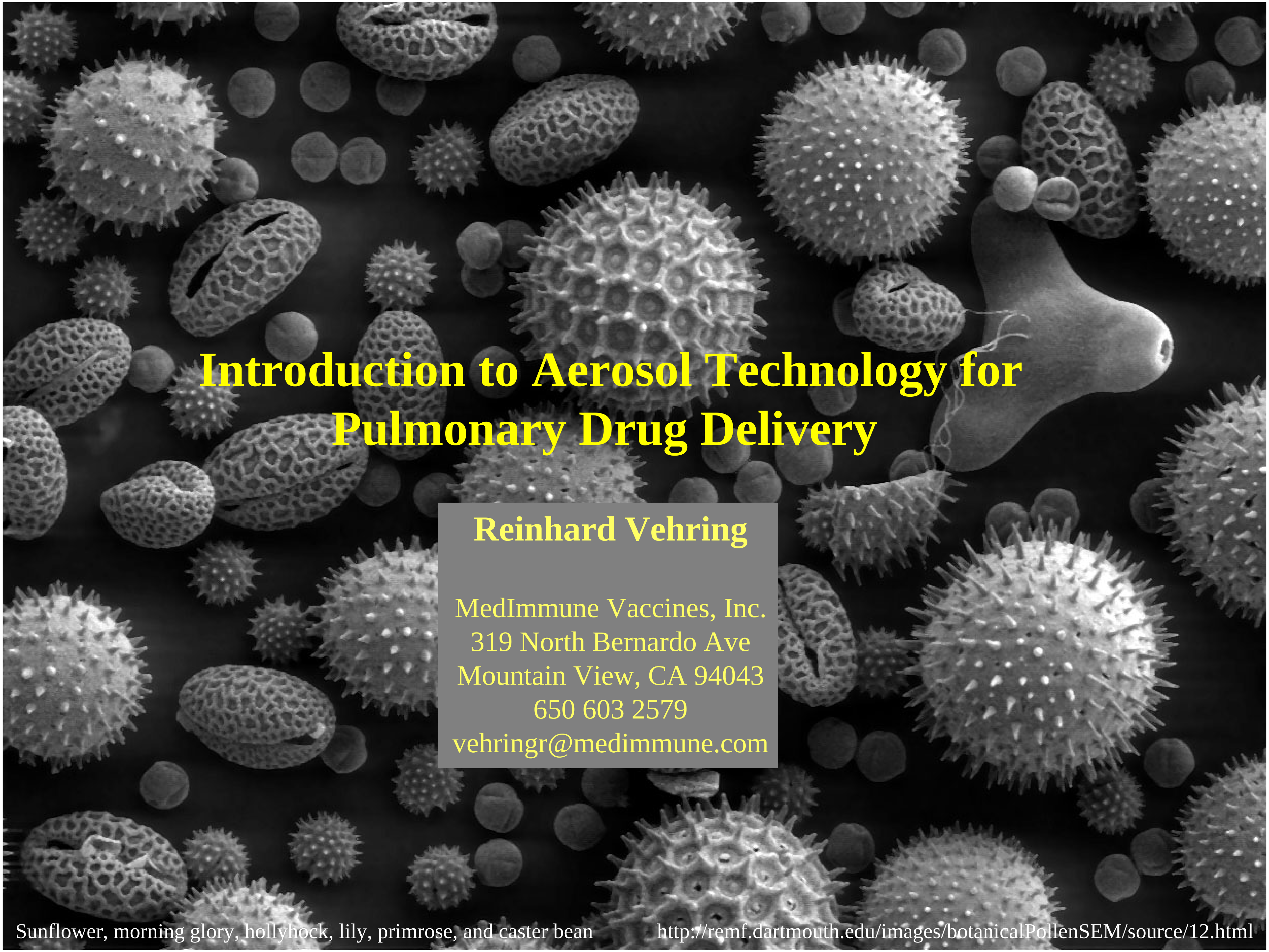


Introduction to Aerosol Technology for Pulmonary Drug Delivery

Reinhard Vehring

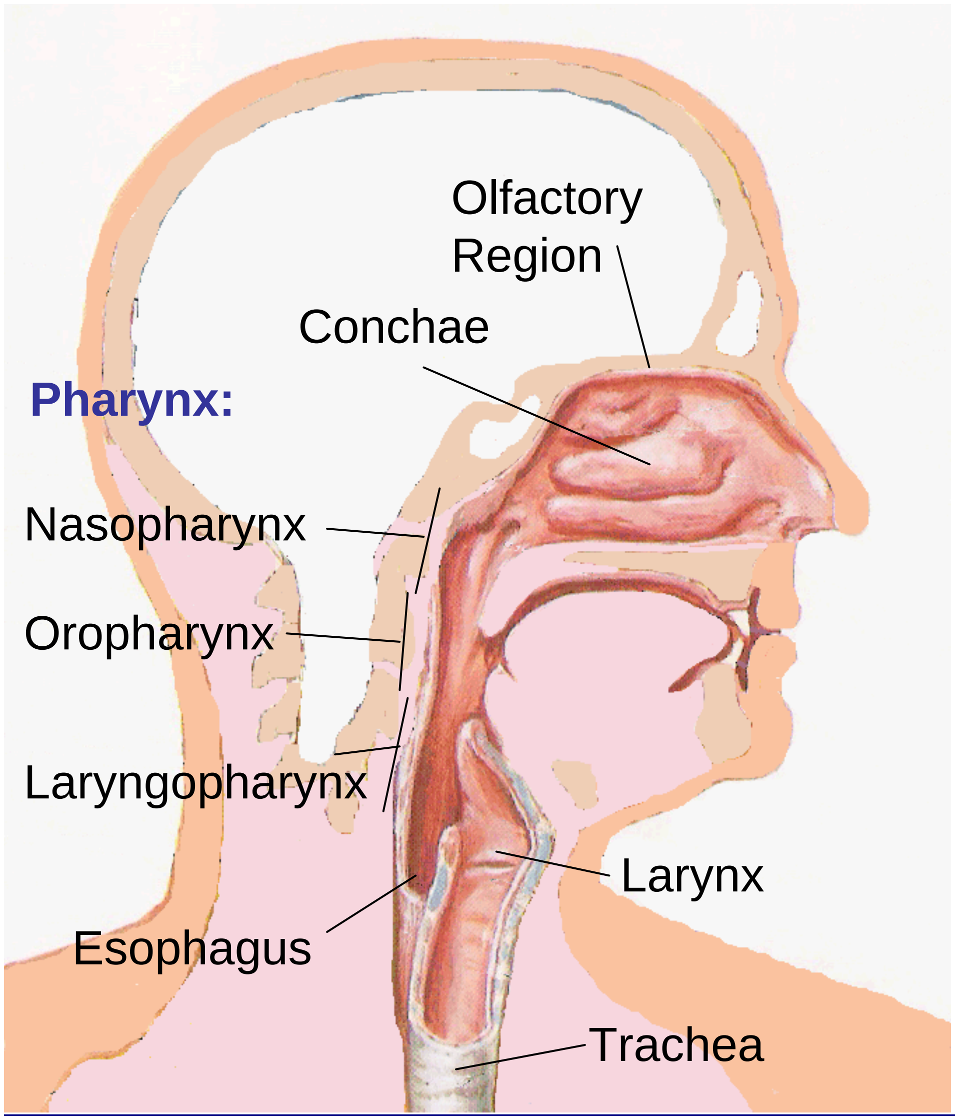
MedImmune Vaccines, Inc.
319 North Bernardo Ave
Mountain View, CA 94043
650 603 2579
vehringr@medimmune.com

Sunflower, morning glory, hollyhock, lily, primrose, and caster bean http://remf.dartmouth.edu/images/botanicalPollenSEM/source/12.html

Outline

- Anatomy and Physiology of the Respiratory System
- Deposition and Pharmacology
- Delivery and Dispersion Devices
- Powder Manufacture
- Particle Engineering
  - Understanding the Spray Drying Process
  - Designing Dispersibility
  - Designing Physical Stability
  - Encapsulation

The Portal: Nose or Mouth



Nose

- Variable anatomy
- Warms and filters air
  - Captures > 50 % of particles with an aerodynamic diameter d_a > 3 µm
  - Captures > 90 % of particles with d_a > 10 µm
- Surface area: 150 cm^2
- Cilia and mucus transport particles down the nasal cavity to the pharnyx. Mucociliary clearance takes 15 – 20 min.

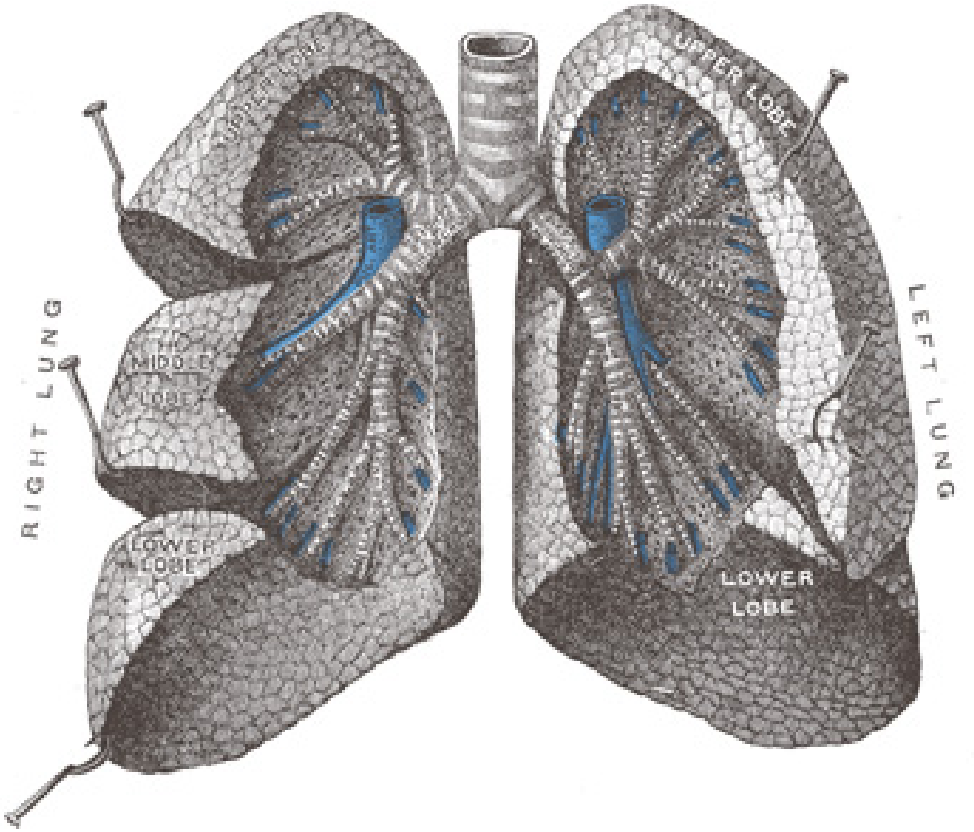
Mouth

- Extrathoracic filter function
  - < 10 % for d_a < 3 µm
  - > 65 % for d_a > 10 µm
  - Depends on jaw and tongue position, and on breathing rate
- Extrathoracic volume: 50 cm^3

Lung Anatomy - Overview

3 lobes

2 lobes



Conducting Zone

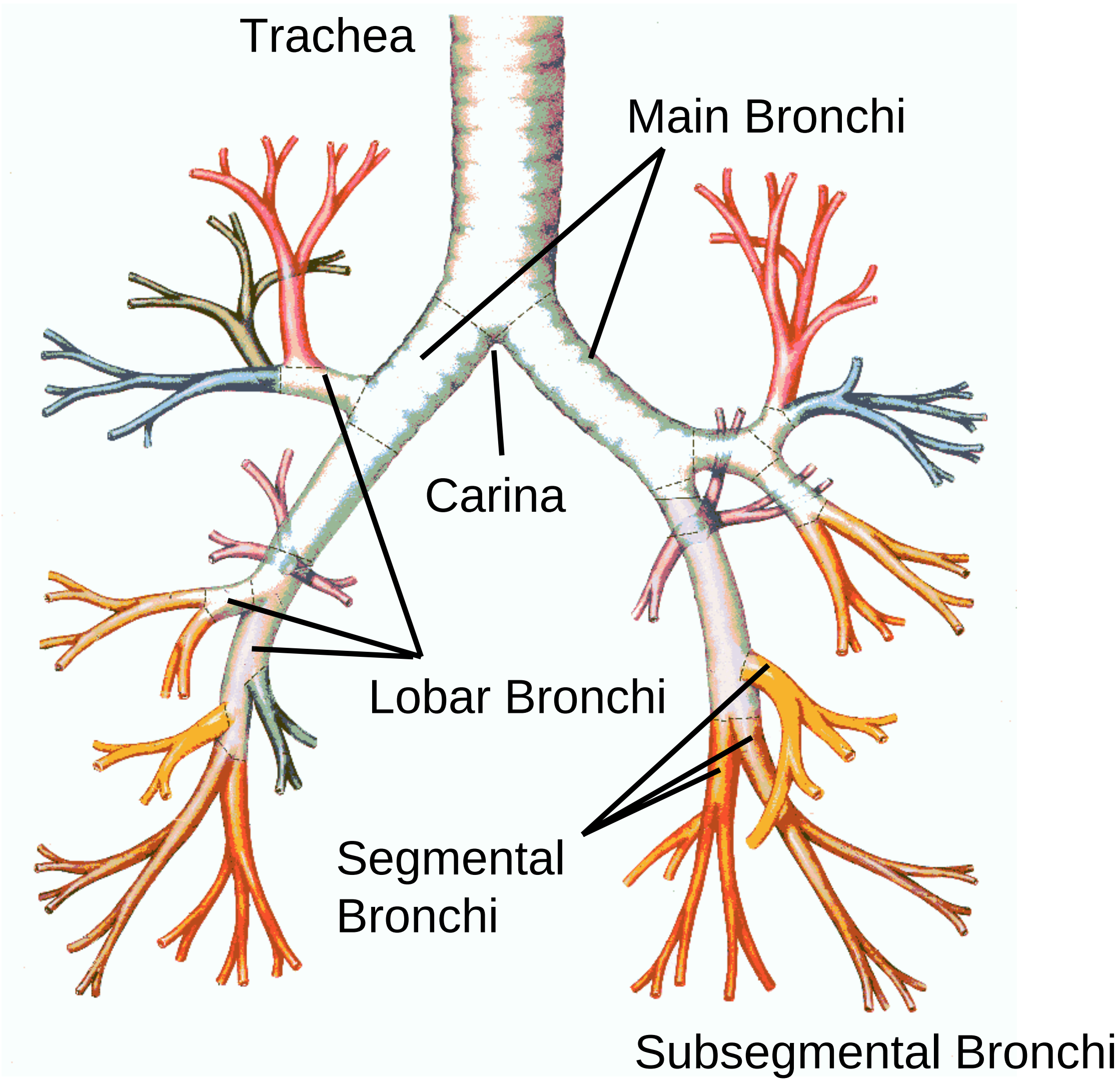
- Trachea
- Bronchi
- Bronchioles
- Terminal Bronchioles
- Volume: 175 cm^3
- Surface Area: 3500 cm^2

Respiratory Zone

- Respiratory Bronchioles
- Alveolar Ducts
- Alveoli
- Volume: 5,000 cm^3
- Surface Area: 100 m^2

Gray’s Anatomy, 1918

Conducting Airways –Trachea and Bronchi



Structure

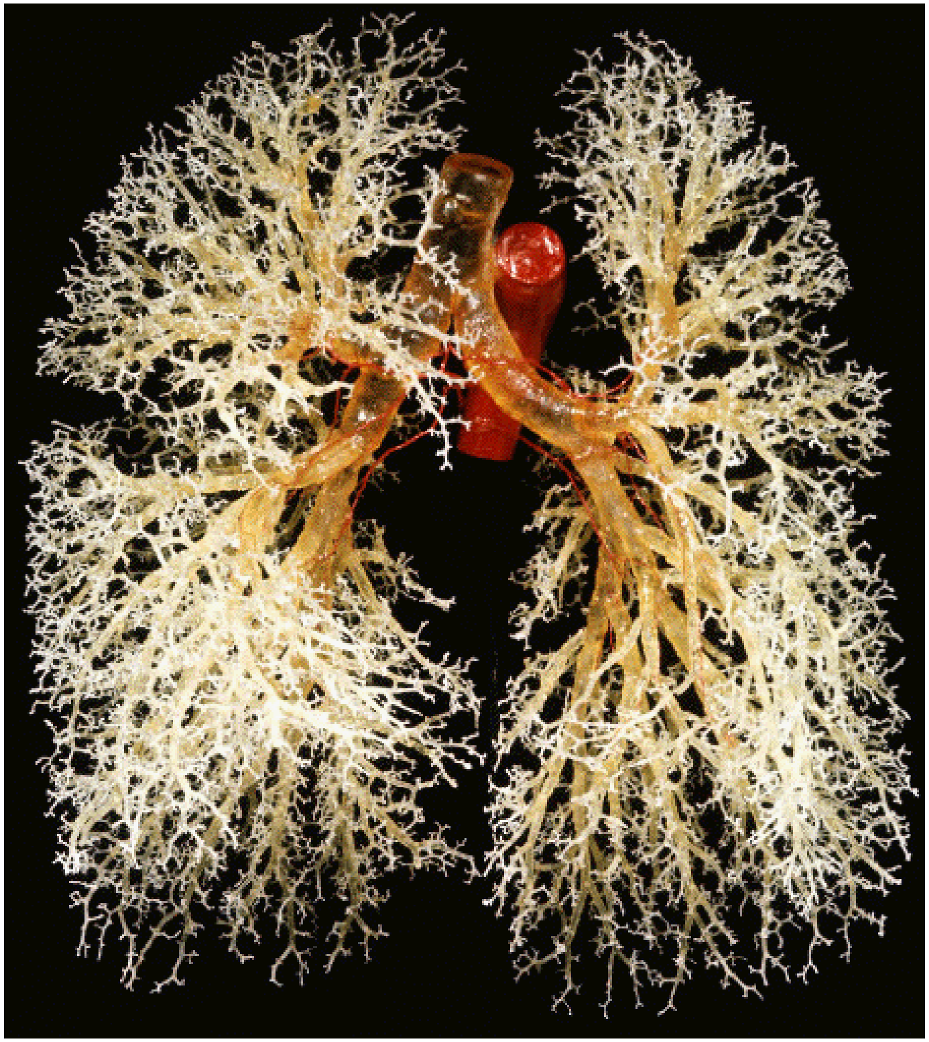
- Cartilaginous
- Longitudinal elastic fibers
- Smooth muscle
- Ciliated
- Mucus layer
- Branching with irregular dichotomy

