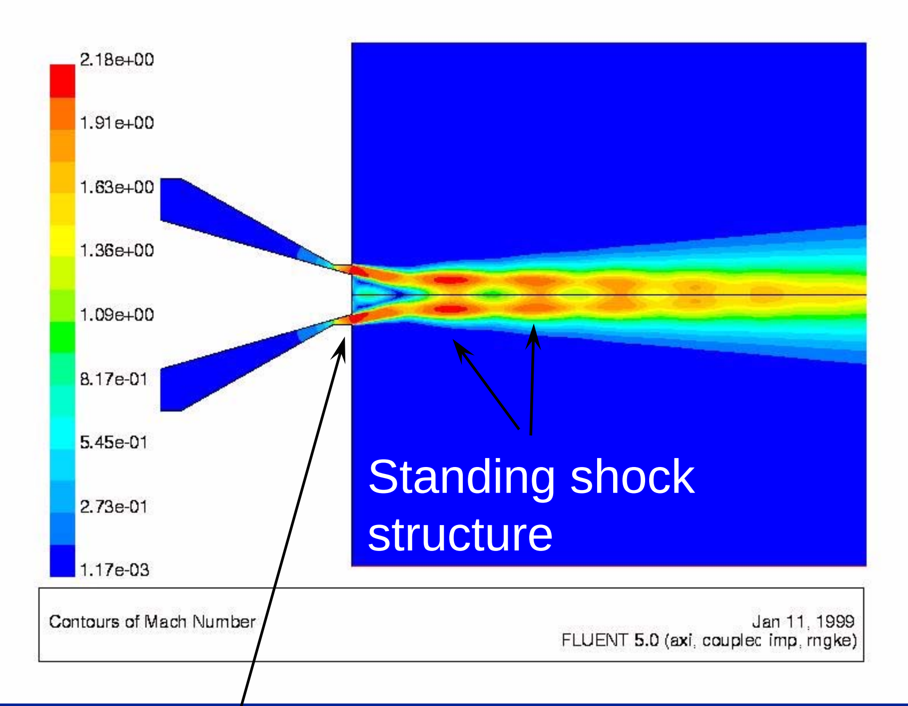
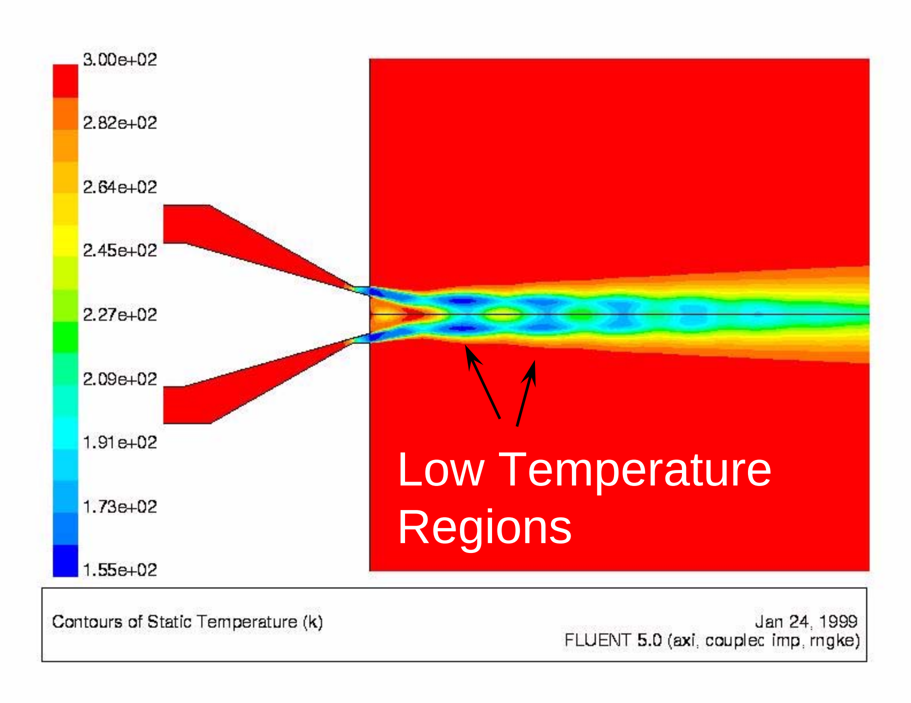
Atomizer Exit Gas Flow- Single Phase CFD

Mach # contours



Temperature contours



Nozzle Exit

Gas Flow

Atomizer design / scale-up supported by CFD

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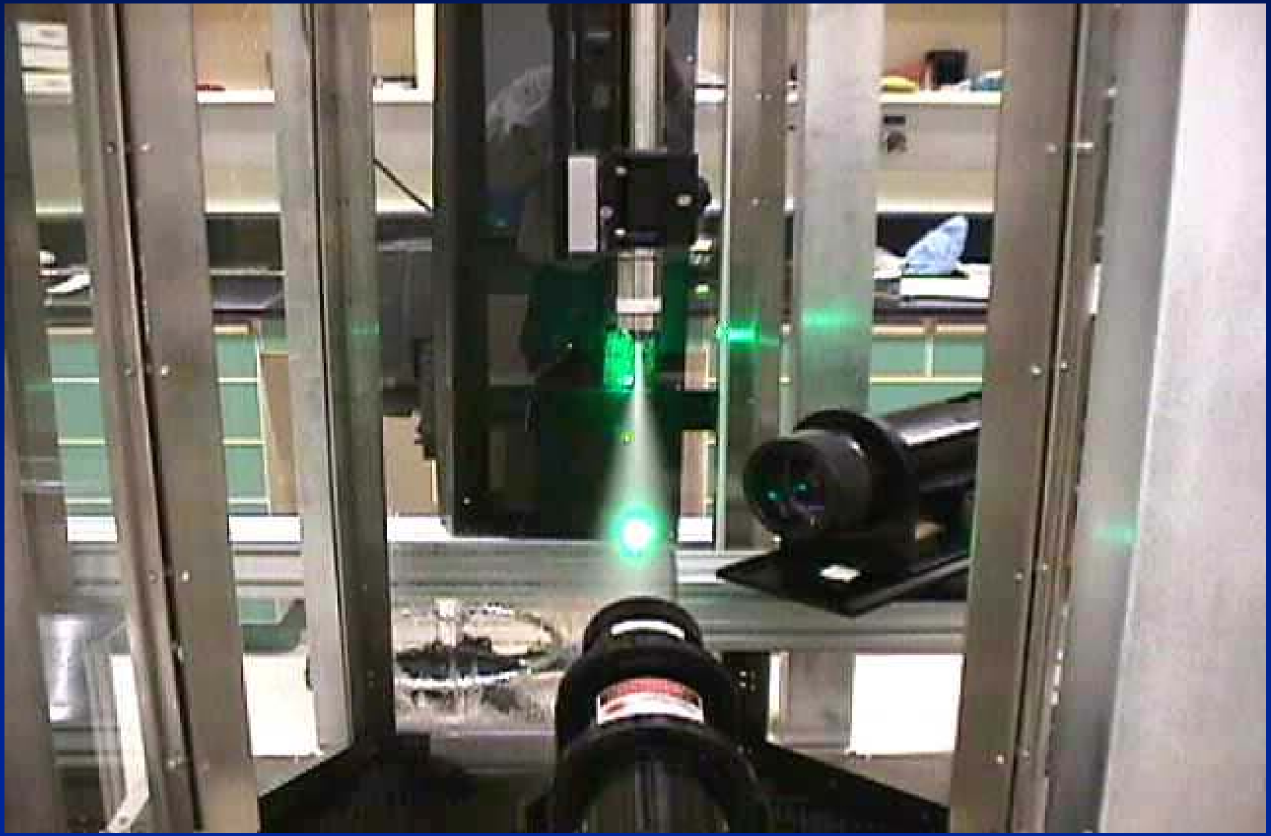
Atomizer Test Facility