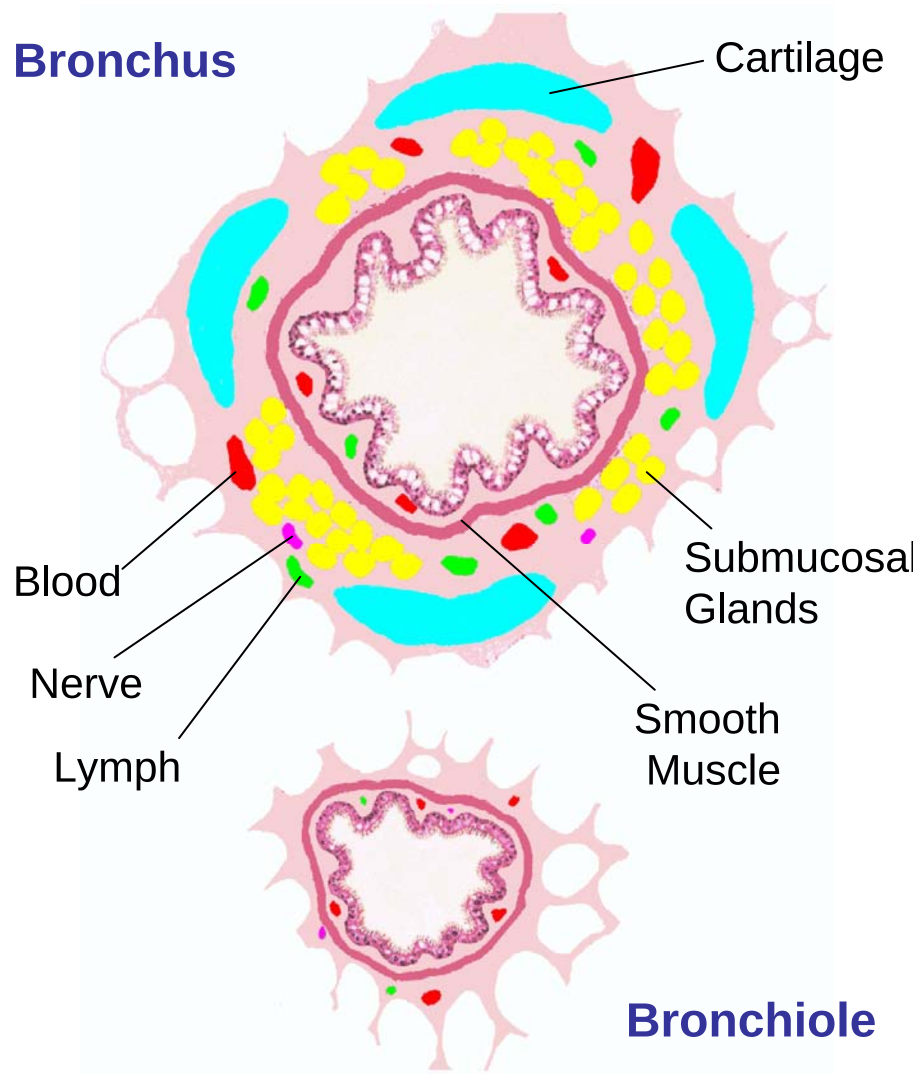
Physiology

- Contributes most of the airway resistance

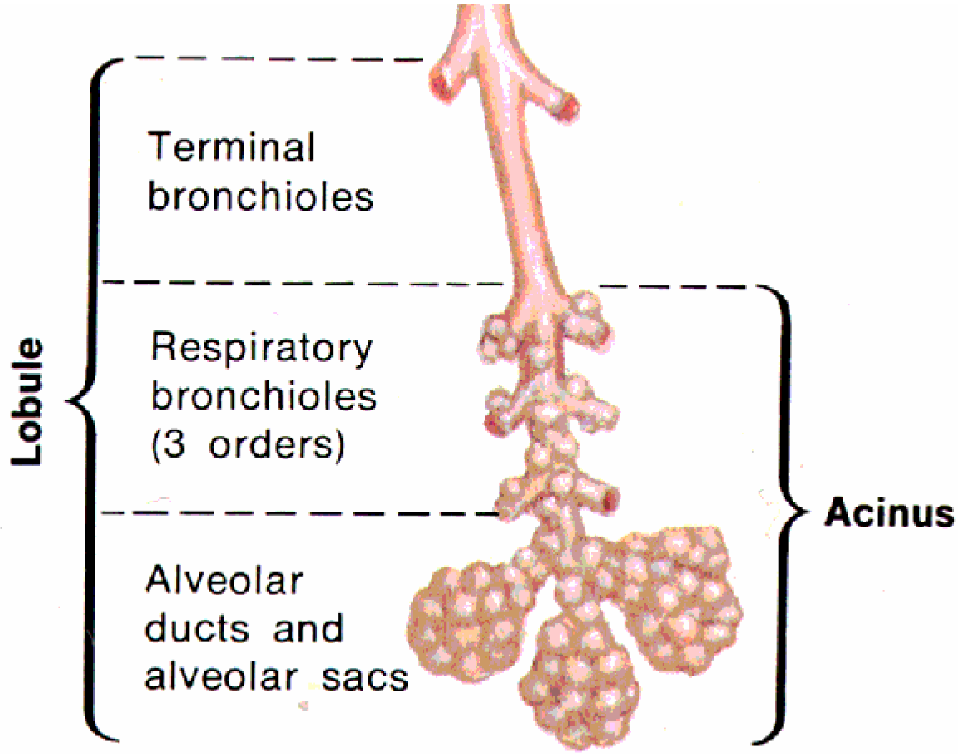
Adapted from: F.H. Netter, Respiratory System, Ciba Geigy, 1992

Conducting Airways - Bronchi and Bronchioles





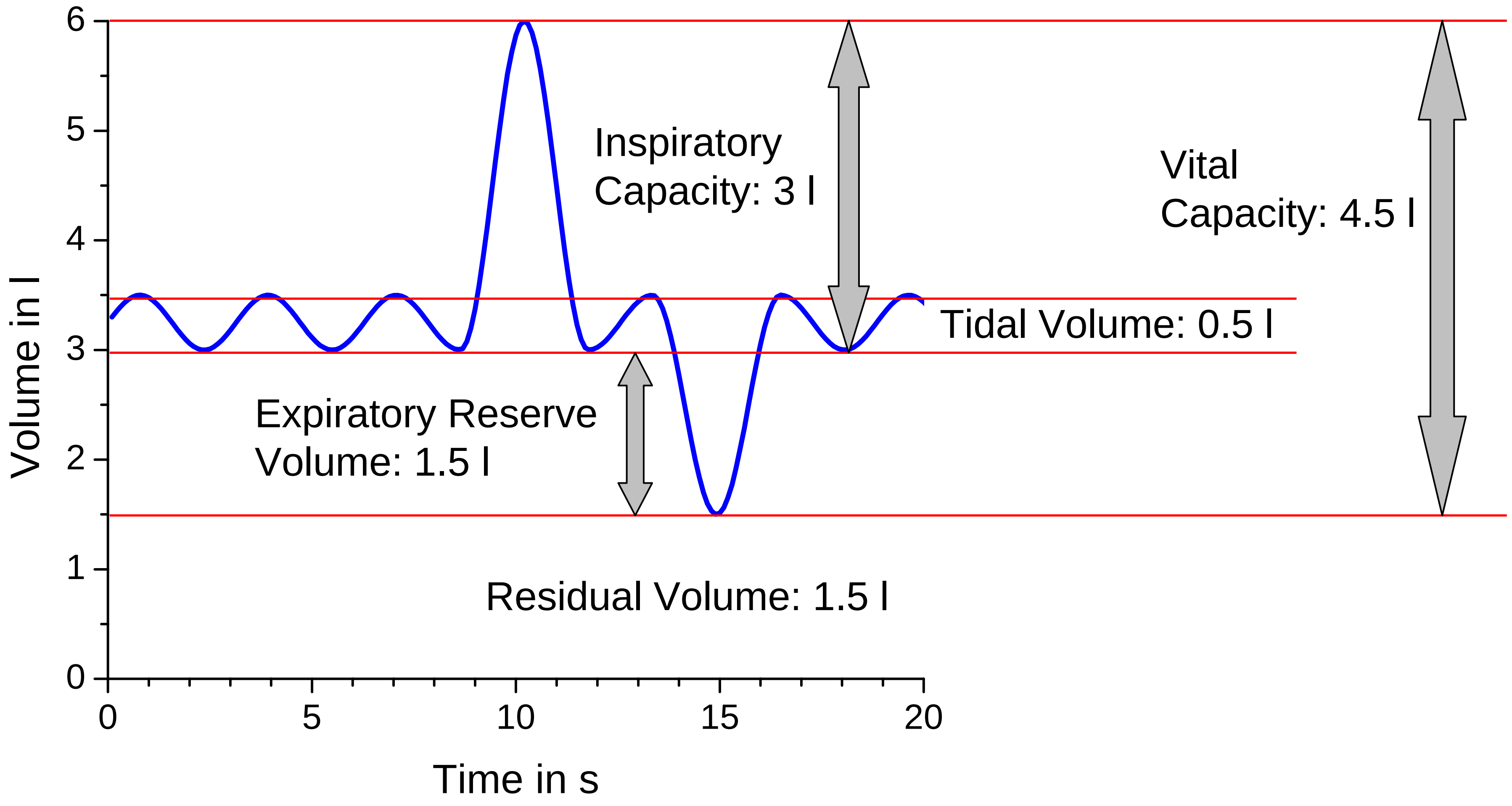
Respiratory Zone



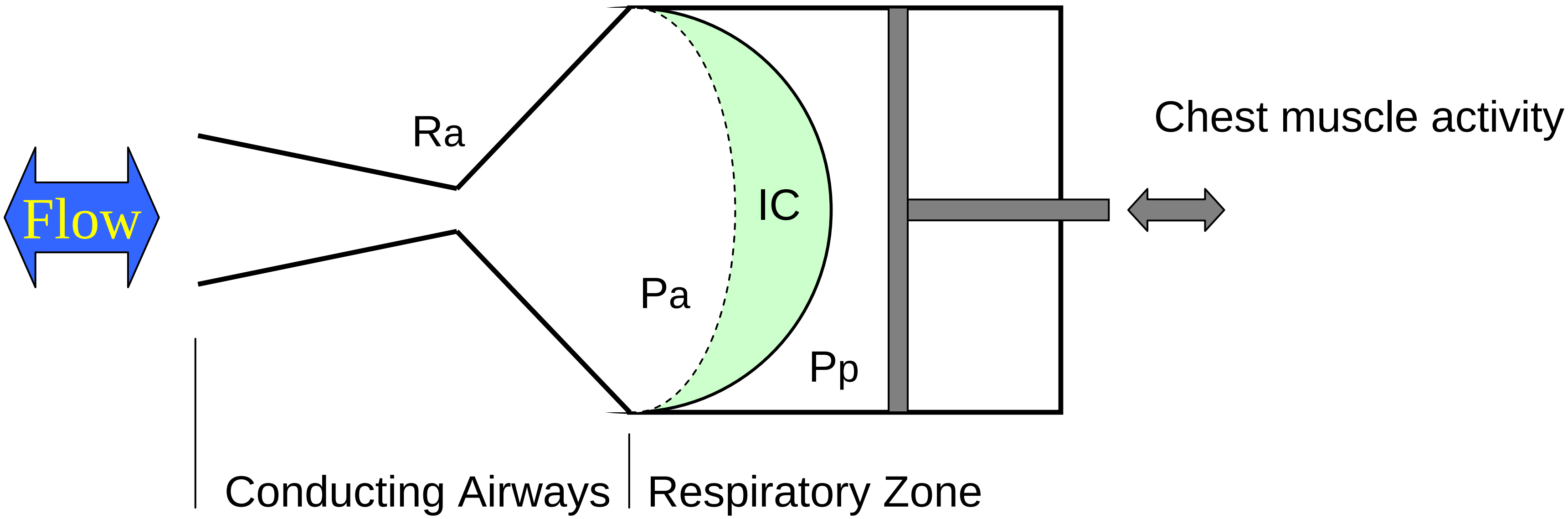
- No cartilage, cilia or mucus
- Few longitudinal elastic fibers and some smooth muscle
- 300 million alveoli provide a large surface area (100 m^2) separated from blood flow by a thin tissue layer.
- The entire blood volume of the body passes through the lungs each minute.

Adapted from: F.H. Netter, Respiratory System, Ciba Geigy, 1992

Lung Volumes



Breathing - Mechanical Analogy

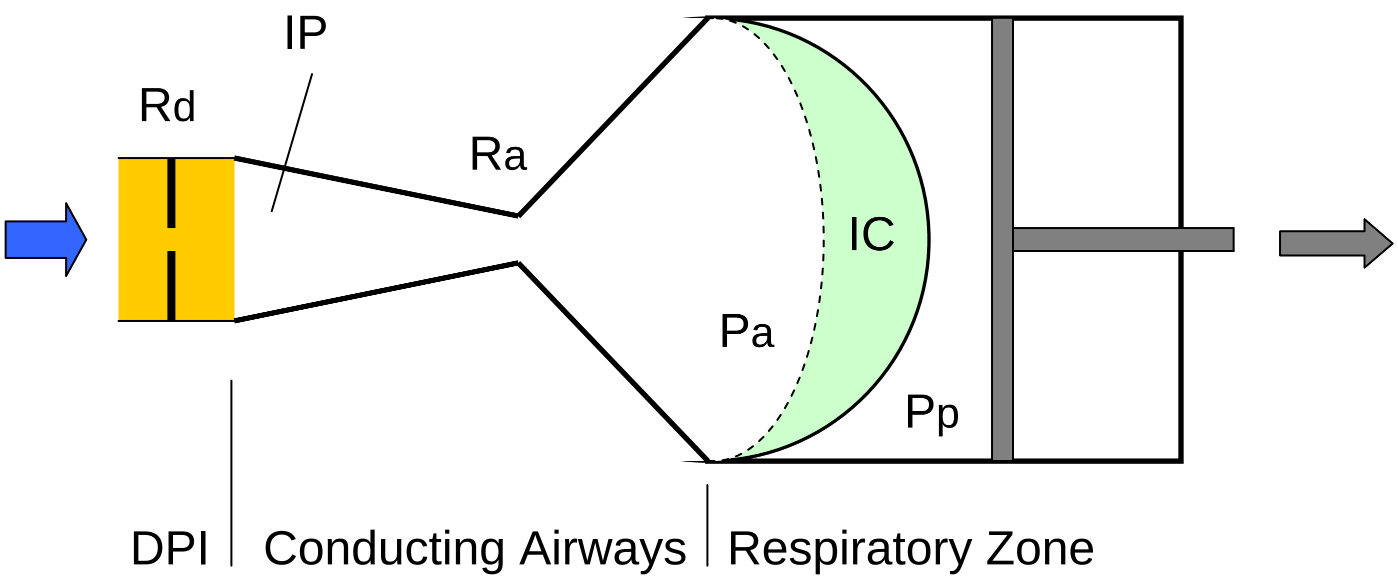


Flowrate: $$Q = \frac{\sqrt{Pa}}{R_a}$$

Ra: Airway Resistance
Pp: Pleural Pressure (Drop)
Pa: Alveolar Pressure (Drop)

IC: Inspiratory Capacity

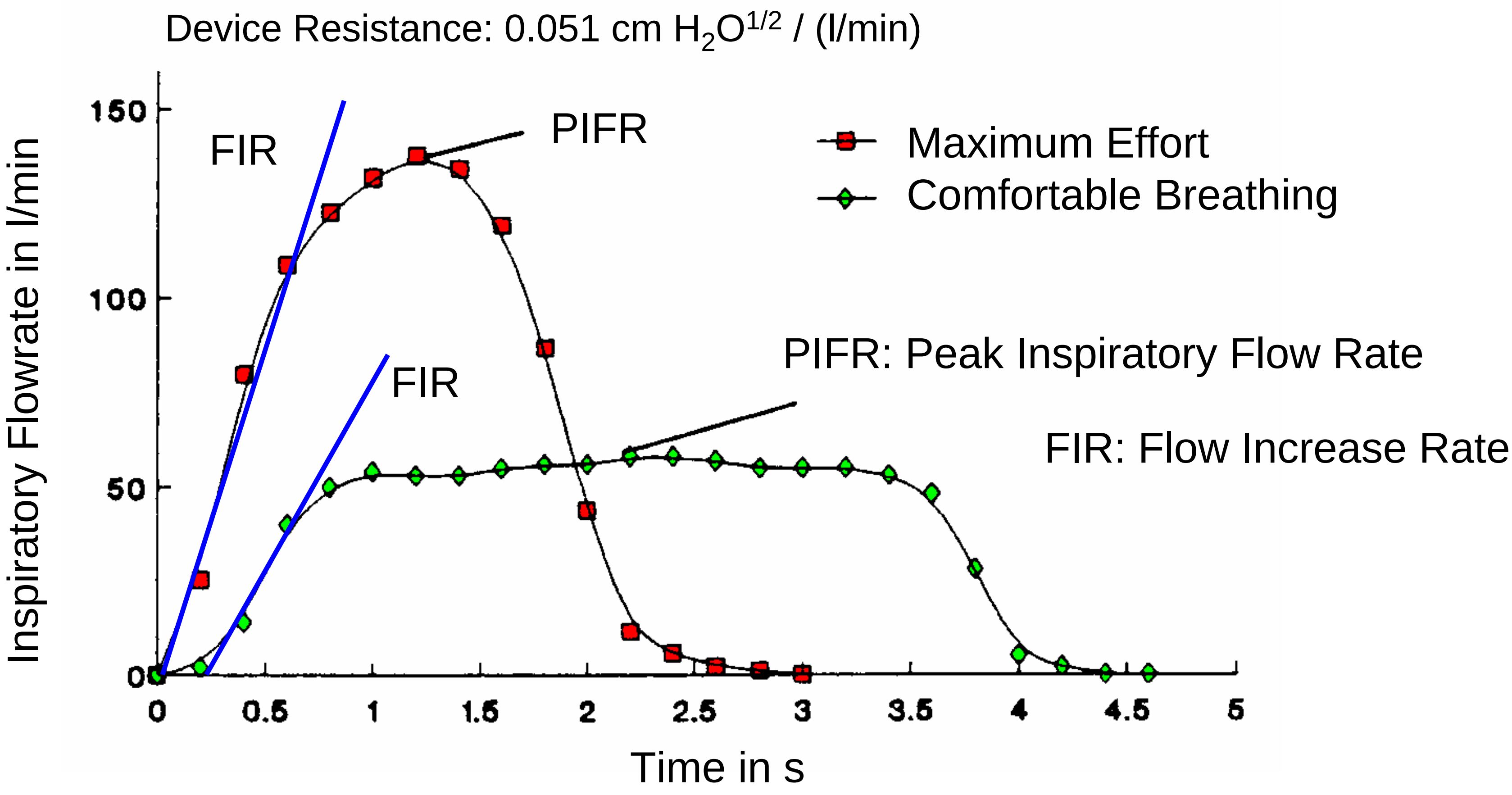
Inspiration through a DPI - Mechanical Analogy



Flowrate: $$Q = \frac{\sqrt{IP}}{R_d}$$, Rd >> Ra

Rd: Device Resistance
Ra: Airway Resistance
Pp: Pleural Pressure (Drop)
Pa: Alveolar Pressure (Drop)
IP: Inspiratory Pressure (Drop)
IC: Inspiratory Capacity

Breathing Profile, Flow versus Time



Adapted from: Clark and Hollingworth, Journal of Aerosol Medicine, **6**, 99, 1993

Outline

- Anatomy and Physiology of the Respiratory System
- **Deposition and Pharmacology**
- Delivery and Dispersion Devices
- Powder Manufacture
- Particle Engineering
  - Understanding the Spray Drying Process
  - Designing Dispersibility
  - Designing Physical Stability
  - Encapsulation

Aerosol Transport – Aerodynamic Diameter

The aerodynamic diameter , d_a, of a particle is the diameter of a sphere with a density of 1 g/cm^3 having the same gravitational settling velocity as the particle.

Gravitational Force

$$F_{Gr} = m_p g \,,$$

Drag Force (Stokes Law, Re < 1))

$$F_D = \frac{3\pi\eta v d_g}{C_C}$$

Settling velocity:

$$v_s = \frac{\rho_p d_g^2 g C_C}{18\eta}$$

Cunningham Slip Correction Factor corrects for non-continuum conditions. (P in kPa, d in µm)

$$C_C = 1 + \frac{1}{Pd}\left(15.39 + 7.518 e^{-0.0741 Pd}\right)$$

d_a is derived equating the settling velocity of the particle and the reference sphere:

$$d_a^2 = \frac{\rho_p C_C}{\rho_{ref} C_{C,ref}} d_g^2$$

$$\boxed{d_a = \sqrt{\rho_p}\, d_g}$$

Assuming that the slip correction factors are nearly identical and using ρ in g/cm^3:

Stokes Number and Impaction Parameter

The dimensionless Stokes number is the ratio of the stopping distance and a characteristic dimension of the gas flow. It describes how well particles are able to follow the gas flow.

$$Stk = \frac{s}{x} = \frac{v_0 \tau}{x} \qquad \tau = \frac{d_a^2 C_C}{18\eta}$$

The stopping distance is the initial velocity of a particle times the relaxation time.

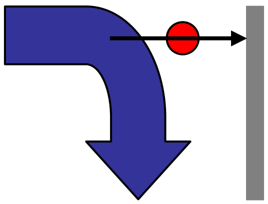
For the impaction of a gas jet onto a surface the characteristic dimension is the jet radius. The particle velocity is assumed to be the same as the gas velocity.

$$\boxed{Stk = \frac{v d_a^2 C_C}{9 \eta d_j}}$$

$$K = d_a^2 Q = Stk \cdot \frac{18\eta}{C_C x^3} \quad (13)$$

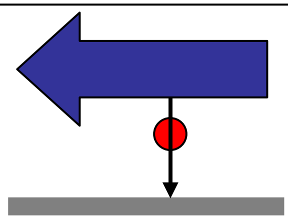
For lung deposition a related parameter, called impaction parameter or inertial parameter, is often used, where Q is the inspiratory flow rate. This is less accurate, because it assumes a fixed geometry.

Lung Deposition - Mechanisms



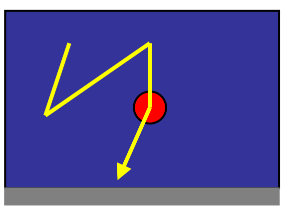
Impaction

Primary mechanism for big particles and upper airways



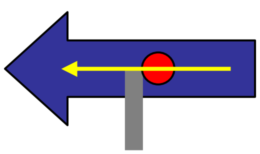
Sedimentation

More important in smaller airways and affected by breath-hold



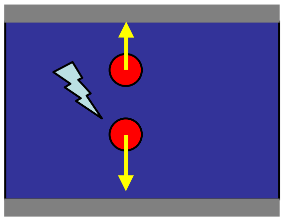
Diffusion

Primary mechanism for small particles in the respiratory zone



Interception

Important for non-spherical particles



Electrostatic Precipitation

Plays a role in triboelectrically charged aerosol

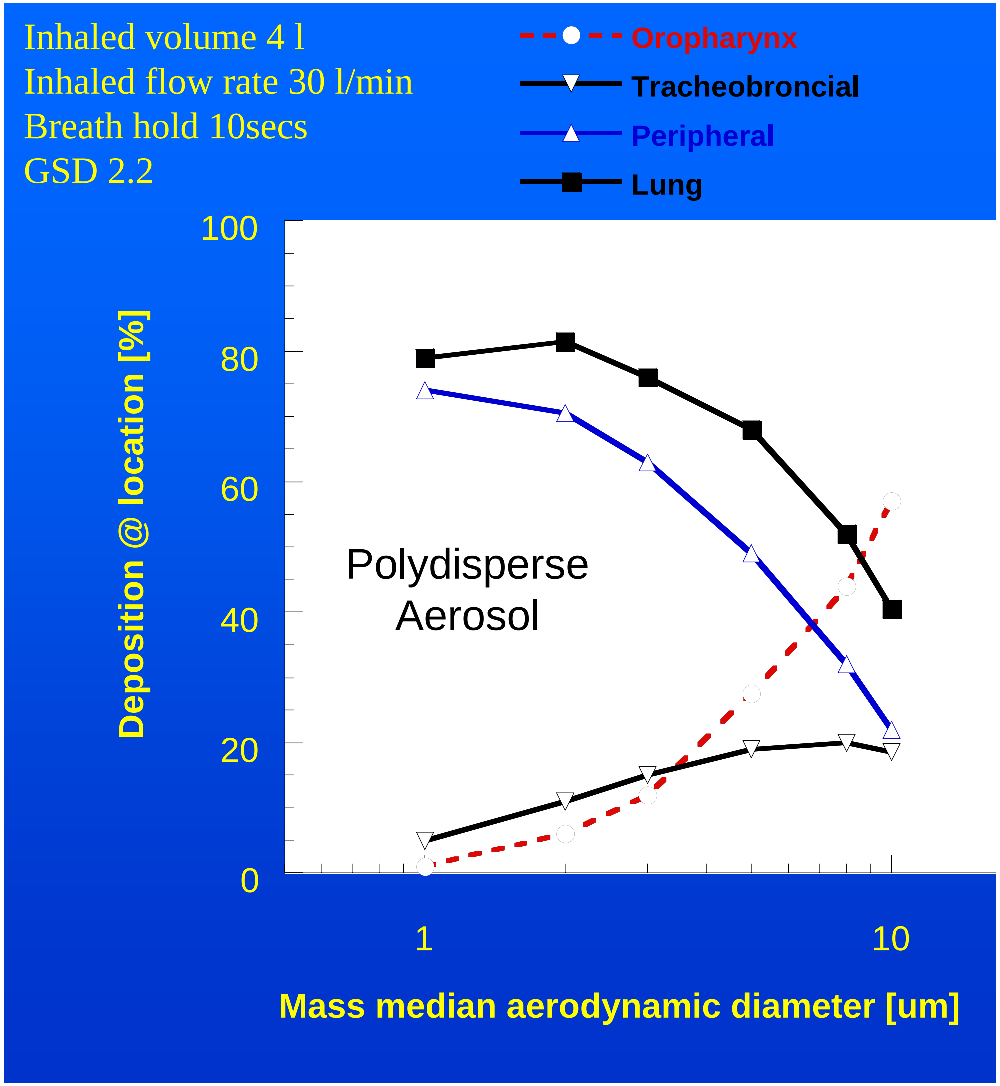
Factors Affecting Lung Deposition

- Aerodynamic particle diameter
  - Primary aerodynamic particle diameter
  - State of agglomeration
  - Hygroscopic growth / droplet evaporation
- Inspiratory flow
  - Flow increase rate
  - Peak inspiratory flow rate
  - Inspiratory capacity
  - Breath hold
- Lung volume
- Aerosol concentration and initial velocity
  - Inhalation device design
  - Delivered dose

Determined by

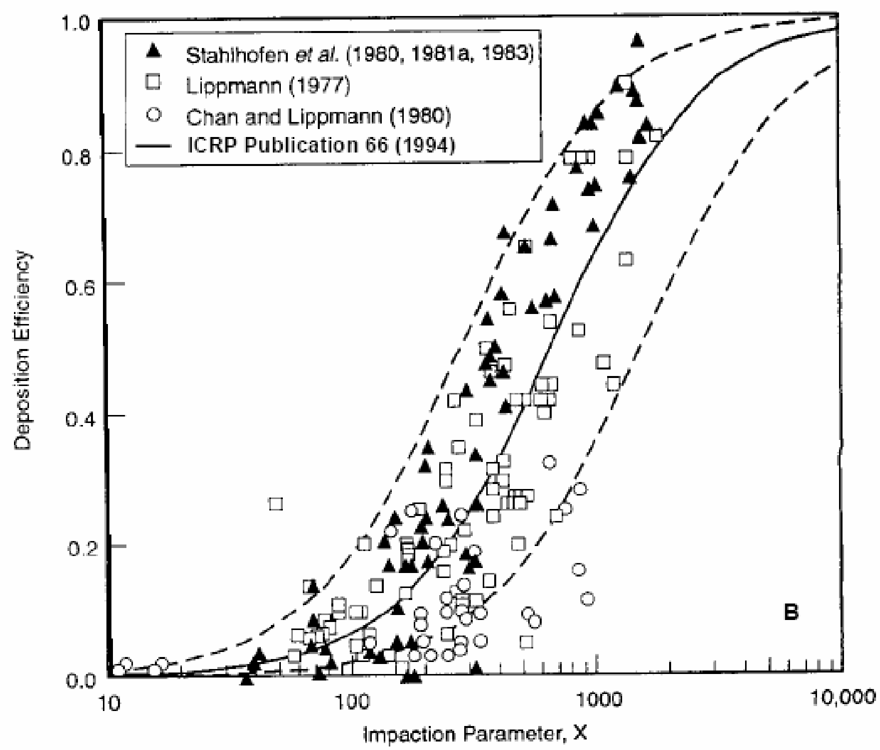
- Formulation
- Delivery Device
- Patient
  - Gender
  - Age
  - Training
  - Disease state
  - Inspiratory Effort

Deposition as a Function of Particle Size and Flow Rate



Extrathoracic Deposition

Particles inhaled through a mouthpiece

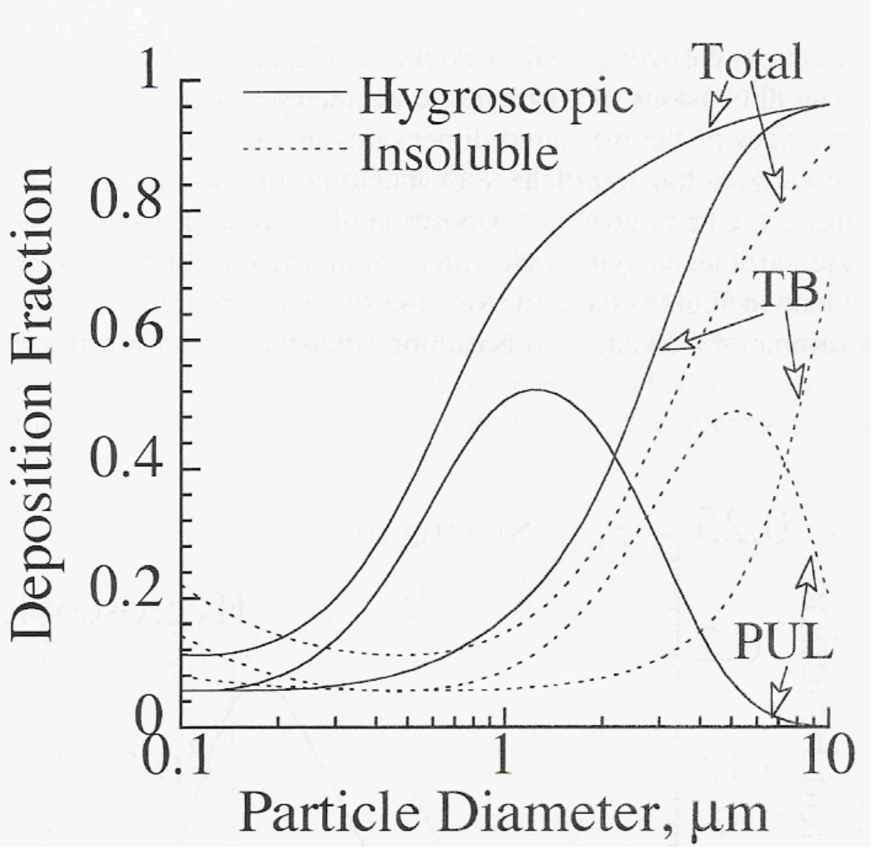


$X = d_a^2 Q^{0.6} V_T^{-0.2}$ [$\mu m^2 cm^{1.2} s^{0.6}$]

After Clark & Egan, J Aerosol Sci., **25**, 175, 1994; ICRP Publication 66, 1994

Hygroscopicity Influences Deposition

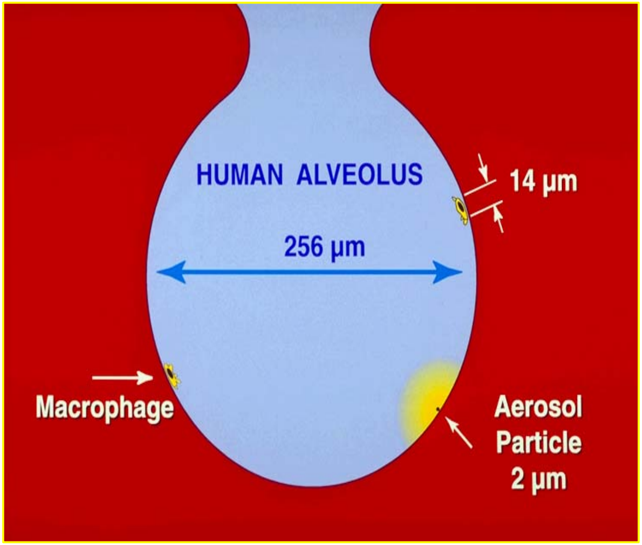
Regional and Total Deposition
Oral Breathing

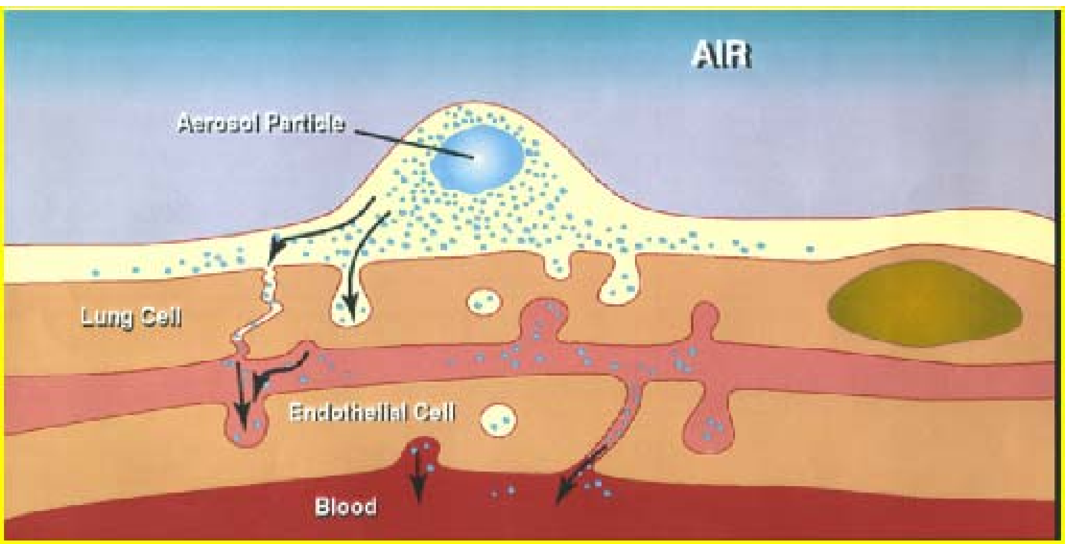


Numerical model results
Tidal volume: 625 ml
Breathing frequency: 15 / min
Monodisperse NaCl particles

Ashgarian, B. Aerosol Sci Technol **38**, 938, 2004

Pharmacology - Systemic Drug Delivery





Transport Across the Alveolar Wall

A typical aerosol dose (1 – 50 mg) deposits only a few particles per alveolus onto a thin alveolar wall (200 nm)

Transport mechanisms

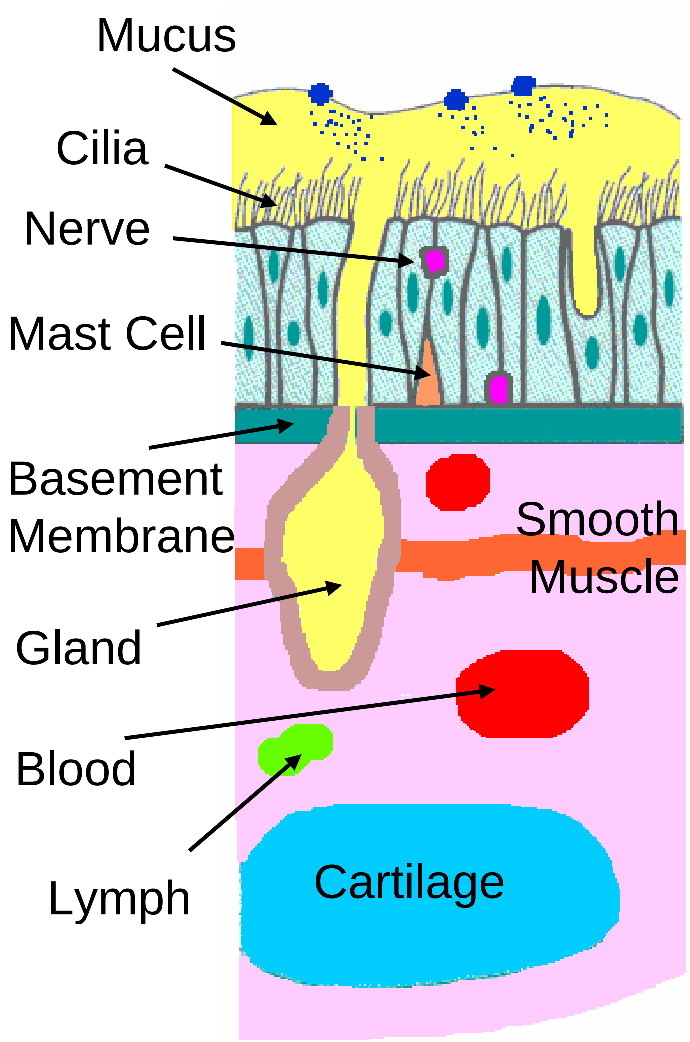
- Paracellular
  - Tight junctions - epithelium
  - Loose junctions - endothelium
- Transcellular
  - Diffusion
  - Transcytosis
  - Receptor mediated

Absorption kinetics are fast and depend on

- Molecular weight
- Solubility
- Partition coefficient.

Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002

Pharmacology - Local Drug Delivery



Across the Bronchiolar Epithelium

Transport mechanisms

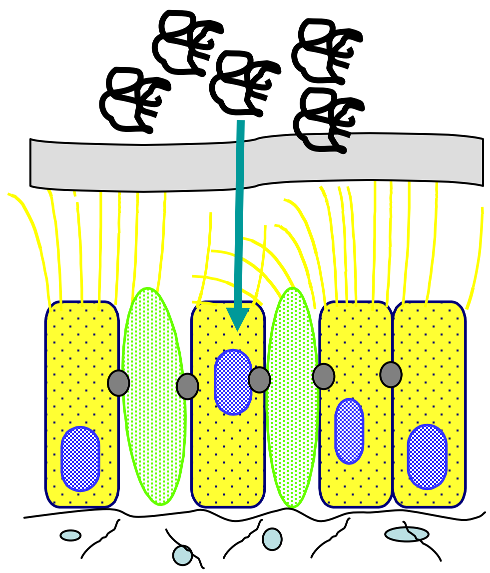
- Local aerosol concentration higher, because of smaller surface area
- Diffusion in mucus layer competes with mucociliary clearance, solubility is important
- Bioavaliability depends on location of local target
- Larger distances favor small molecules
- Active transport present, e.g. for immunoglobulins

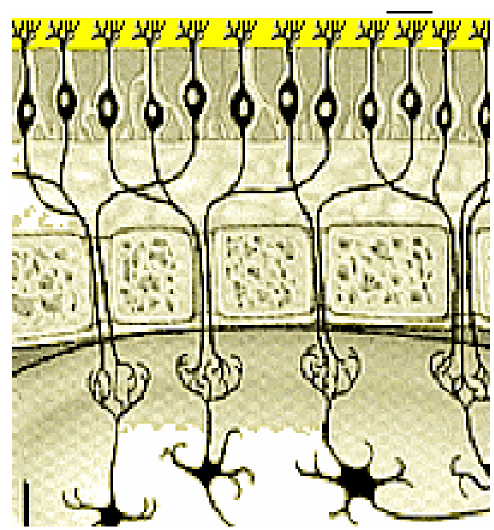
Absorption Kinetics

- Slower but targeting the conducting airways is difficult
- Interstitial tissue may act as reservoir

Pharmacology - Intranasal Drug Delivery

- Transport competes with mucociliary clearance.
- High bioavailability for small molecules (< 1 kDa) with rapid uptake (1 - 5 min)
- Low bioavailability (~ 1 – 5 %) for large molecules (>1 kDa) coupled with small surface likely requires penetration enhancers. Slower uptake (5 – 20 min)
- Drug delivery to the CNS via the olfactory region under investigation.
- Optimal droplet / particle size 20 - 100 µm to avoid lung deposition or dripping. Smaller particle sizes possible with bi-directional nasal delivery.





Olfactory Region

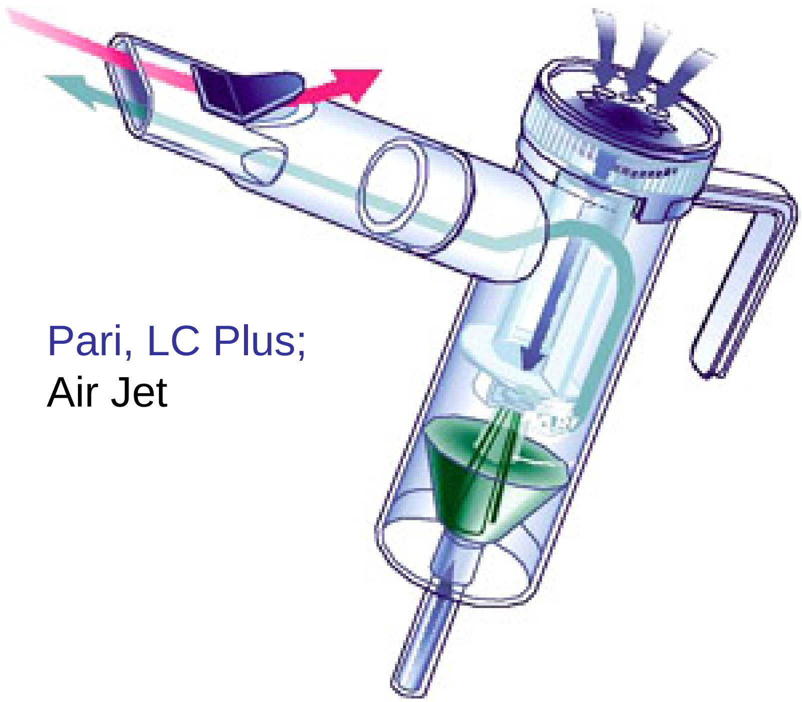
http://casweb.cas.ou.edu/pbell/Histology/Captions/Respiratory/106.nasal.epithel.40x.html

Outline

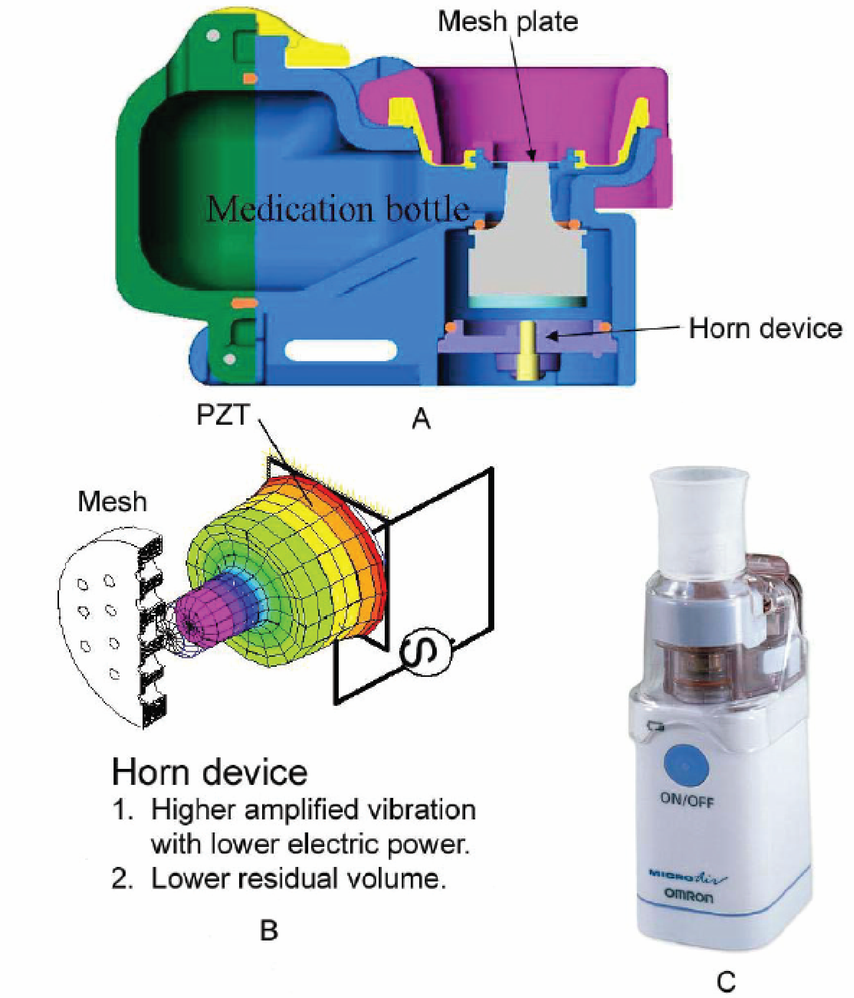
- Anatomy and Physiology of the Respiratory System
- Deposition and Pharmacology
- **Delivery and Dispersion Devices**
- Powder Manufacture
- Particle Engineering
  - Understanding the Spray Drying Process
  - Designing Dispersibility
  - Designing Physical Stability
  - Encapsulation

Delivery Devices – Nebulizers

Nebulizer Types



Pari, LC Plus;
Air Jet

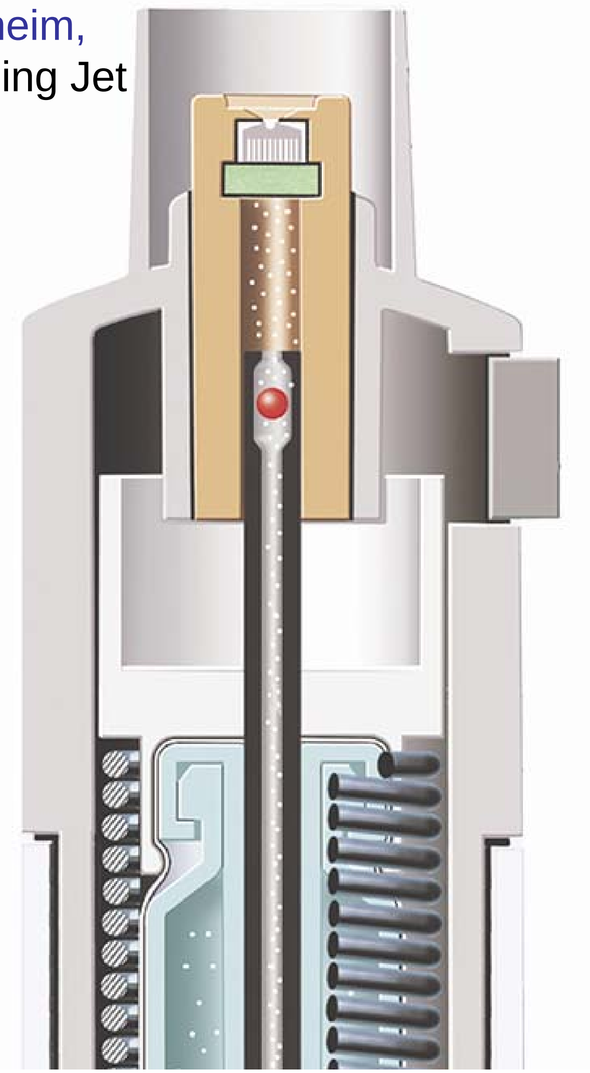


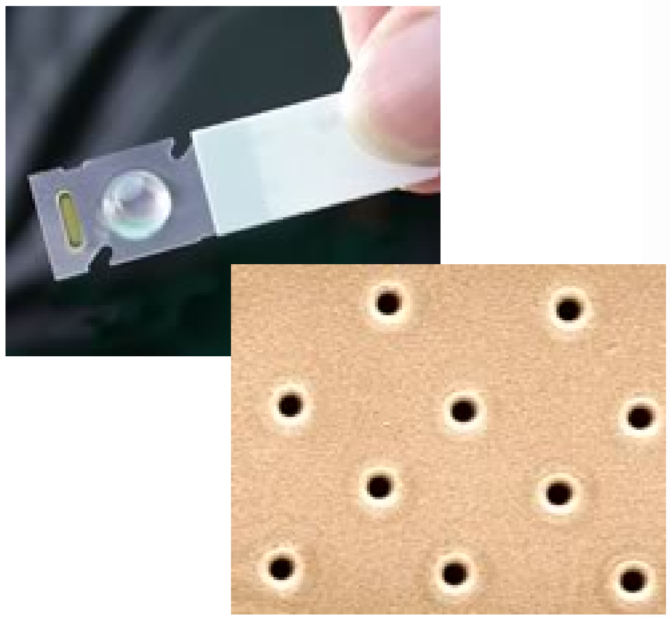
Omron, MicroAir; Ultrasonic / Vibrating Mesh