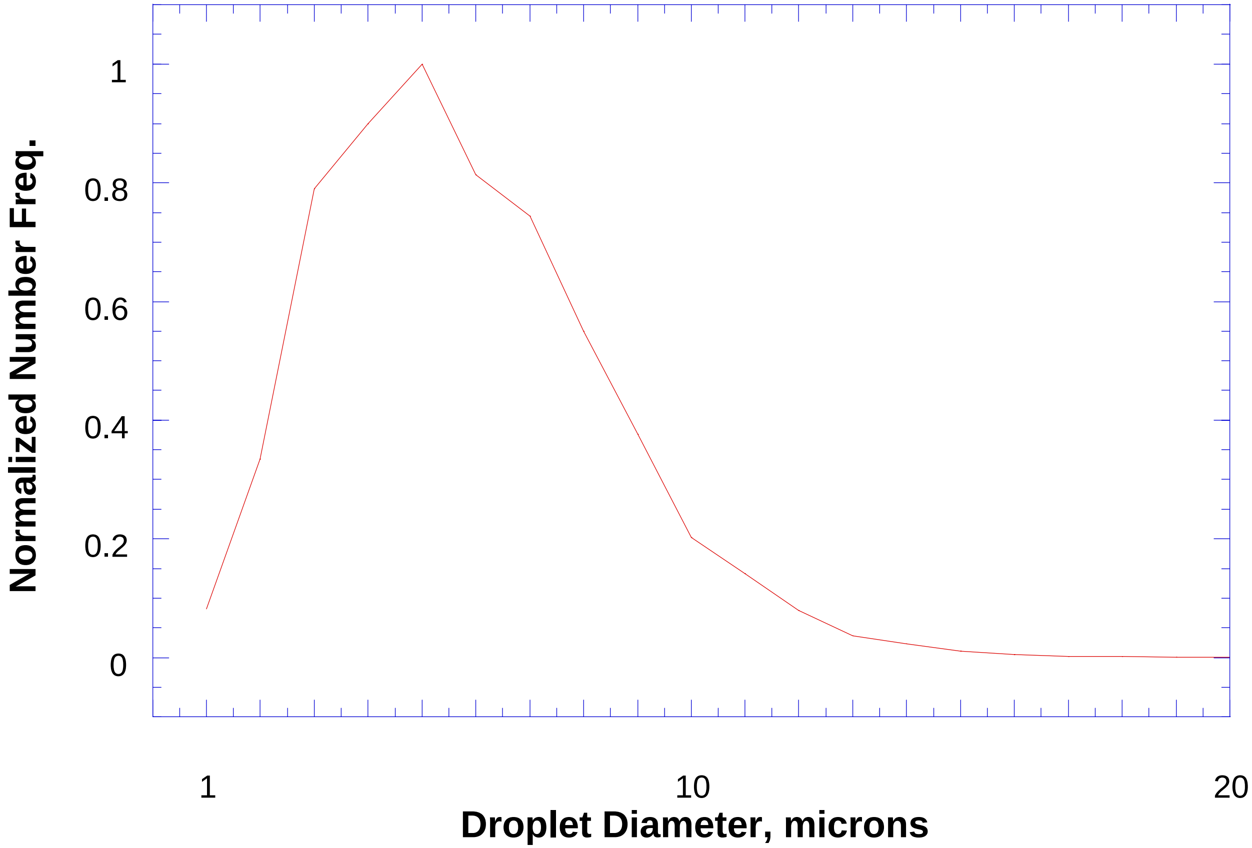
Phase Doppler Measurements



Atomizer operating conditions controlled and performance verified

Cross-sectional droplet size distribution

Small droplet size from custom atomizers leads to a commercially attractive process



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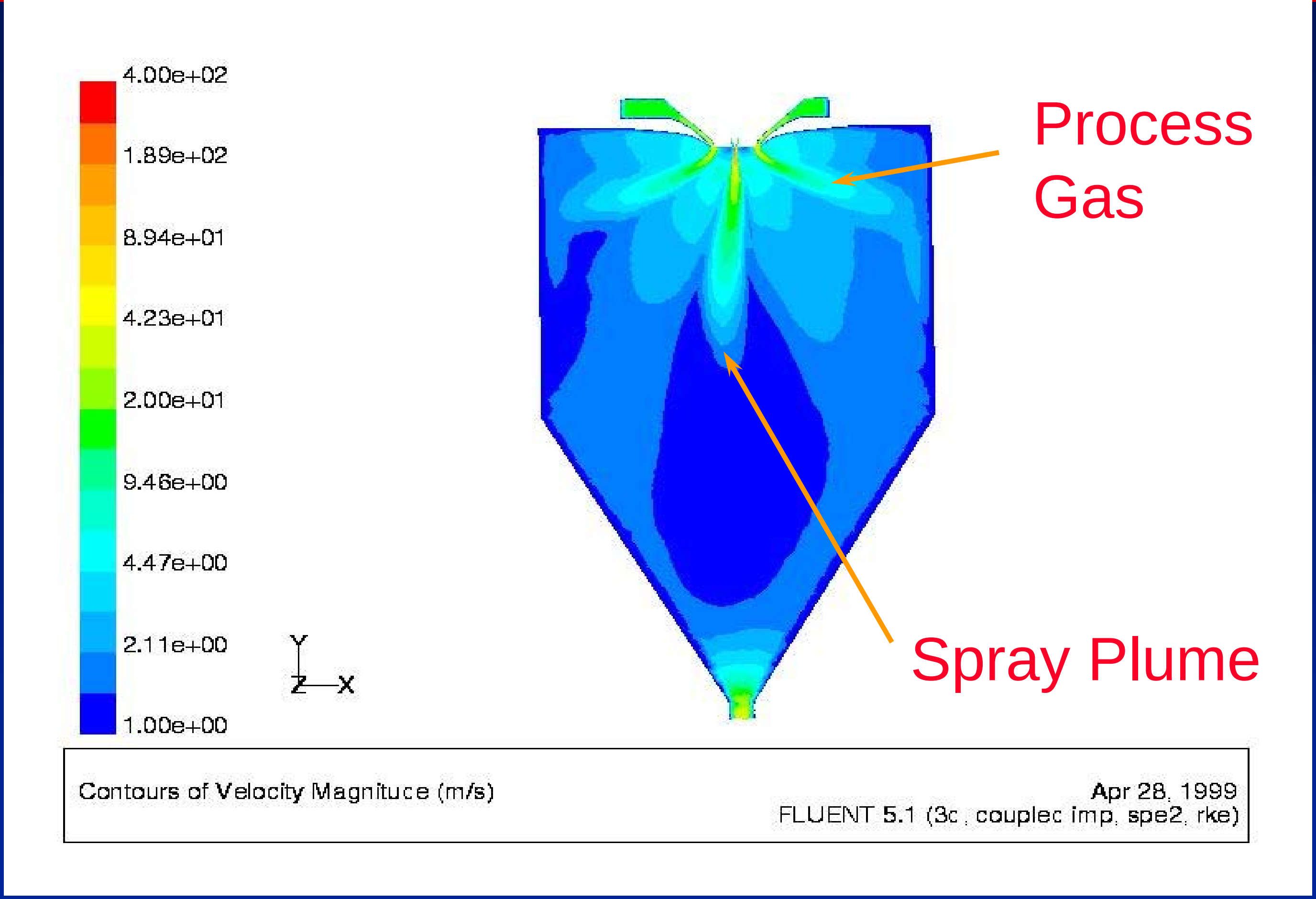
Drying Chamber and Cyclone

Preclinical

Clinical

Commercial

Internal Spray Dryer Gas Flow Field



CFD models help maintain similar gas phase conditions throughout different scales

Studying the Droplet Drying Process

- **Two phase flow in the spray dryer is complex. It is more effective to perform particle formation research on model systems.**
- **Approach: Isolate relevant subprocesses and study them in idealized environments**
  - Numerical model of droplet evaporation on single droplets in stagnant gas phase
  - Experimental studies on monodisperse droplets in a laminar flow field

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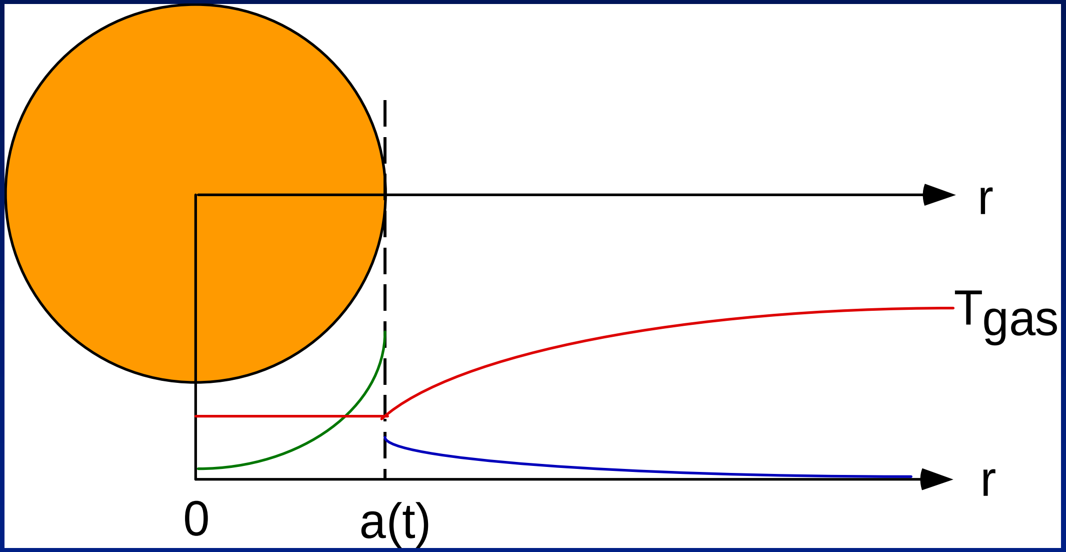
Numerical Model of Droplet Evaporation