Delivery Devices - Nebulizers

Nebulizer Types

Boehringer Ingelheim, Respimat; Impinging Jet

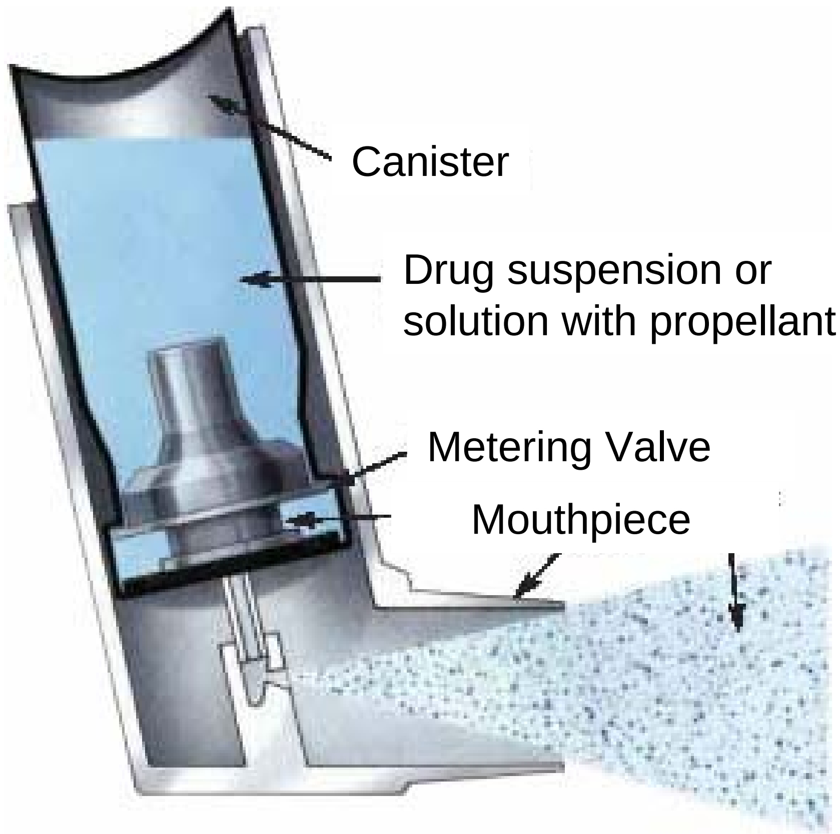


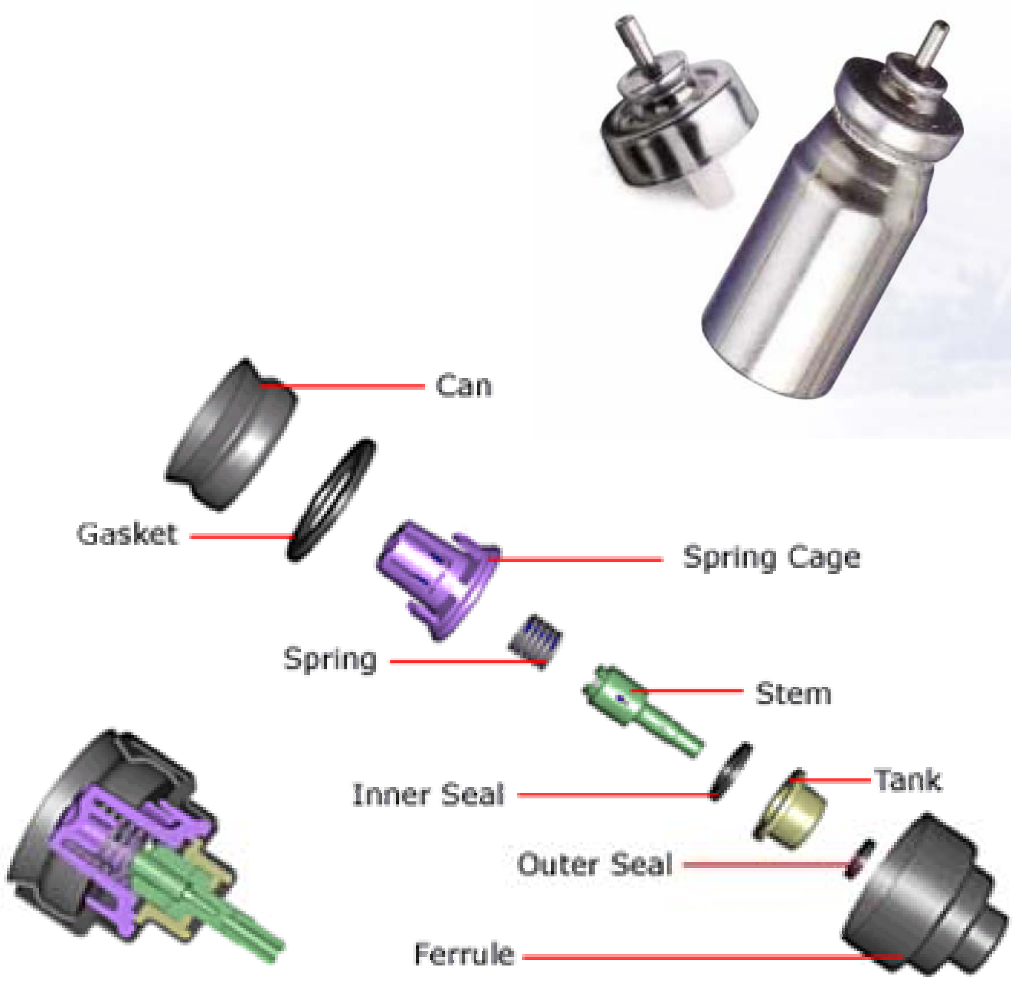


Aerogen / Nektar, OnQ; Micropump

Aradigm AERx; Microorifice / Disintegrating jet

Delivery Devices - Pressurized Metered Dose Inhalers



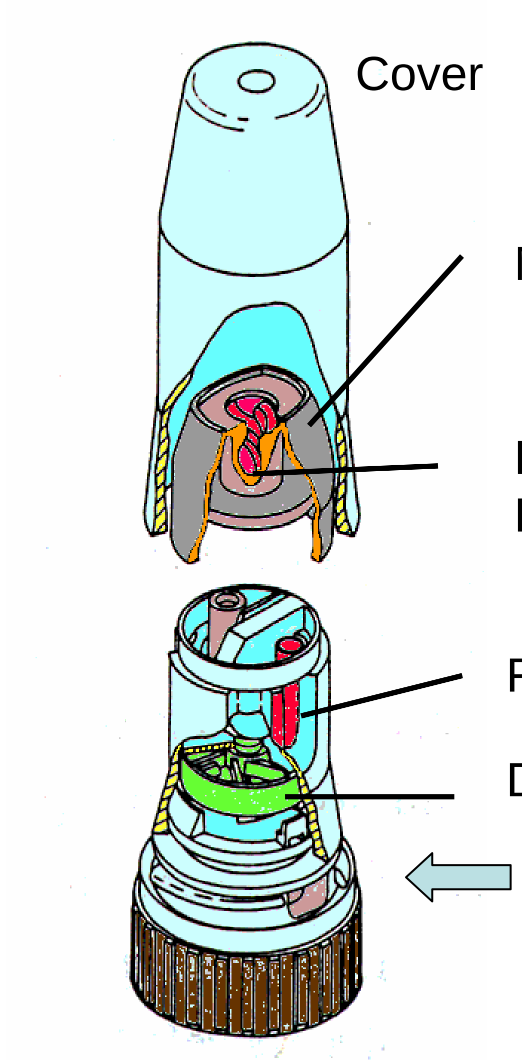


www.3m.com/us/healthcare/manufacturers/dds/jhtml/mdi_anatomy.jhtml; www.solvay-fluor.com

Dry Powder Inhalers - Classification

- By dosage form
  - Single Dose (blister, capsule)
  - Multi-Dose (reservoir, unit packaged)
- By source of dispersion energy
  - Active (compressed air)
  - Passive (patient inspiratory effort)
    - Uncontrolled
    - With patient control or feedback

Multi-dose Dry Powder Inhaler - Reservoir

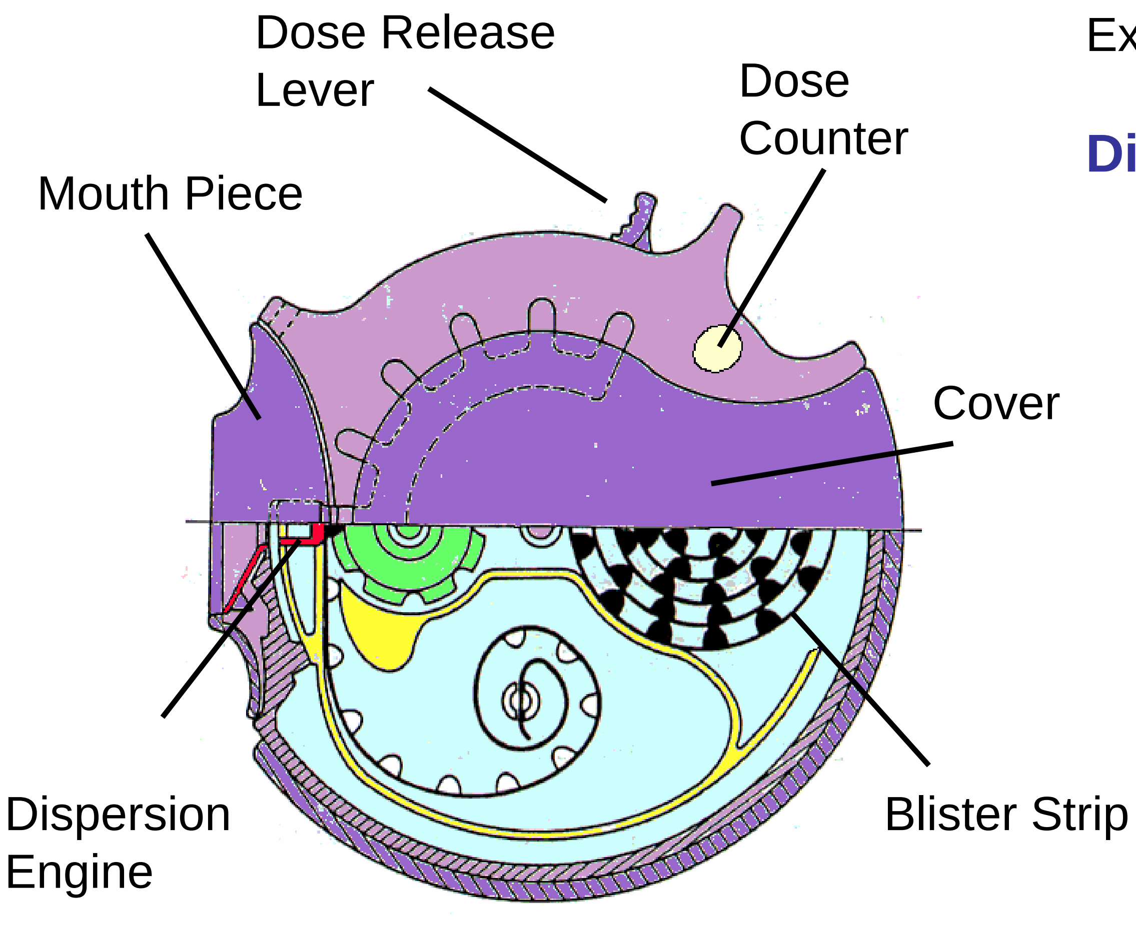


Example:

Turbuhaler (Astra Zeneca)

- Micronized neat drug or with lactose carrier
- 50 – 200 doses
- Dose counter
- ~ 50 mg reservoir capacity
- Flow rate dependent lung dose

Multi-dose Dry Powder Inhaler - Blister

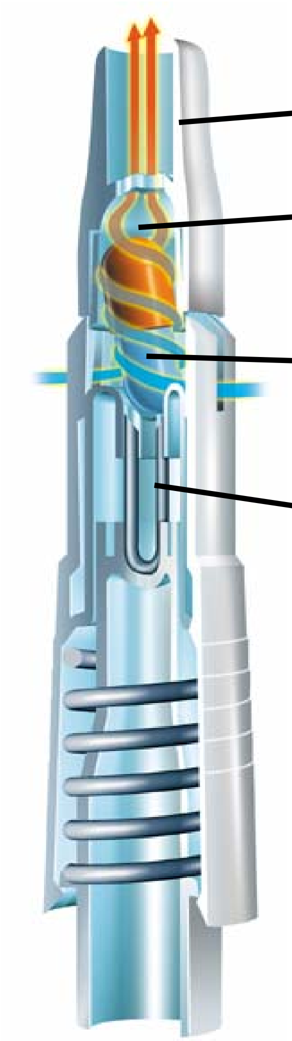


Example:

Diskus (GSK)

- Uses lactose carrier
- 60 metered doses
- Dose counter
- Small mouthpiece

Single-dose Dry Powder Inhaler - Capsule



Turbospin (PH&T)

- Several products in development using a similar concept
- Capsules contain ~ 5 to 50 mg of powder

- Moisture protection can be achieved by secondary packaging

Example: Spiriva capsules, Boehringer Ingelheim / Pfizer

Single-dose Active Dry Powder Inhaler - Blister

Nektar PDS

- Decouples inspiration and dispersion
- Uses compressed air for dispersion
- Foil blisters contain 2 – 5 mg of powder
- Aerosol is dispersed into collapsible holding chamber

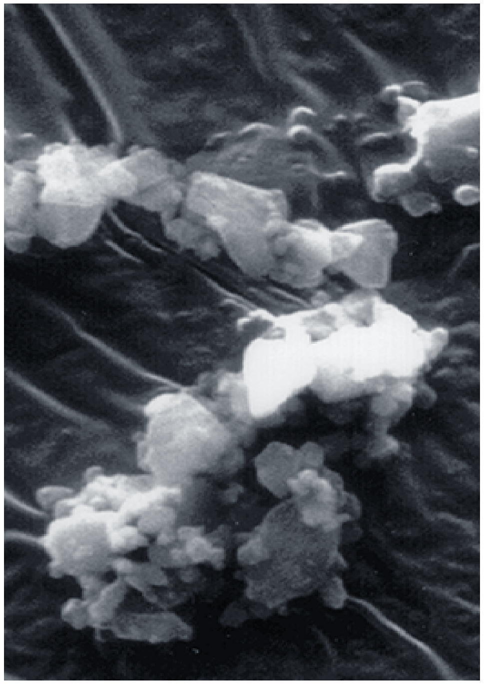
Outline

- Anatomy and Physiology of the Respiratory System
- Deposition and Pharmacology
- Delivery and Dispersion Devices
- **Powder Manufacture**
- Particle Engineering
  – Understanding the Spray Drying Process
  – Designing Dispersibility
  – Designing Physical Stability
  – Encapsulation

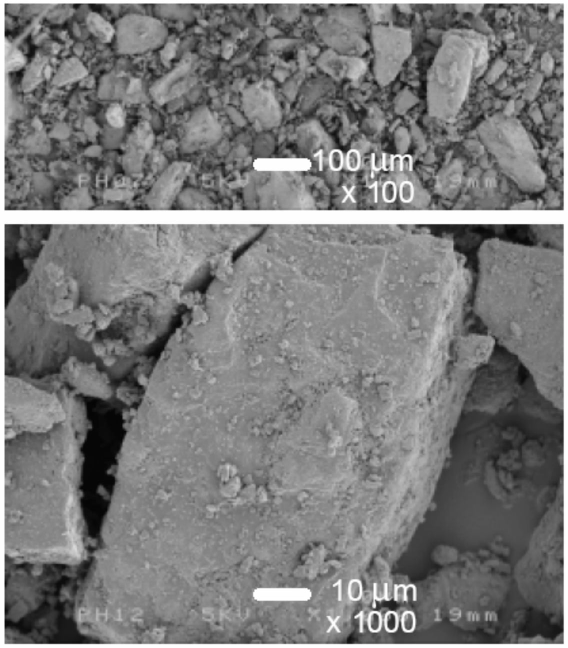
Powder Manufacturing Methods – Milling and Blending

Milling
- Jet-milling (dry)
- Homogenization (wet)
- Cryo-milling (cold)

Blending
- with larger carrier particles
- with smaller "force control agents"



Micronized Budesonide

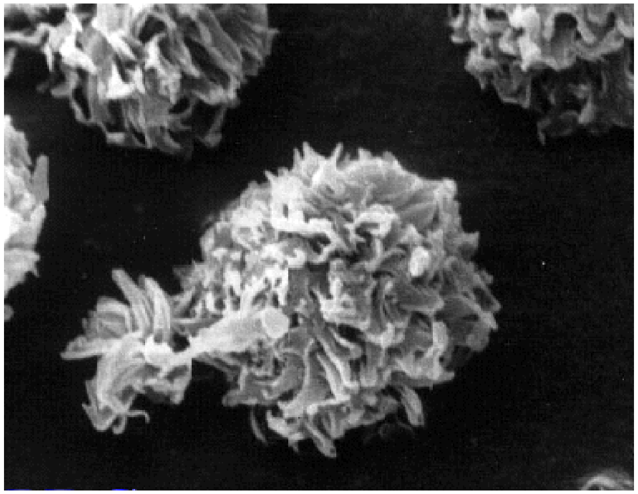


Lactose Blend

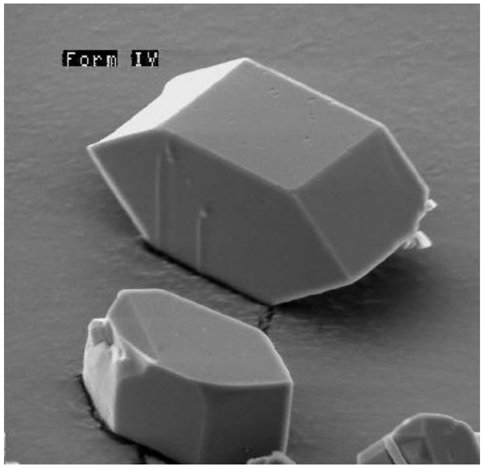
Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002

Powder Manufacturing Methods – Precipitation and SCF

Precipitation

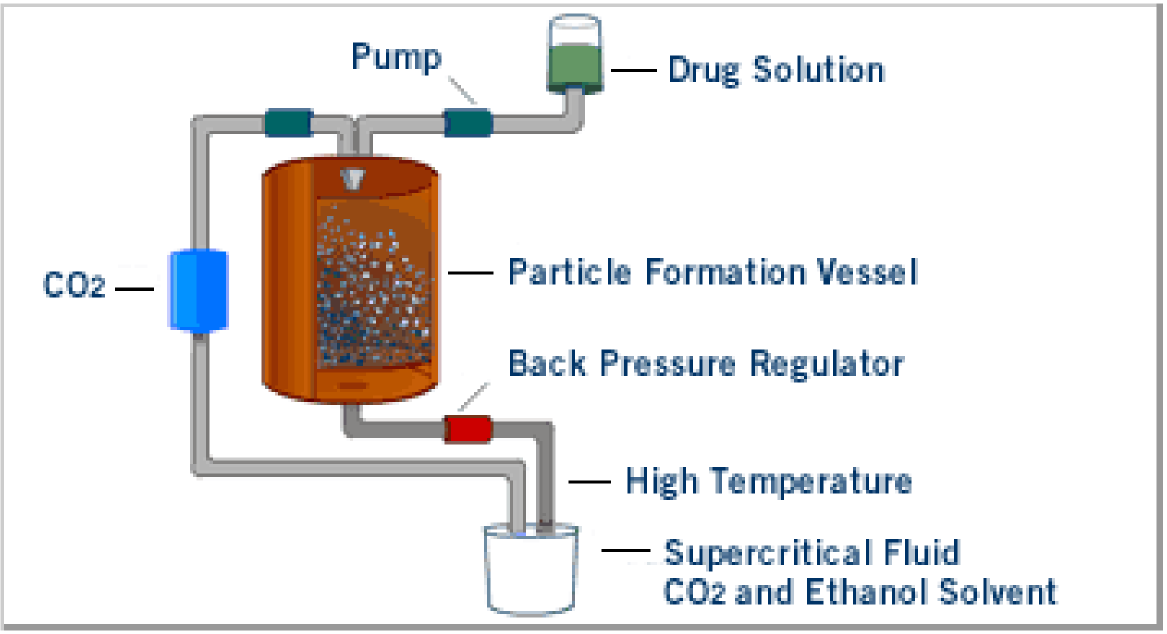


Example:
Mannkind Technospheres:
Self Assembling Particles
Precipitation induced by pH shift



Supercritical Fluid Particle Technology

Dispersion and solvent extraction by supercritical fluids

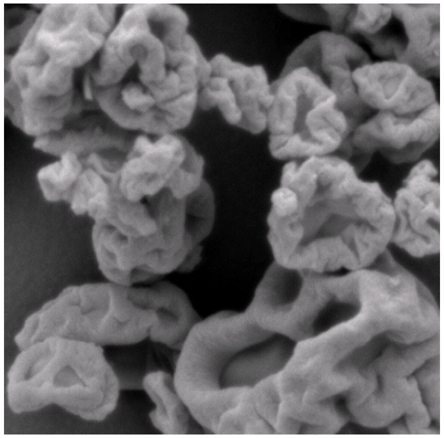


Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002; www.nektar.com

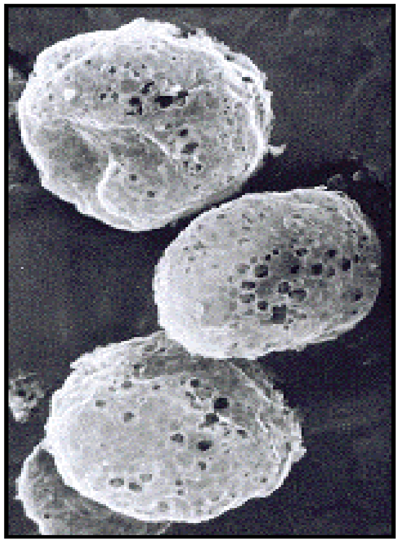
Powder Manufacturing Methods – Spray Drying