- 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

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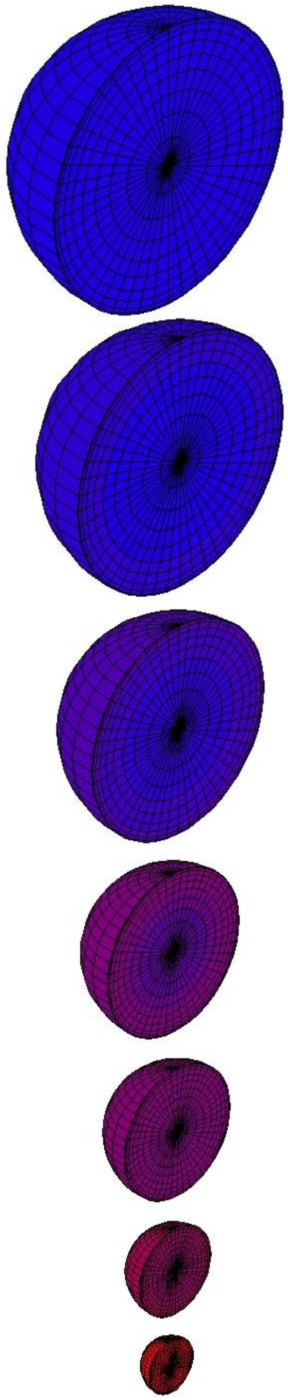
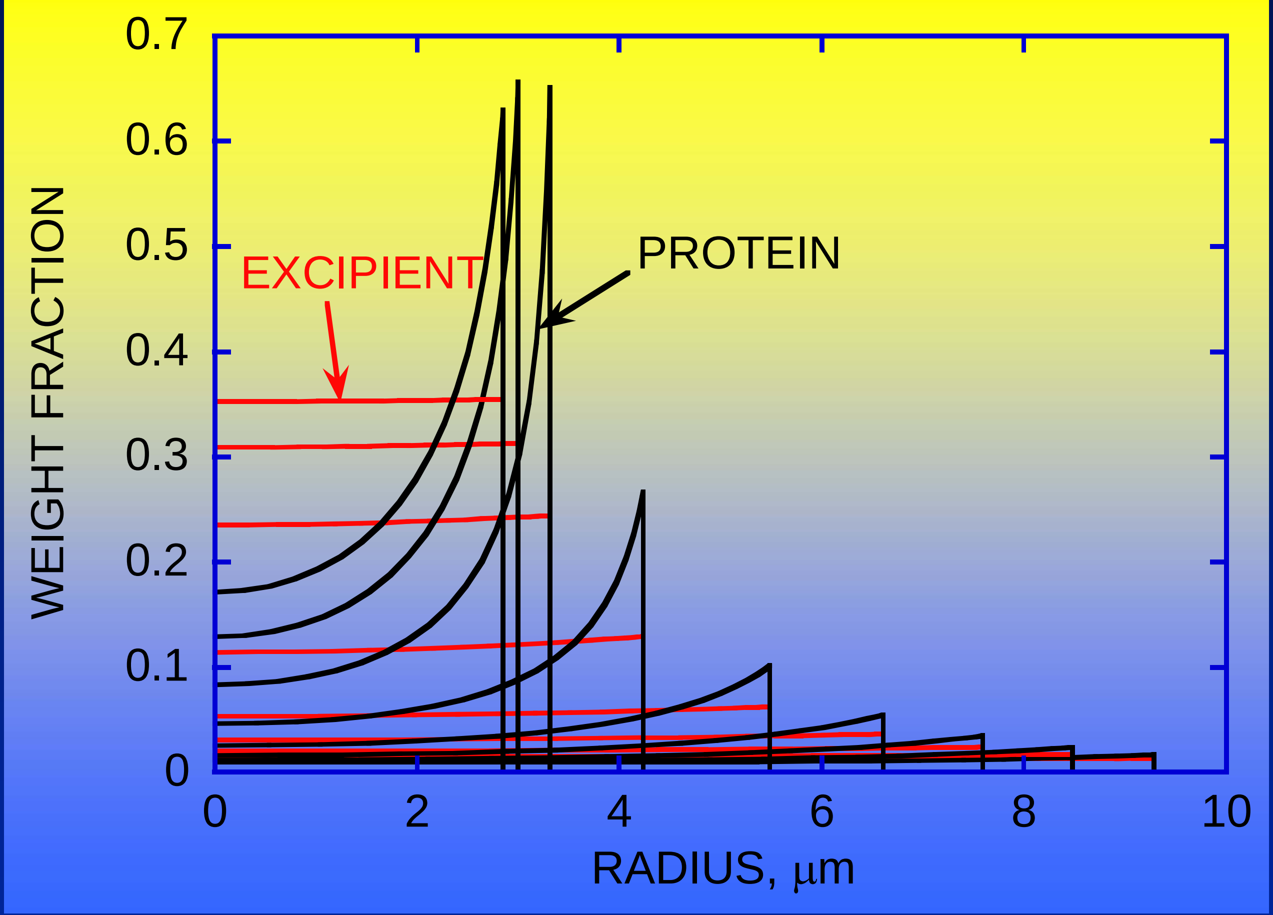
Internal Distribution of Components During the Drying Process





The model can be used to predict the influence of processing conditions and formulation on the structure of the dry particle

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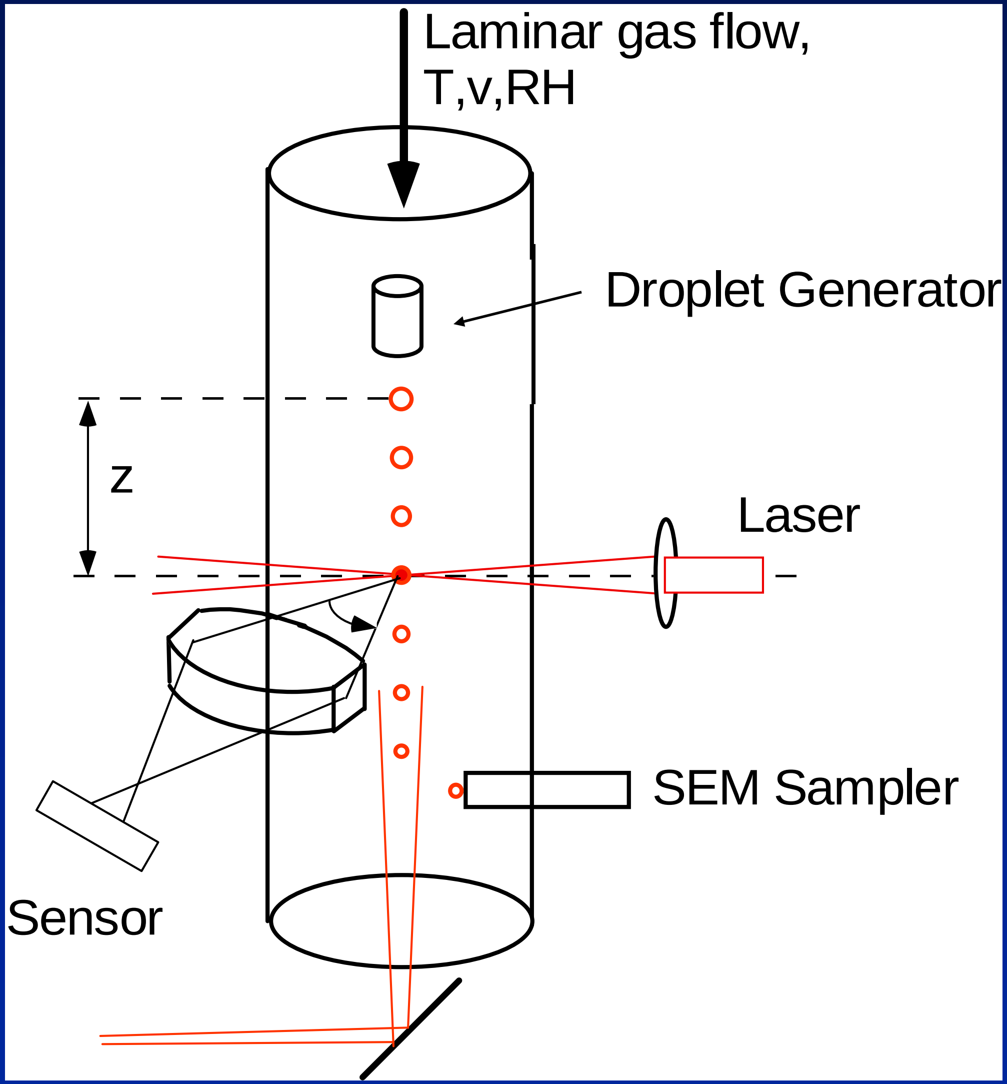
Experimental studies on monodisperse model particles



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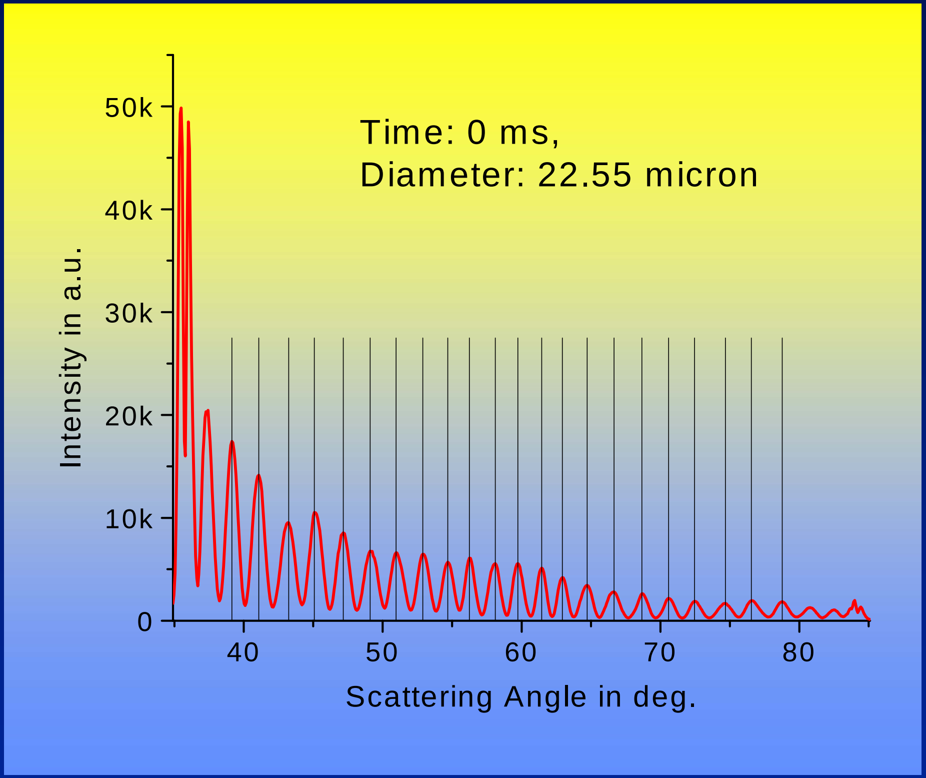
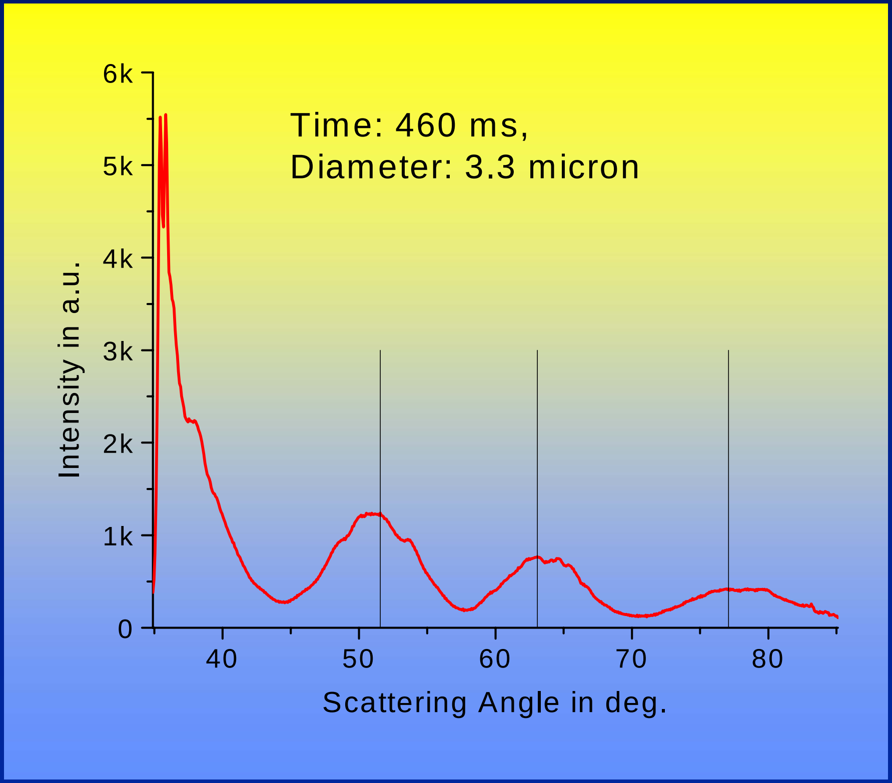
Droplet size measurements using elastic light scattering





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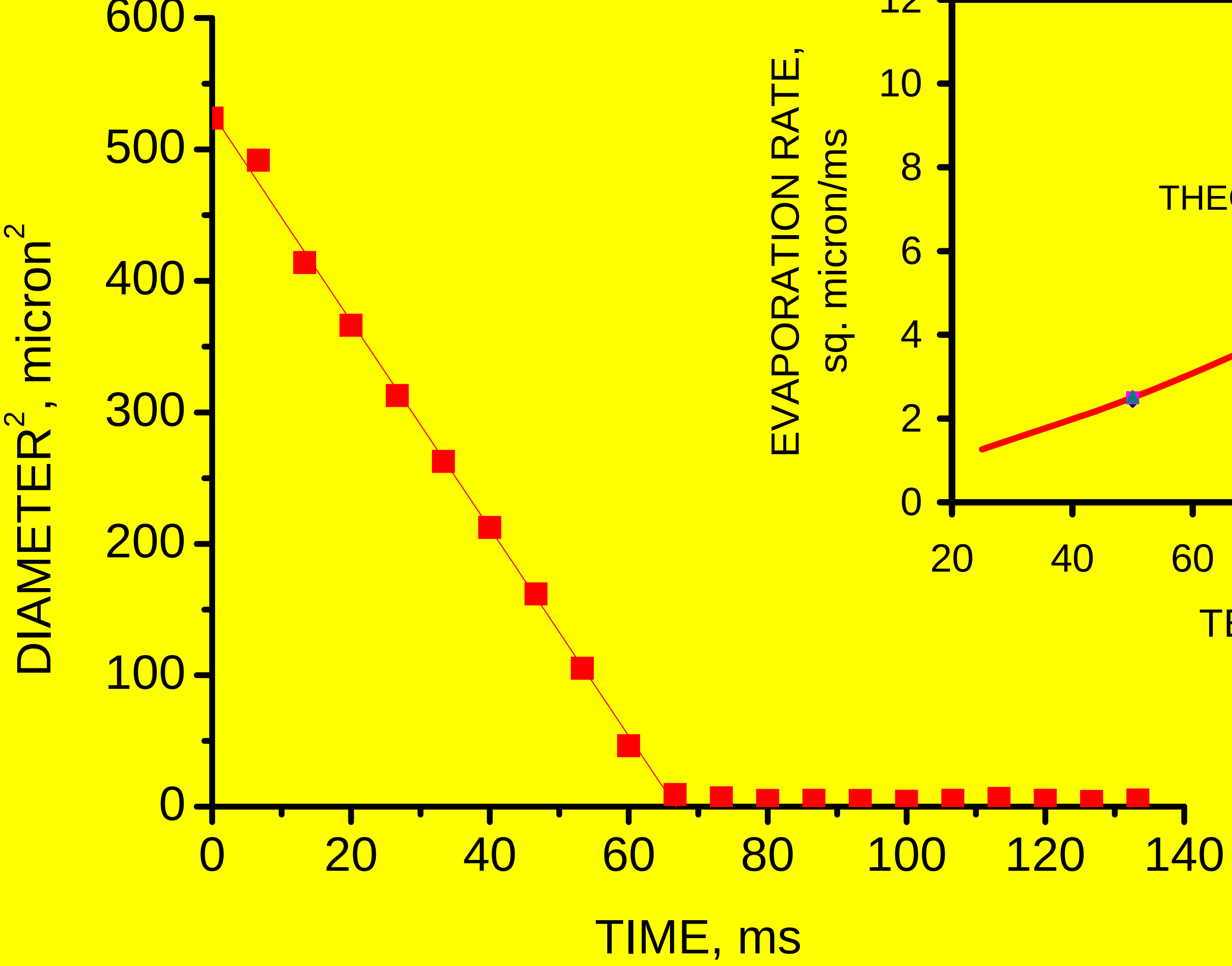
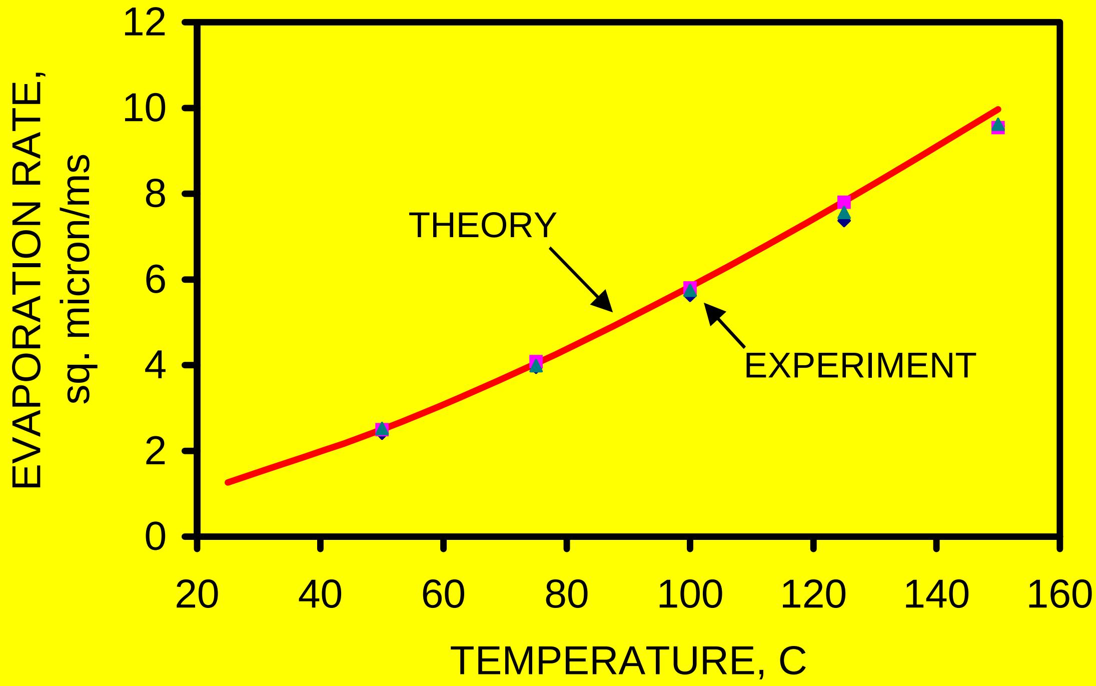
Evaporation Rate and Droplet Lifetime