Spray Drying

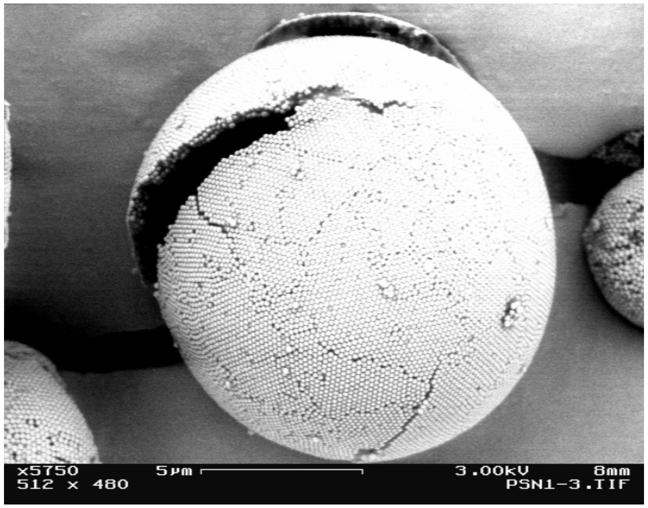
- •Solutions
- •Suspensions
- •Emulsion
- •Co-solvent
- •With blowing agent



Protein solution



With Blowing Agent



Nanoparticle suspension

http://people.deas.harvard.edu/~ntsapis/AIR.html

Spray Drying at Different Scales

Benchtop

Büchi 191
Evaporates 0.5 kg / h

Intermediate Scale

Niro Mobile Minor
Evaporates 7 kg / h

(Very) Large Scale

Kaolin Plant
Evaporates 16,000 kg / h

Outline

- Anatomy and Physiology of the Respiratory System
- Deposition and Pharmacology
- Delivery and Dispersion Devices
- Powder Manufacture
- **Particle Engineering**
  - **Understanding the Spray Drying Process**
  - **Designing Dispersibility**
  - **Designing Physical Stability**
  - **Encapsulation**

The Ideal Particle

Provides good dispersibility

- Low density, rough surface, hydrophobic surface

Provides long shelf life

- Excipients for chemical and physical stabilization

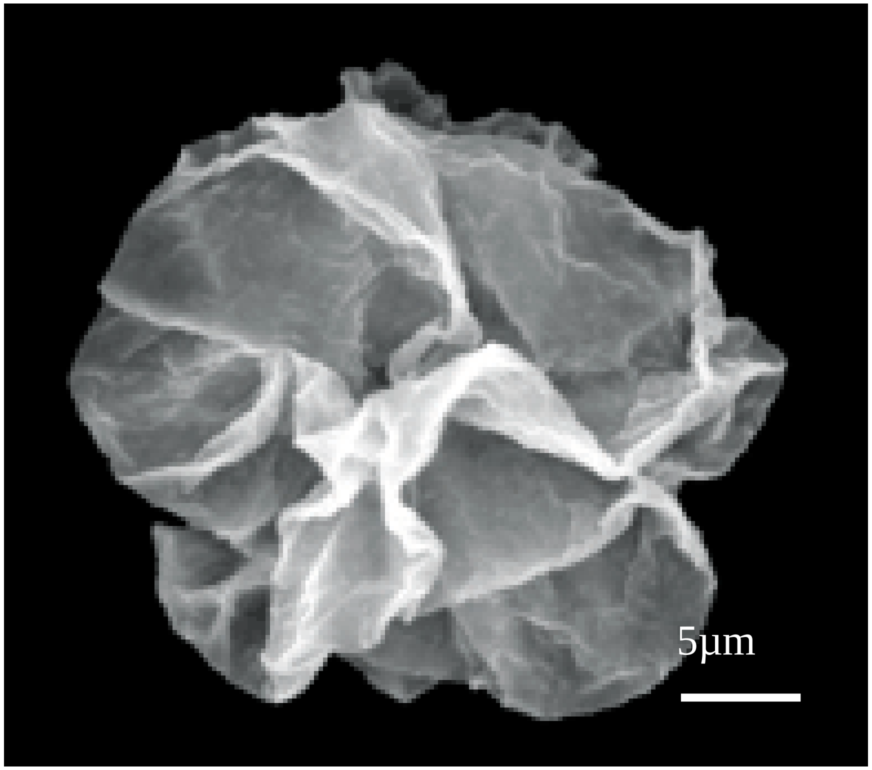
Provides environmental robustness

- Encapsulation
- Reduced hygroscopicity / low tendency to crystallize

Feasible for commercial development

- Reproducible, economical powder production
- Low product development costs

Example 1: Large Porous Particles (Alkermes / AIR)



- Large particles with small aerodynamic diameter

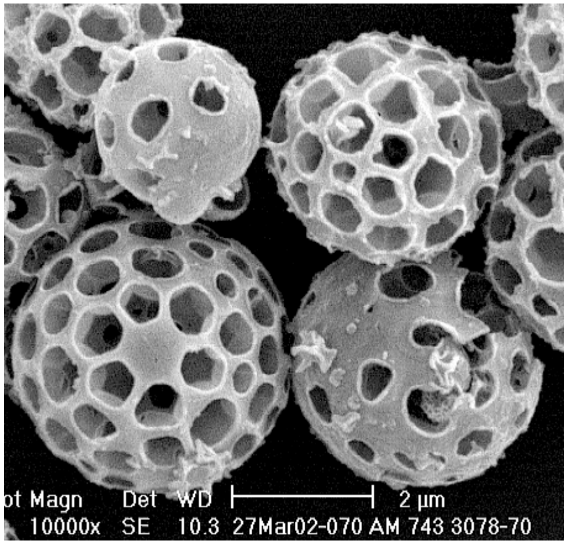
$$D_a = D_p \sqrt{\rho_e}$$

  Provide good dispersibility
- Lipid (DPPC) based
- May use additional excipients such as organic salts

- D_p = 5-30 µm
- D_a = 1-5 µm

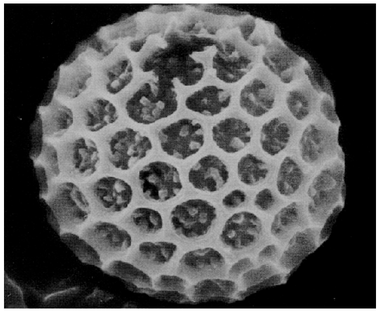
Edwards et al. **Large porous particles for pulmonary drug delivery.** *Science* 1997, **276**:1868-1871.

Example 2: Lipid Based Particles (Nektar Therapeutics)

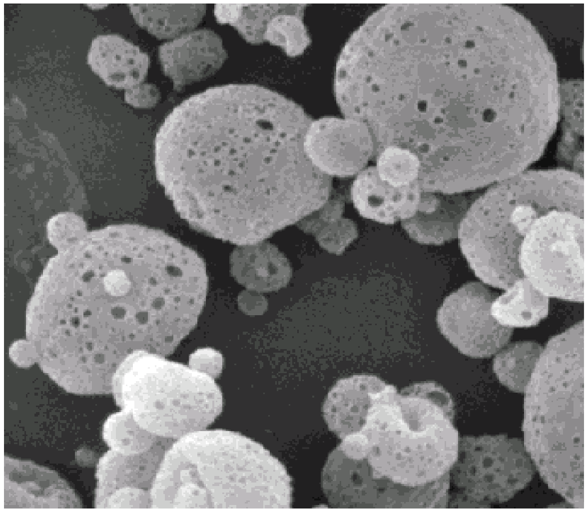


Small Molecule Formulation

- Small porous particles provide good dispersibility and facilitate transport to the peripheral lung
- Lipid (DSPC) based
- May use blowing agent to lower and control particle density



Mushroom Spore

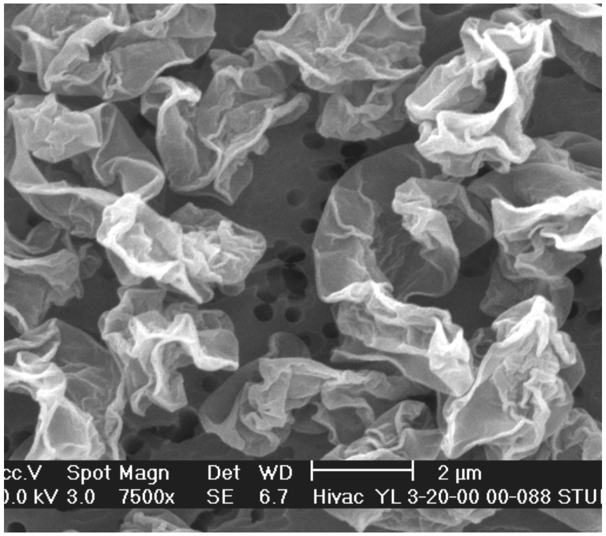


Calcitonin

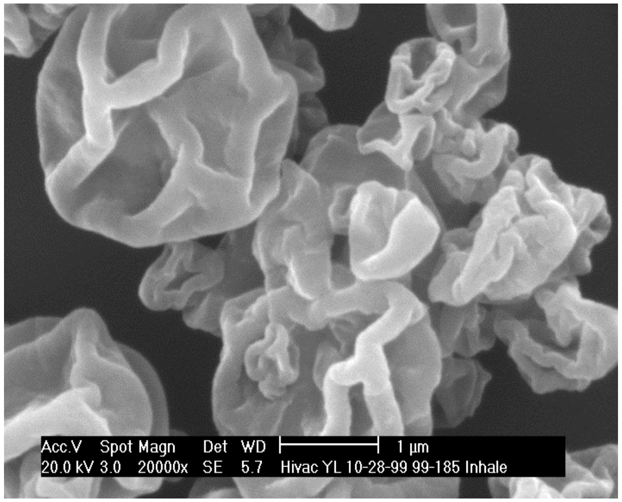
Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

Example 3: Amino Acid / Sugar Based Particles (Nektar)

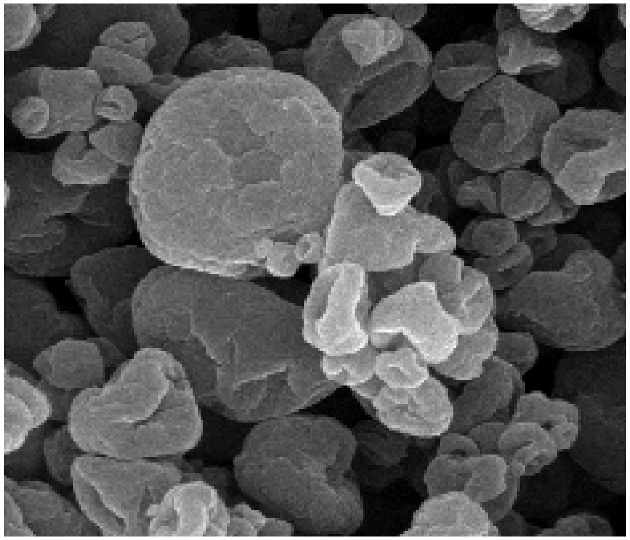
Trileucine Shell



Protein Formulation



Crystalline Amino Acid Shell

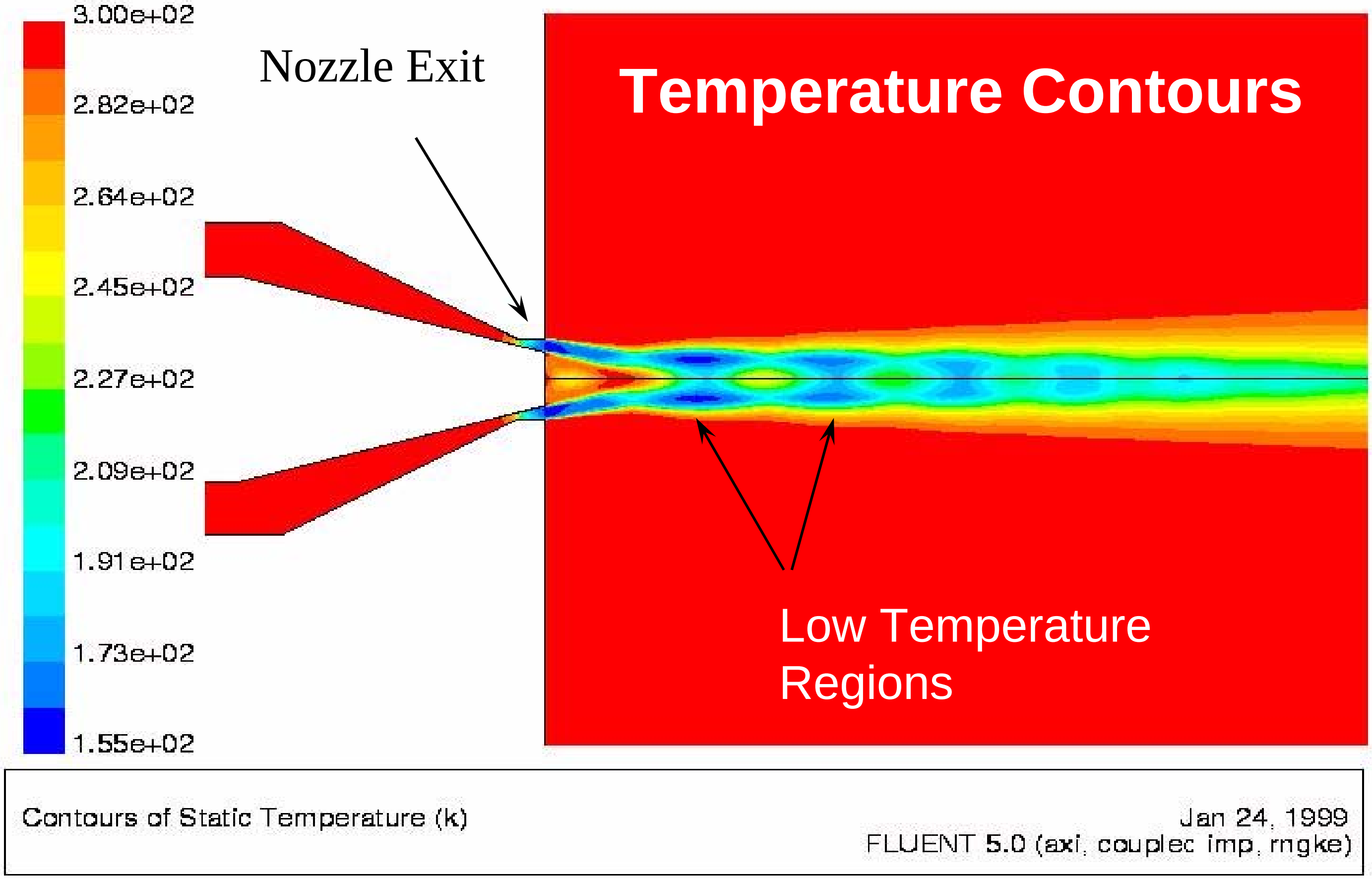


Typical Excipients

- Amino acids, di-, tripeptides
- Sugars
- Organic Salts

US Pat.: 6,685,967; 6,673,335; 6,589,560; 6,136,346, 6,372,258, 6,518,239

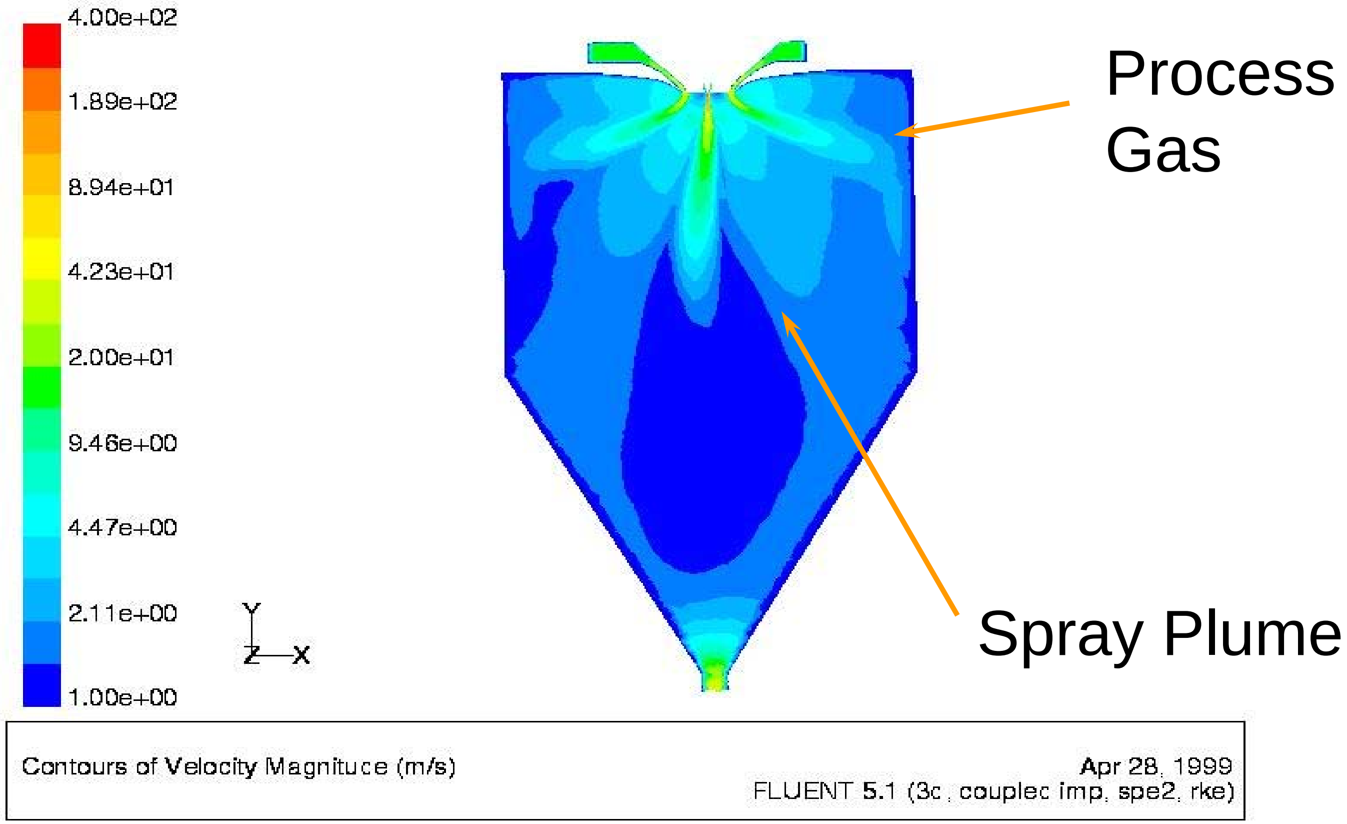
Understanding the Atomization Process



Droplets pass through a flow field with large temperature and velocity gradients.

Snyder, et al., 12th Annual Conf. on Liquid Atomization and Spray Systems. Indianapolis, IN, 1999

Spray Dryer Internal Gas Flow Field



The flow field in the spray dryer is inhomogeneous.

Snyder, et al., 12th Annual Conf. on Liquid Atomization and Spray Systems. Indianapolis, IN, 1999

Studying the Particle Formation Process

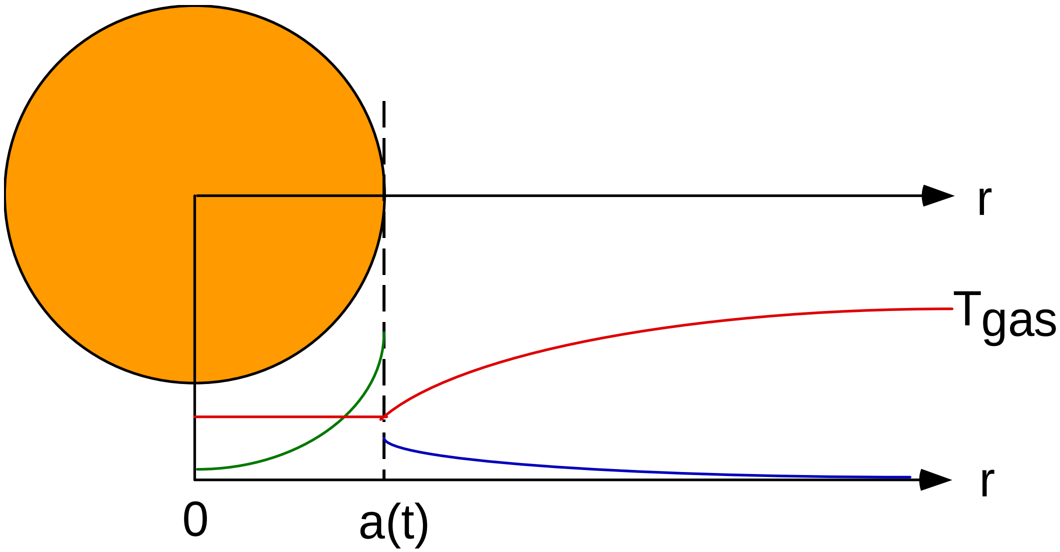
The two phase flow in a spray dryer is complex.
Heat and mass transfer processes are difficult to study *in situ*.

Approach:

Isolate and study relevant sub-processes in idealized environments

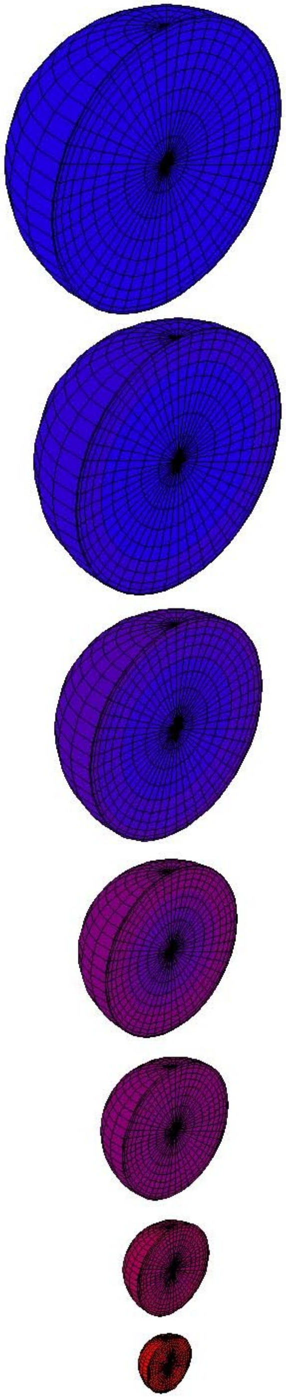
- Numerical model of droplet evaporation on single droplets in stagnant gas phase
- Analytical model for constant rate evaporation
- Experimental studies on monodisperse droplet drying in a laminar flow field

Numerical Model of Droplet Evaporation

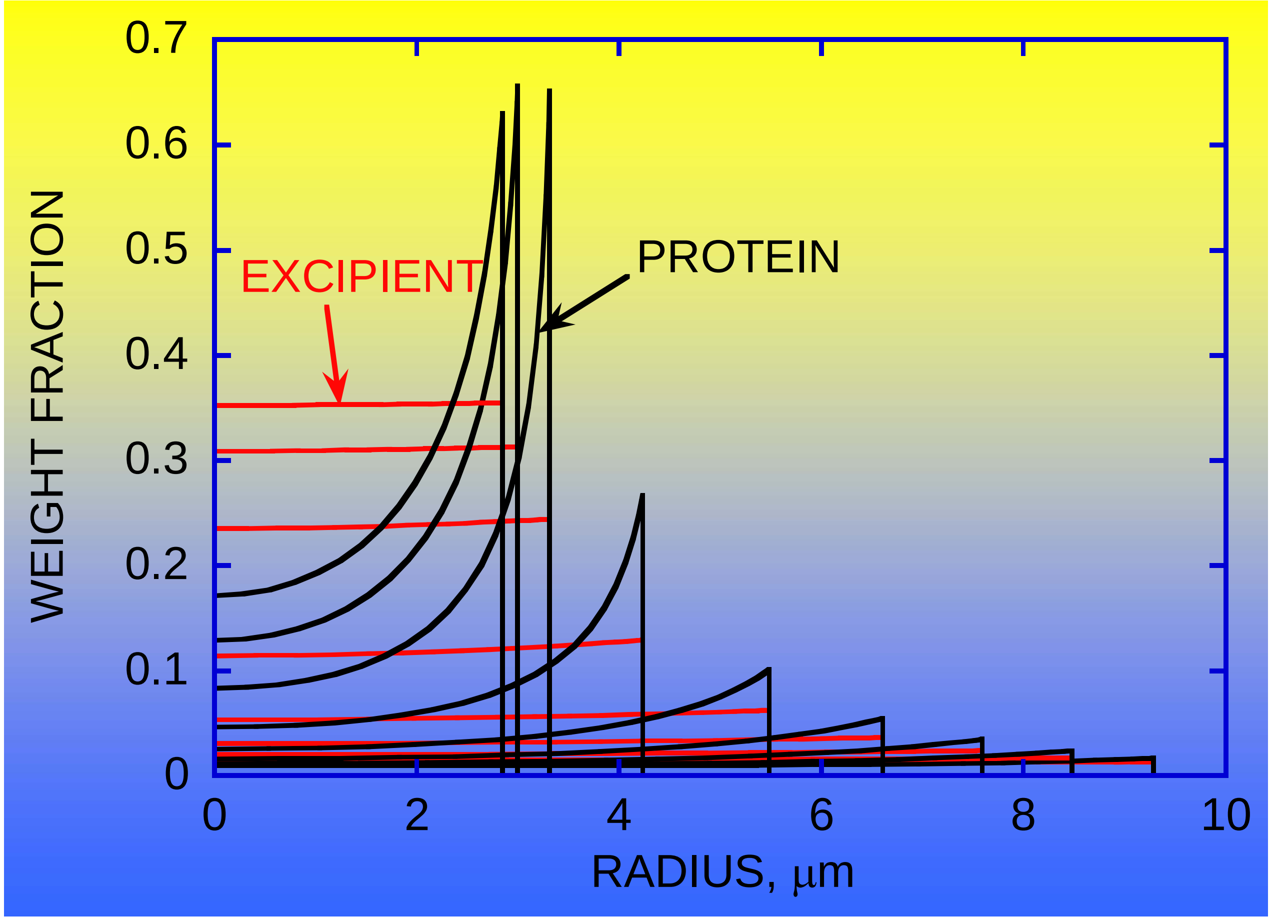


- Transient evaporation of a radially symmetric droplet
- Finite difference mesh moves with interface
- Concentration and temperature profiles in liquid and gas
- Temperature and concentration dependent material properties
- Multiple solutes and solvents
- Accounts for surface activity

Vehring, R.; Foss, W. R., et al. AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, 2002.



Internal Distribution of Components



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

Simplifying the Theoretical 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.

.

Solution

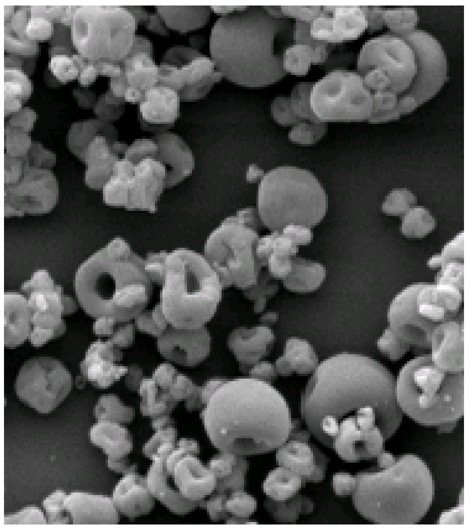
$$c=c_m\frac{\exp\left(-0.5\mathrm{Pe}R^2\right)}{3\int_0^1 R^2\exp\left(-0.5\mathrm{Pe}R^2\right)\mathrm{d}R} \quad , \qquad \mathrm{Pe}=-\frac{r_s\partial r_s}{D\partial t}=\frac{\kappa}{8D}$$

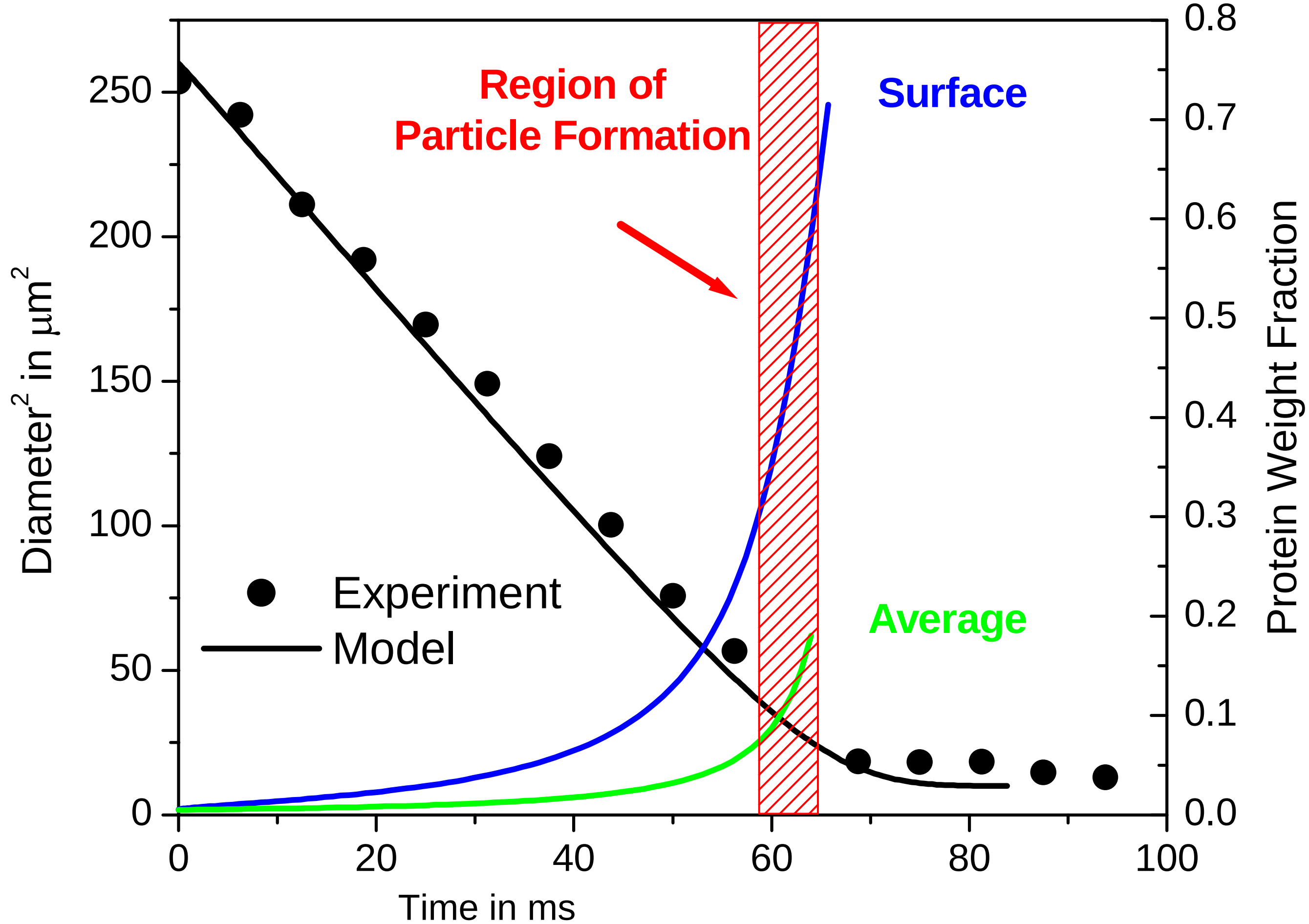
where the concentration is expressed as a function of the average concentration in the droplet, c_m. Pe is the Peclet number.

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

Evaporation Process for a Glycoprotein

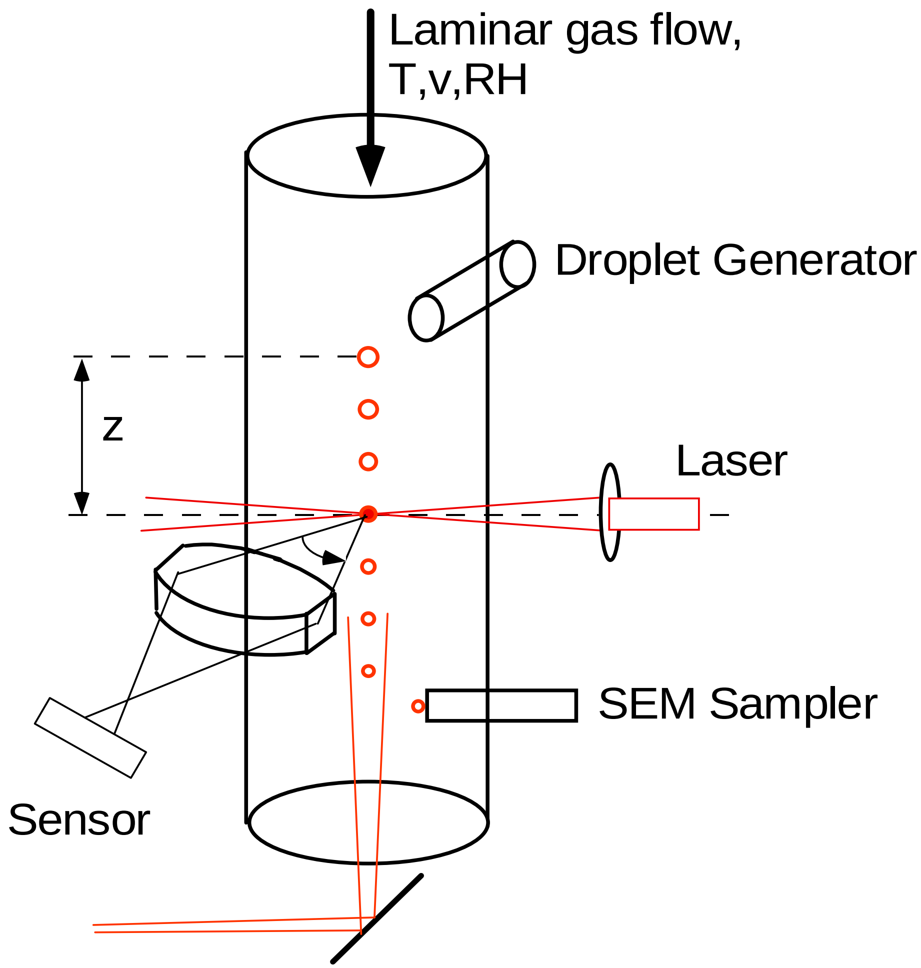
Pe = 10





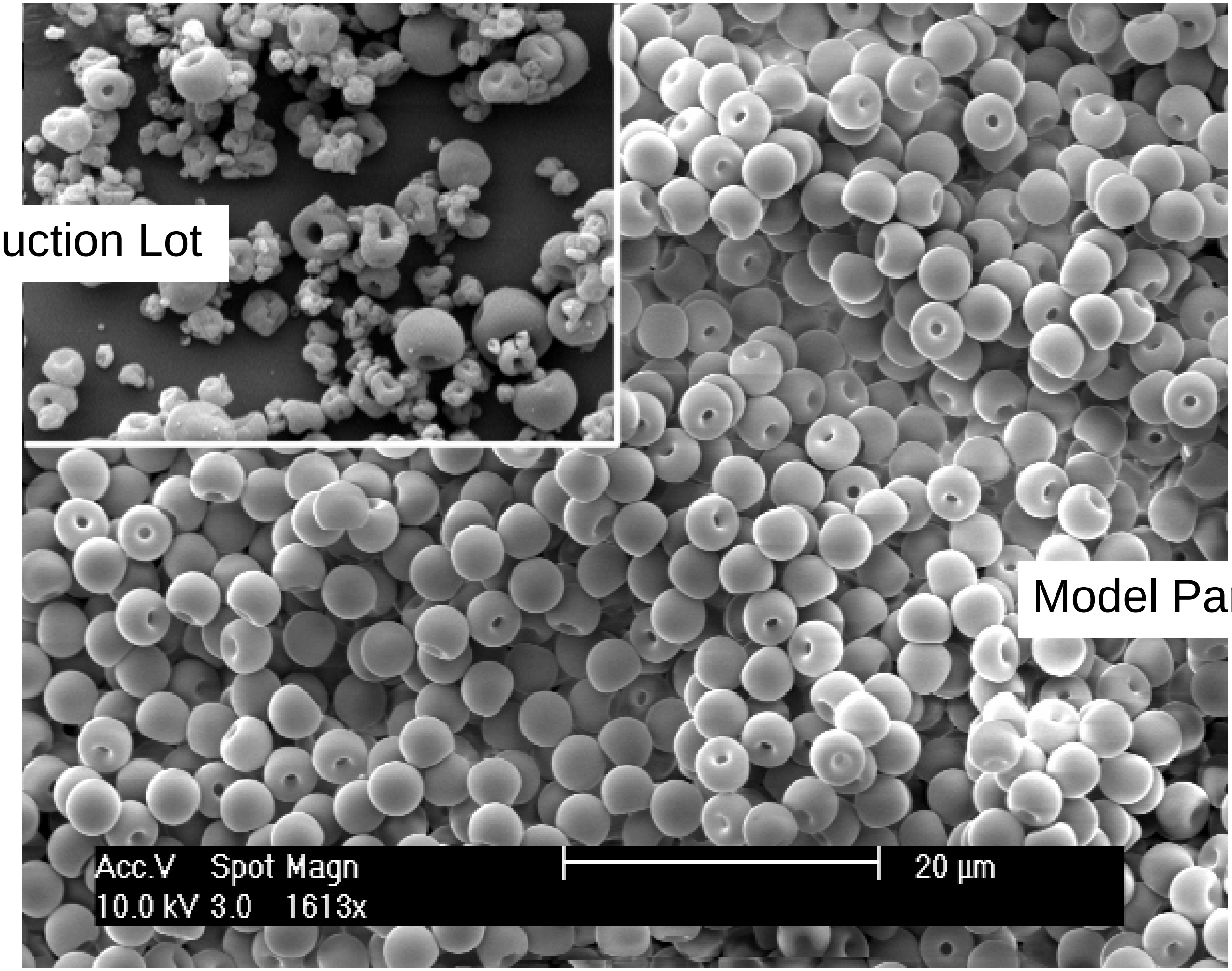
Vehring, et al., AAAR Annual Conf., Atlanta, GA, 2004