H_2O

Method applicable to co-solvent systems and concentrated solutions

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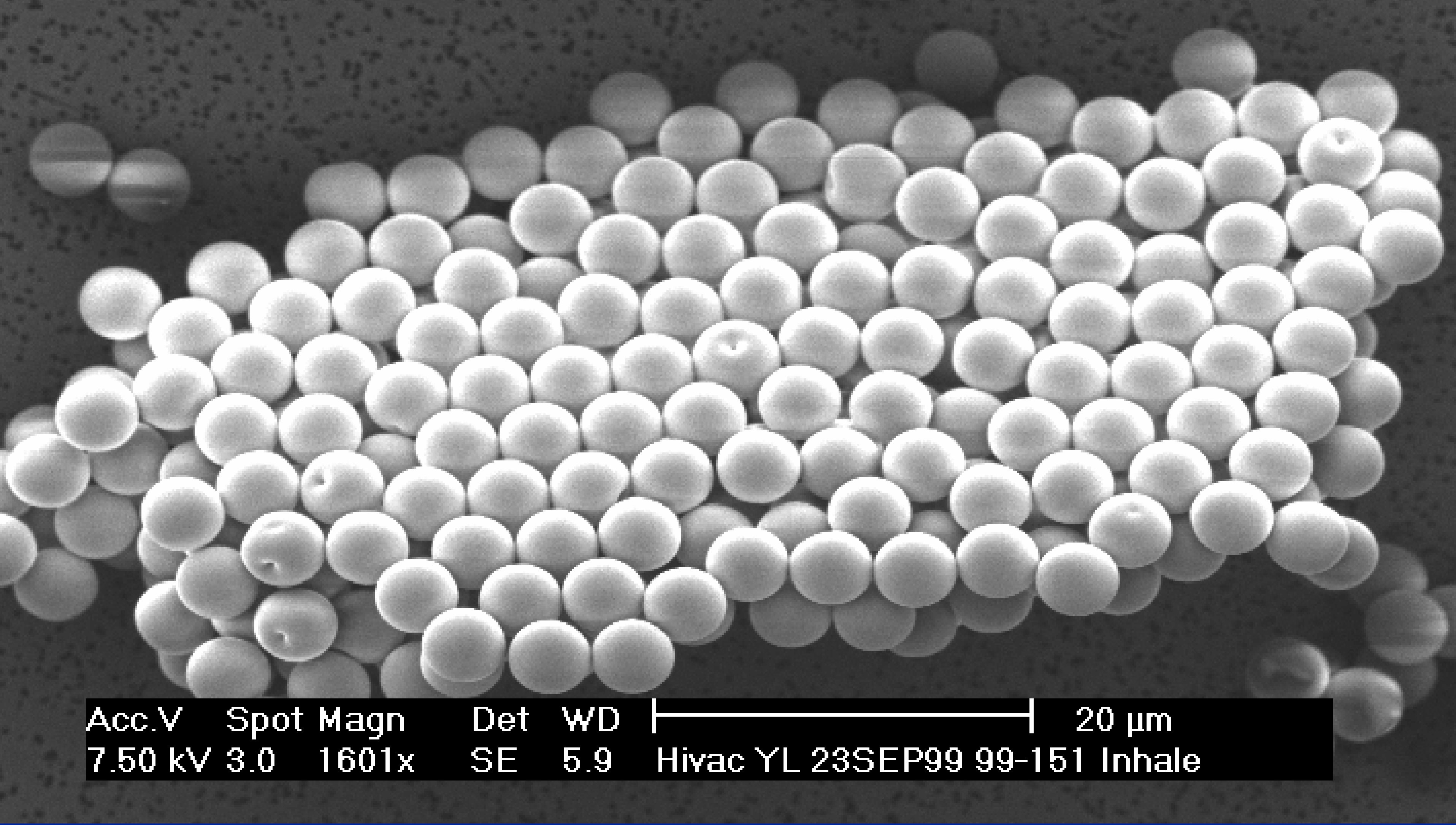
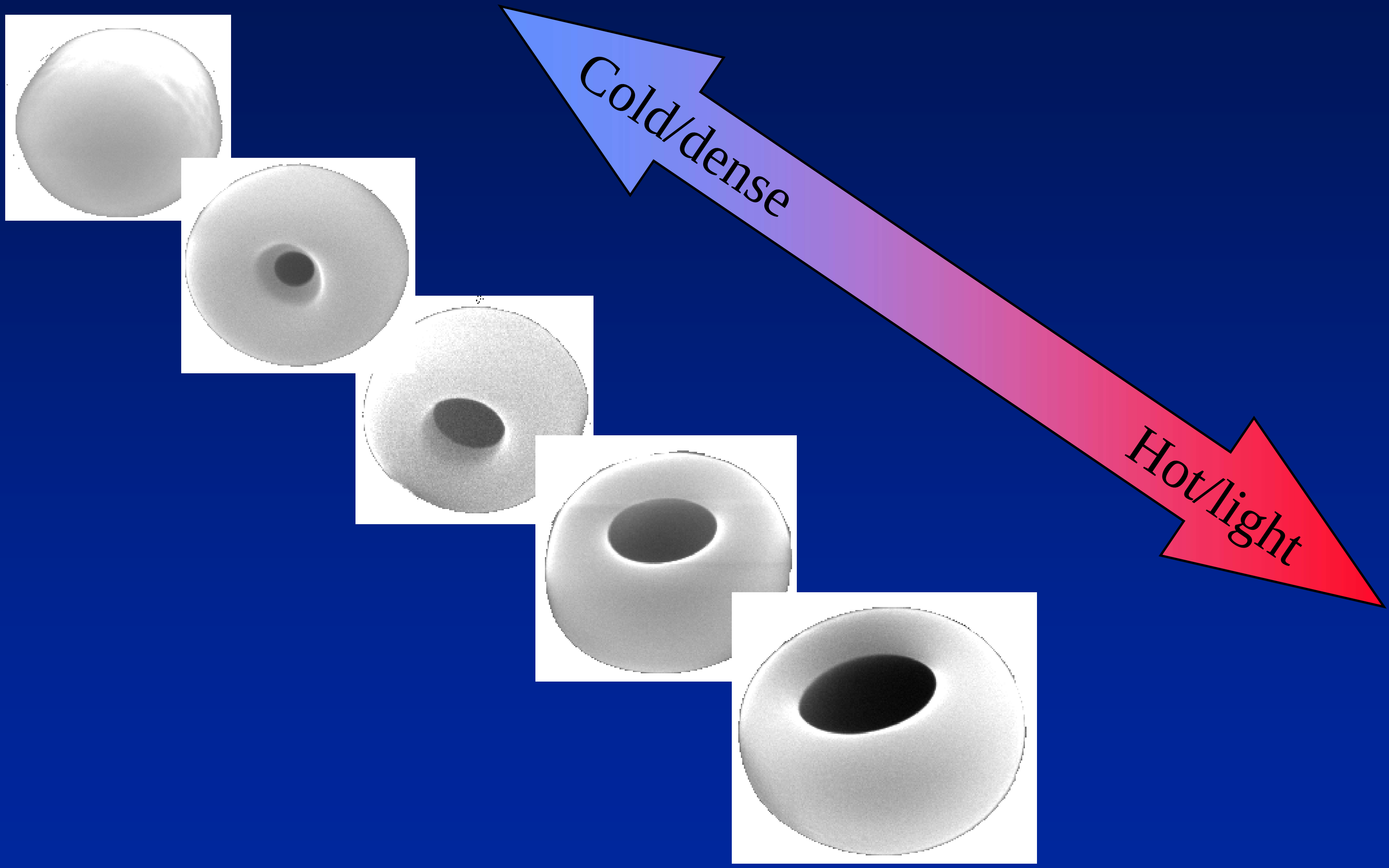
Model Particles: Perfect Control of Size and Morphology



Particle design: Controlling the Particle Density



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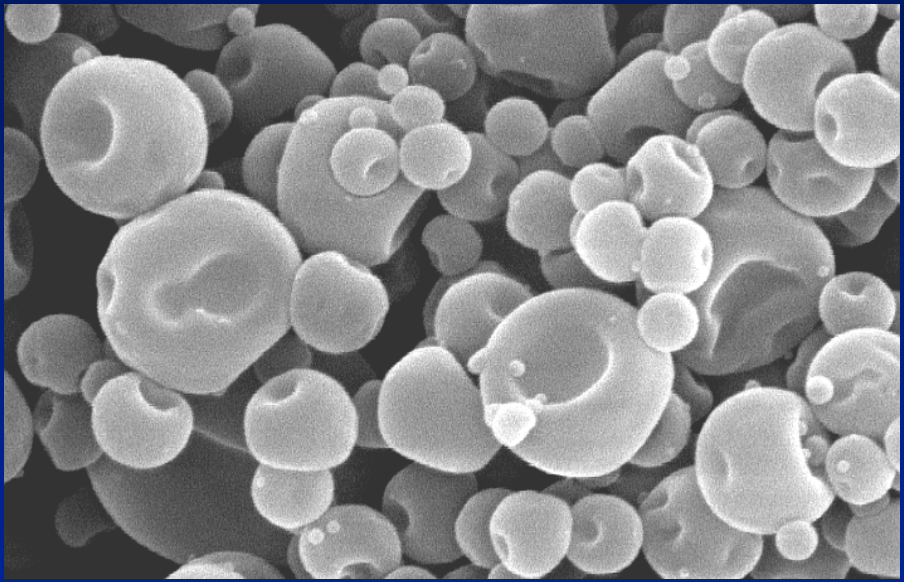
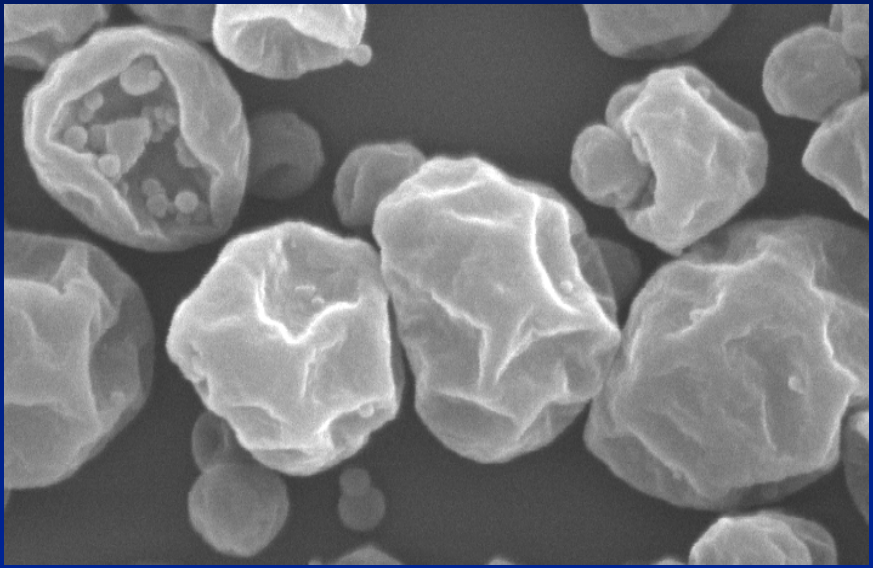
Particle Design: Controlling the Particle Morphology

100 % Large molecule



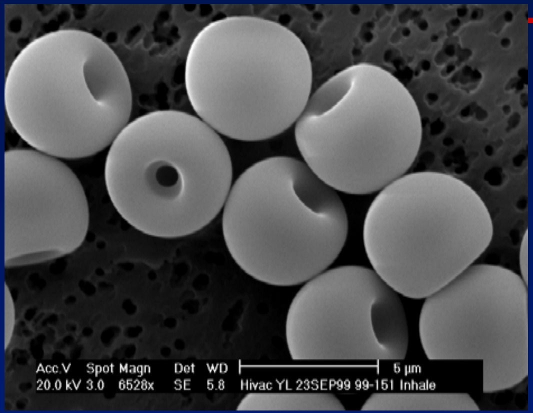
With excipient

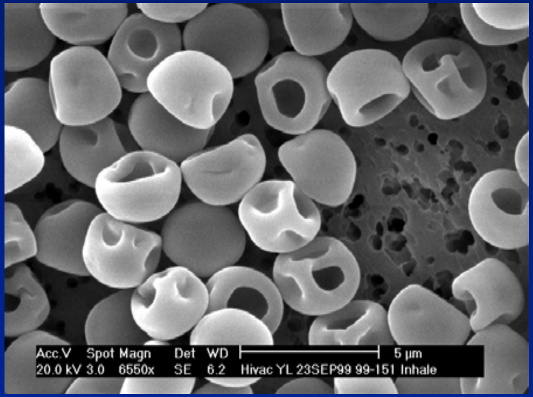


Desirable properties can be designed into powders through control of processing conditions in combination with special excipients

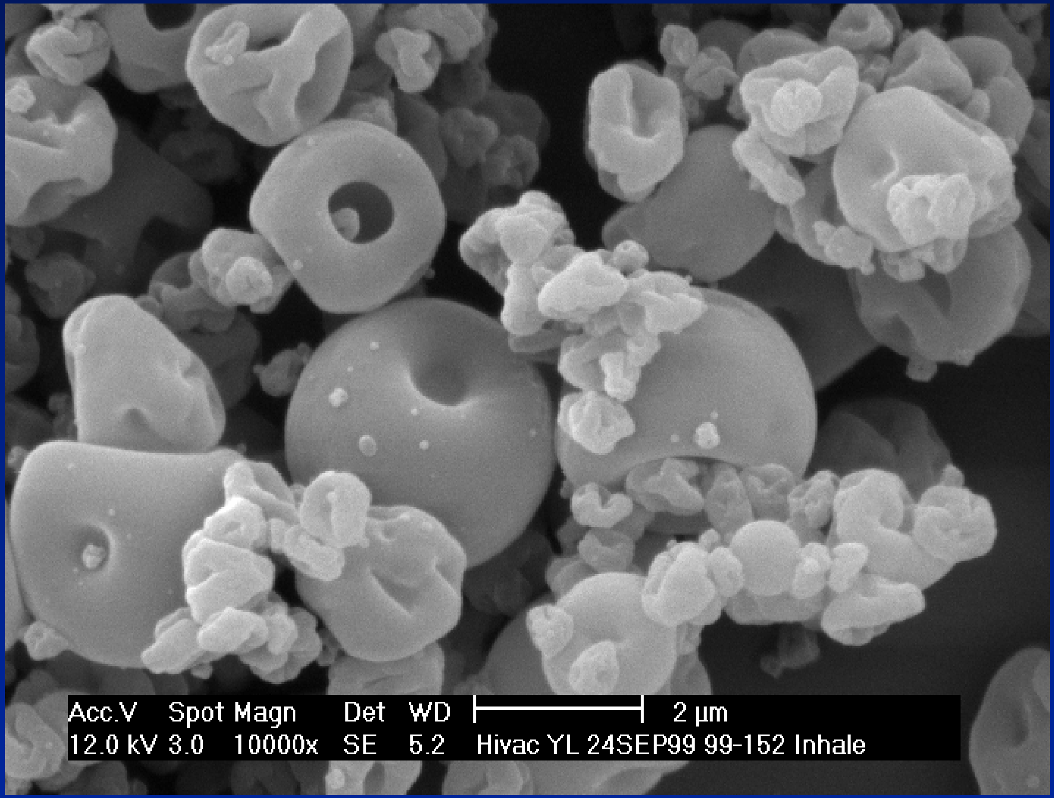
Analyzing and Optimizing

Model Particles





Powder from Spray Drier



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Particle Analysis by Raman Spectroscopy

Goals:

Quantitative analysis of solid state properties, e.g. amorphous fraction and polymorphism.
Analysis of protein conformation.

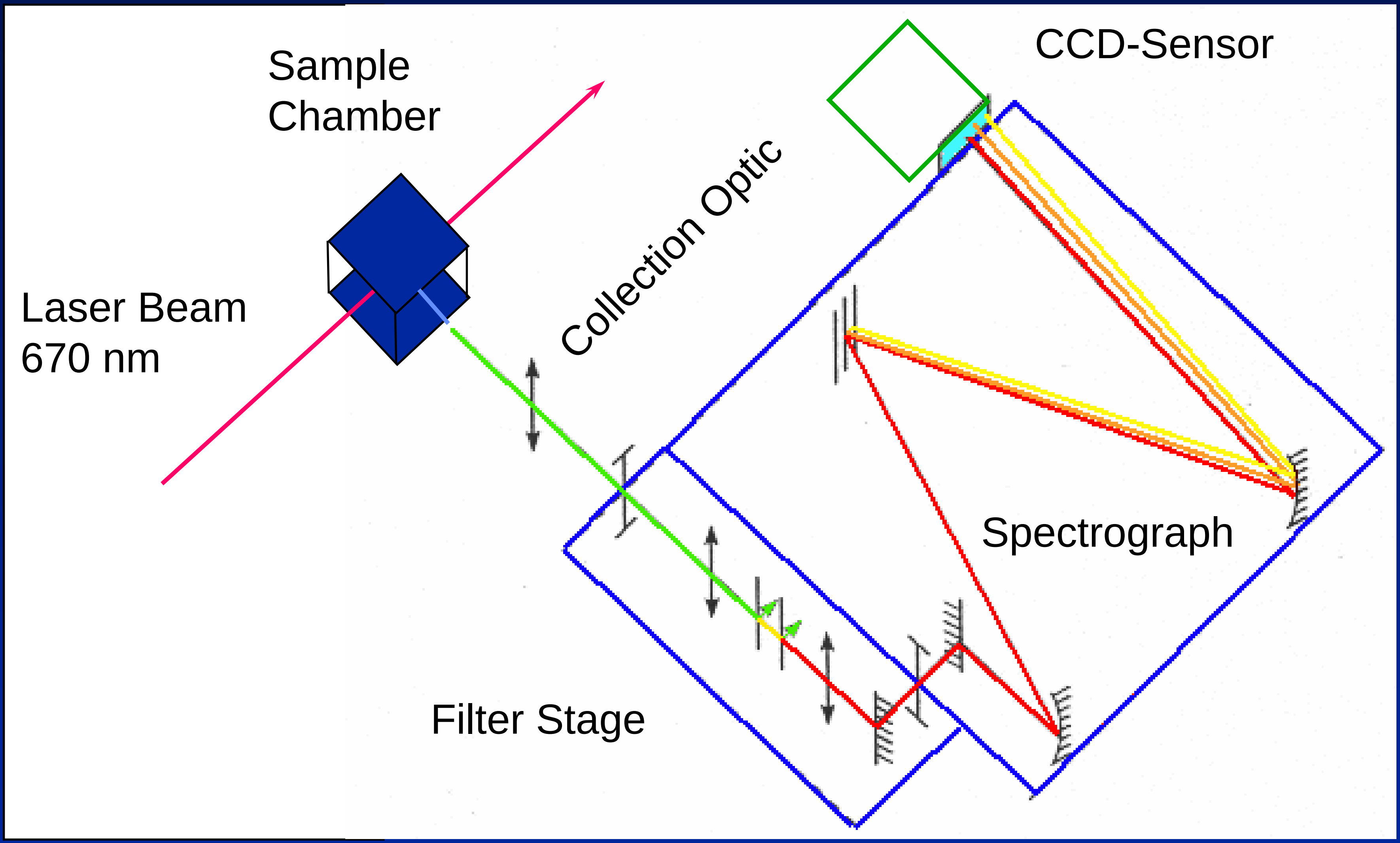
Challenges:

Multicomponent systems,
Model particles - sample mass too low for XRD,
Environmental control of sample (RH, T).

Solution:

Custom-built Raman system

Dispersive Raman with Red Excitation



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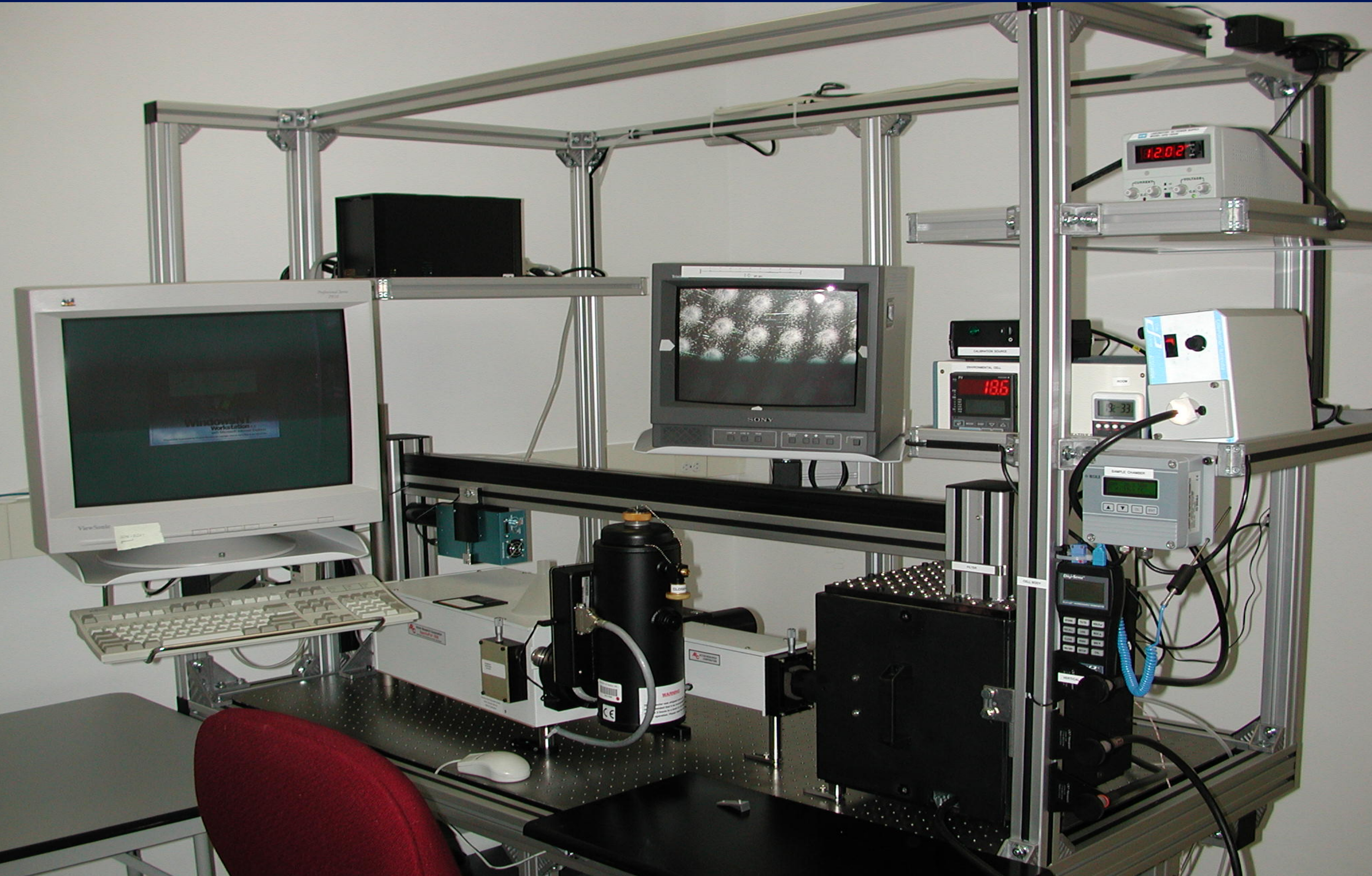
Inhale's Research Raman System



High Sensitivity – Low Sample Mass

Sample mass:
10 μg

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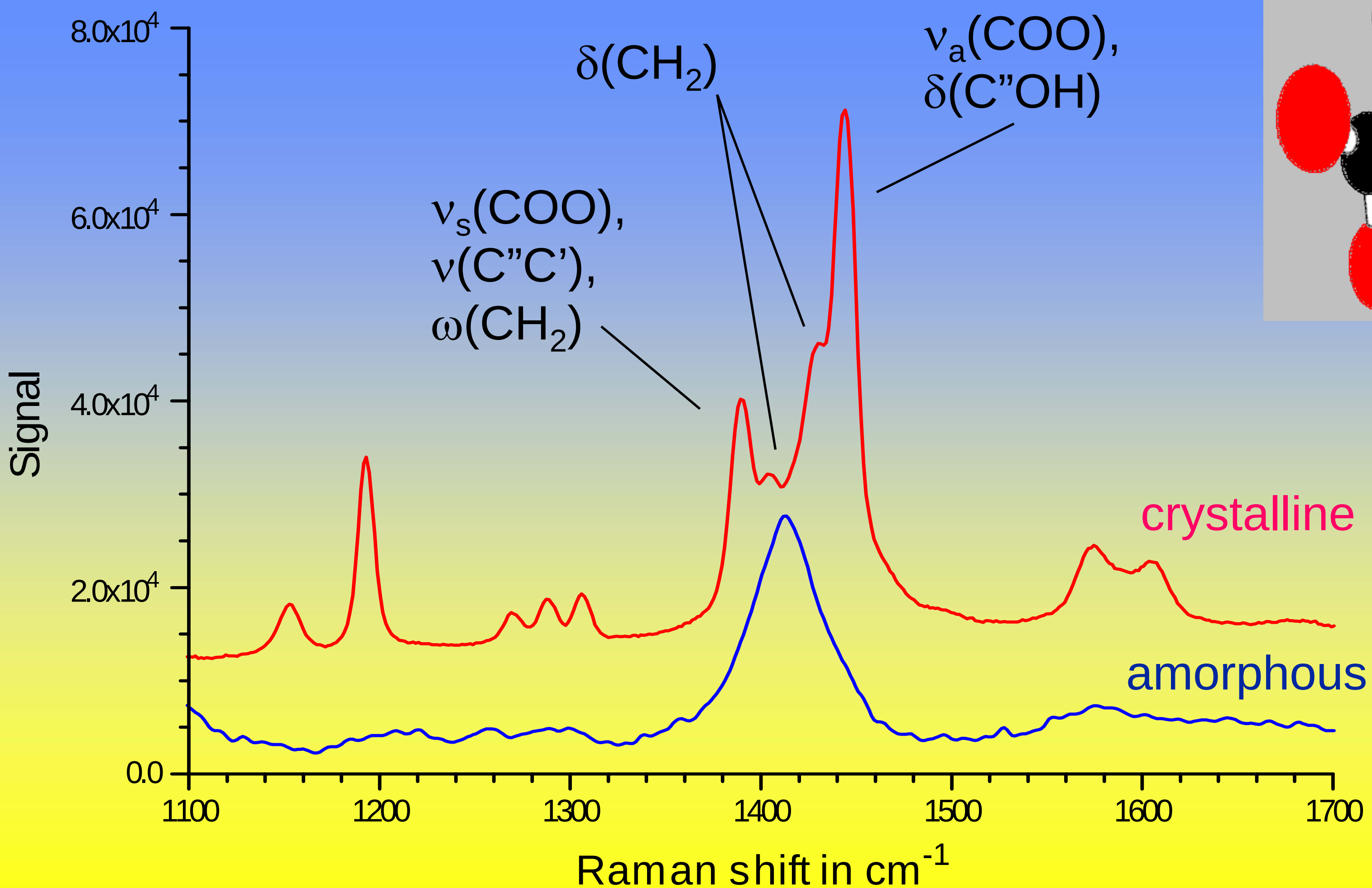
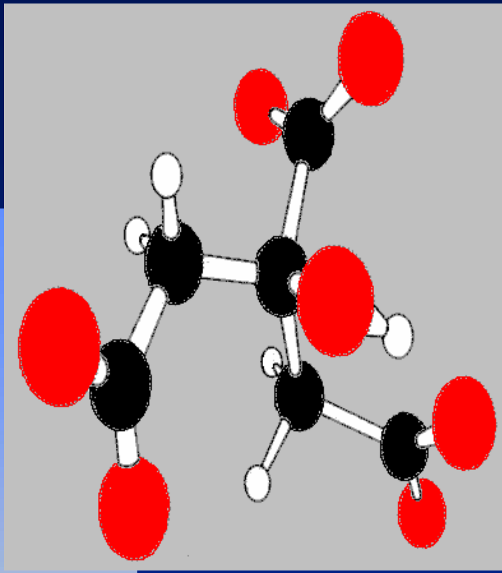
Measuring the Amorphous Content

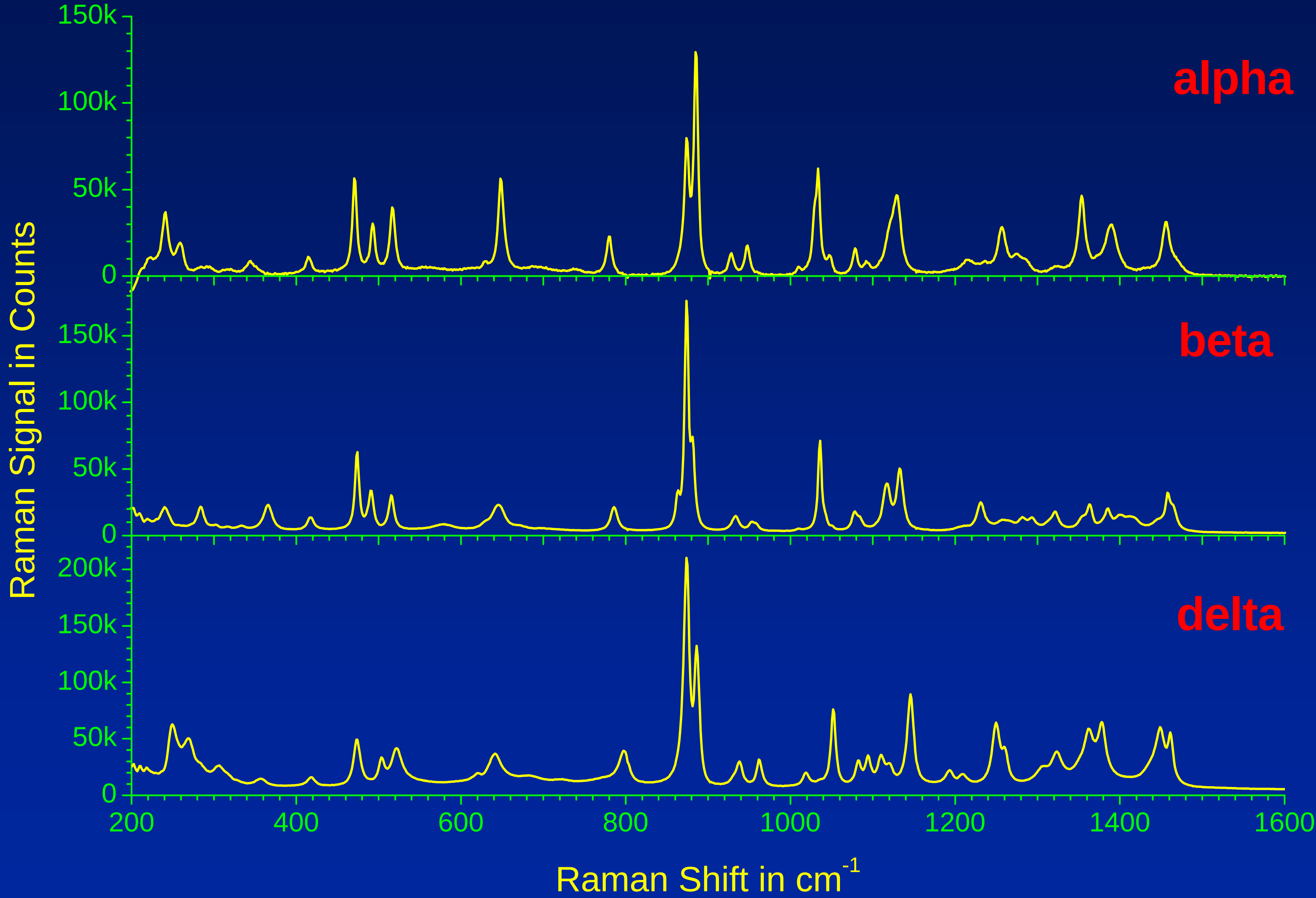
Example: Citrate

Clear differences allow easy identification





Unique Spectral Fingerprints of Mannitol Polymorphs



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Quantitative Measurements by Raman Spectroscopy

The Raman signal is linearly proportional to concentration

The proportionality constant is generally unknown

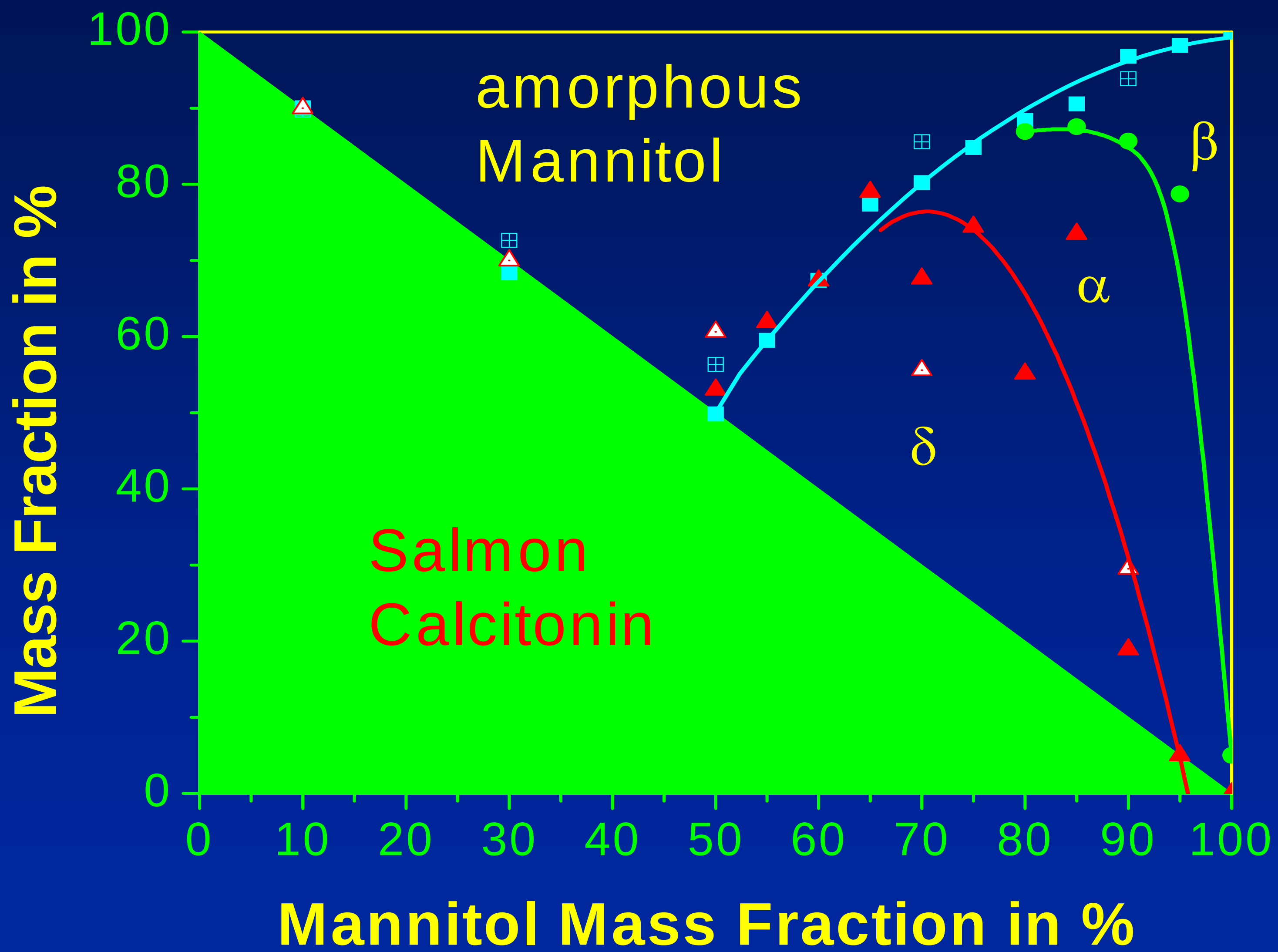
Solution: Measurement relative to an internal standard

Raman signal, Φ_A, of a substance *A*

$$\Phi_A = \phi \bullet c_A N_a V \bullet \sigma_A$$

- ϕ Radiant flux density in the laser focus
  c_A Molar concentration of substance A
  N_a Avogadros Number V Sample volume
- σ_A Scattering cross section

Solid State Analysis in Multicomponent Systems



Summary

Inhale has developed advanced research and development tools and methods to understand and control the spray drying process.

Increased understanding and control lead to shorter development times, saving material and cost, decreased scale-up risk and optimized product performance.

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