Experimental Studies on Monodisperse Model Particles



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

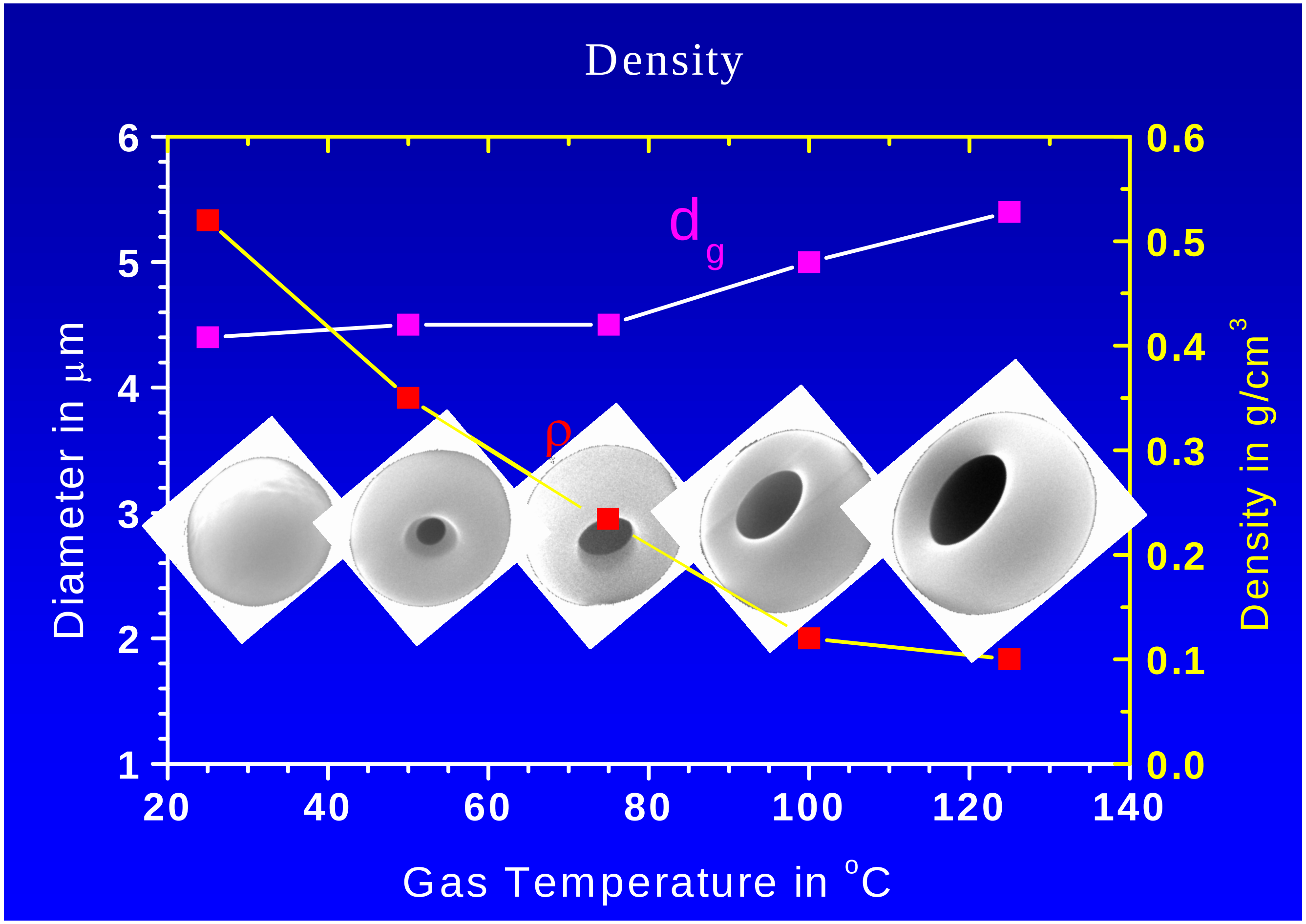
Model Particles: Perfect Control of Size and Morphology



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

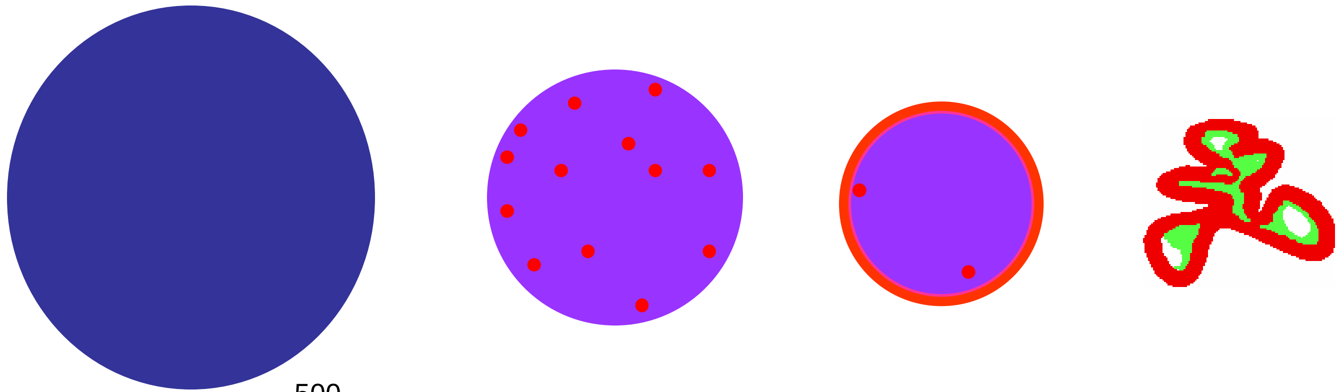
Understanding Particle Morphology

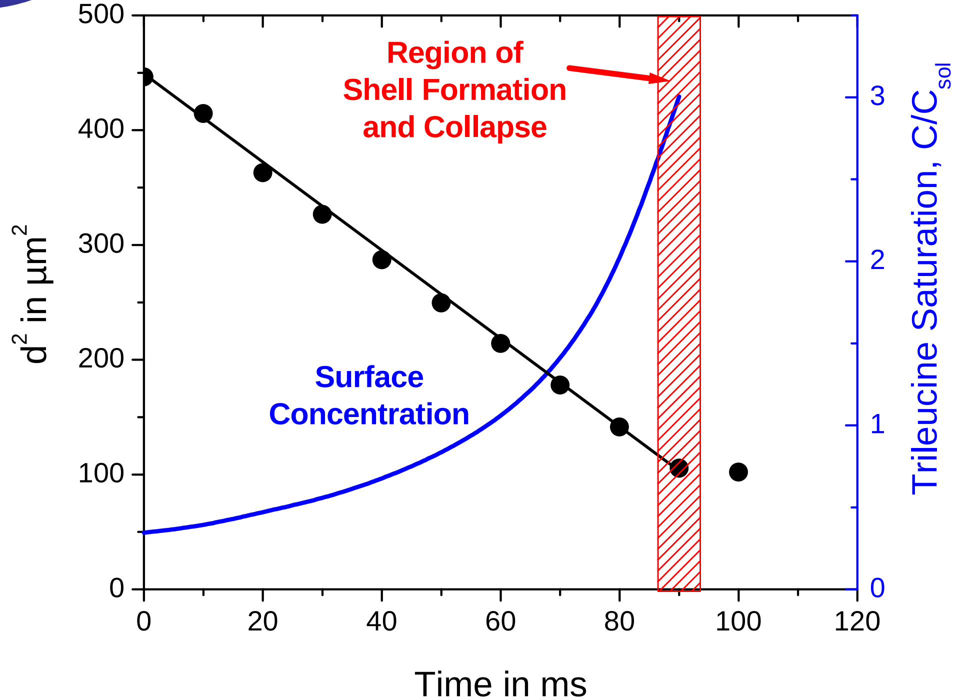
Particle density and geometric diameter as a function of processing conditions



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

Can a Small Molecule Encapsulate a Big Molecule ?





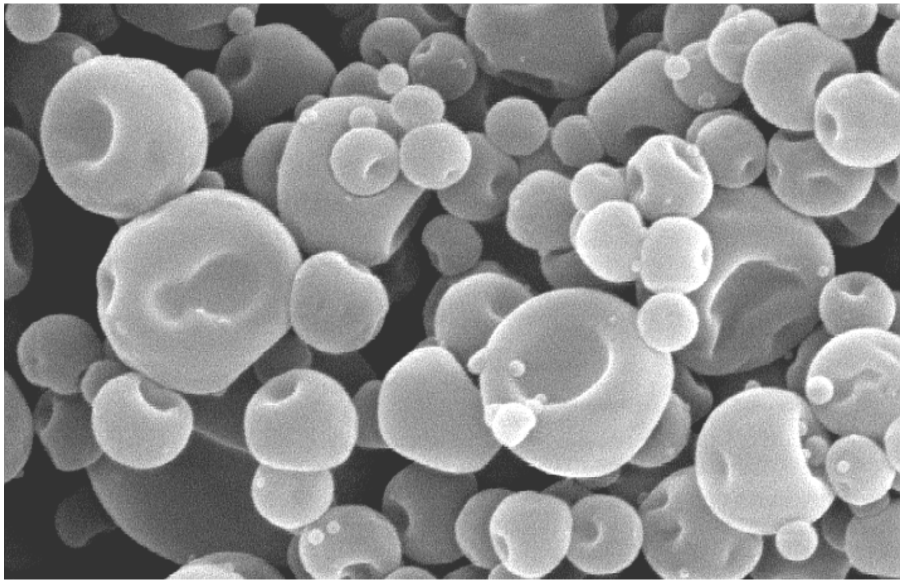
A small molecule acts like a very big molecule after phase separation! The Peclet number becomes very large at this point.

Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

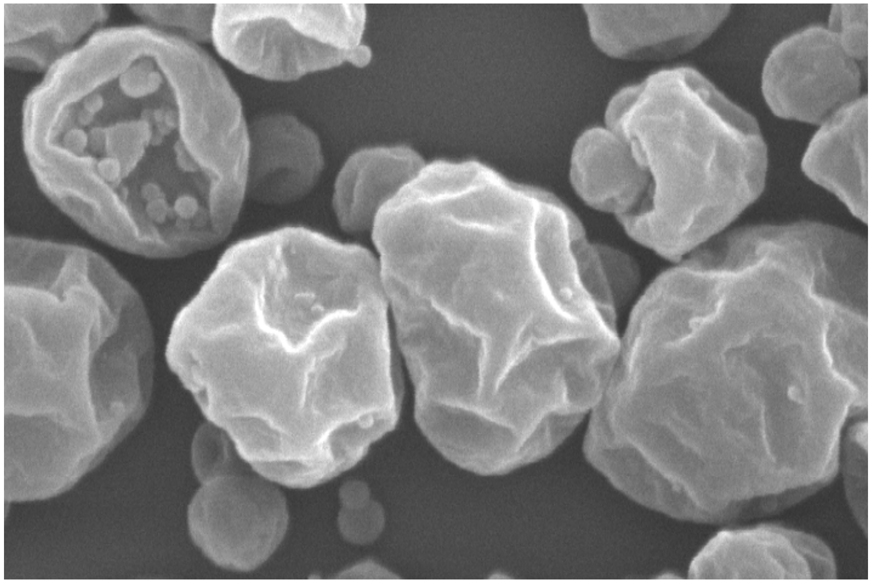
Successful Encapsulation of a Model Molecule

Spray-dried from a co-solvent system:

100 % PVP K17

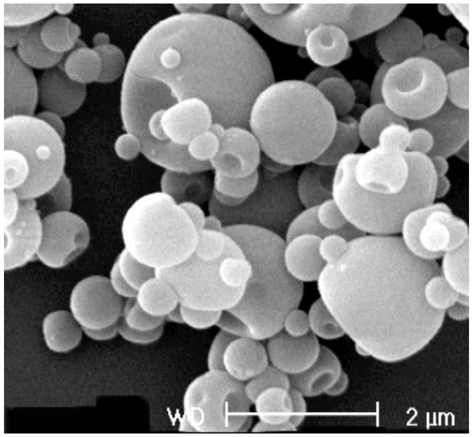


90 % PVP, 10 % Amino Acid

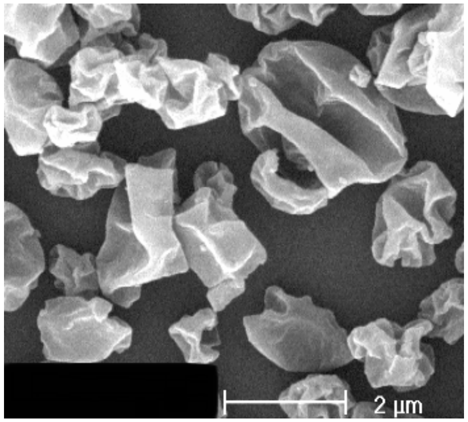


Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002

Designing for Dispersibility

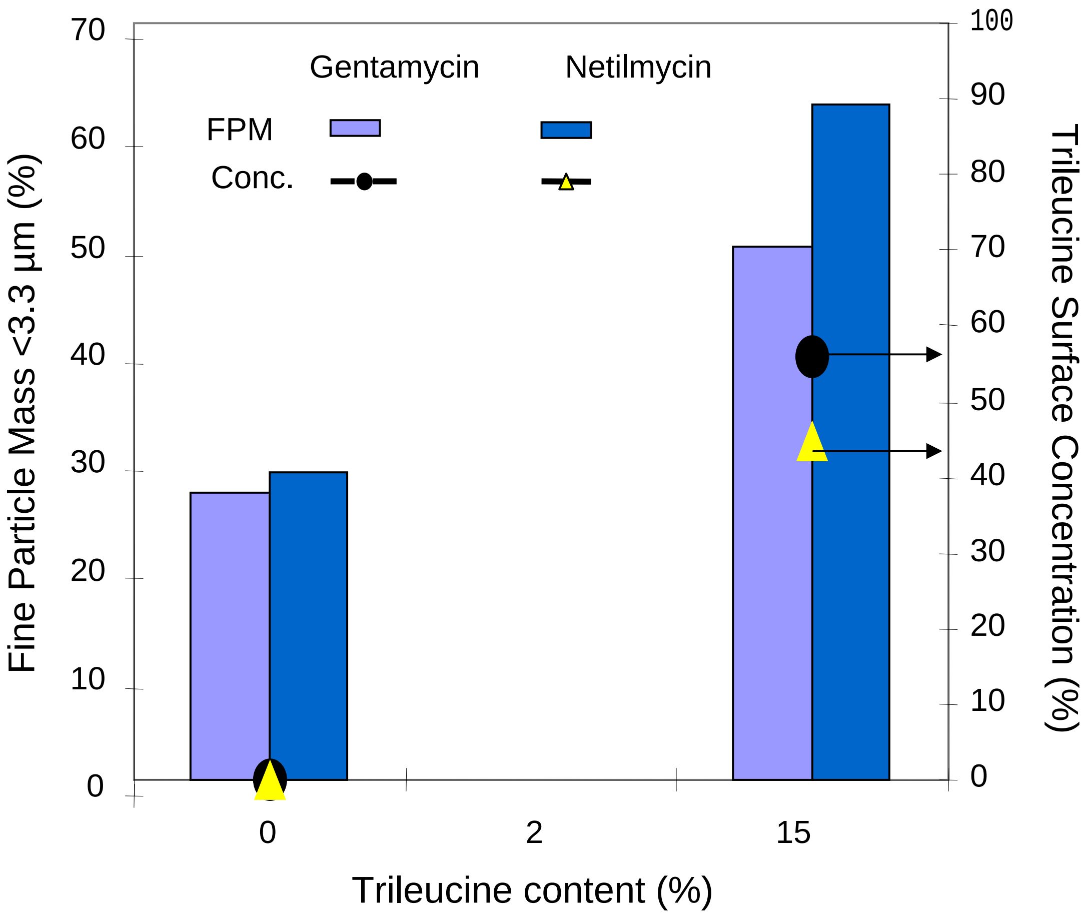


0 % Leu_3



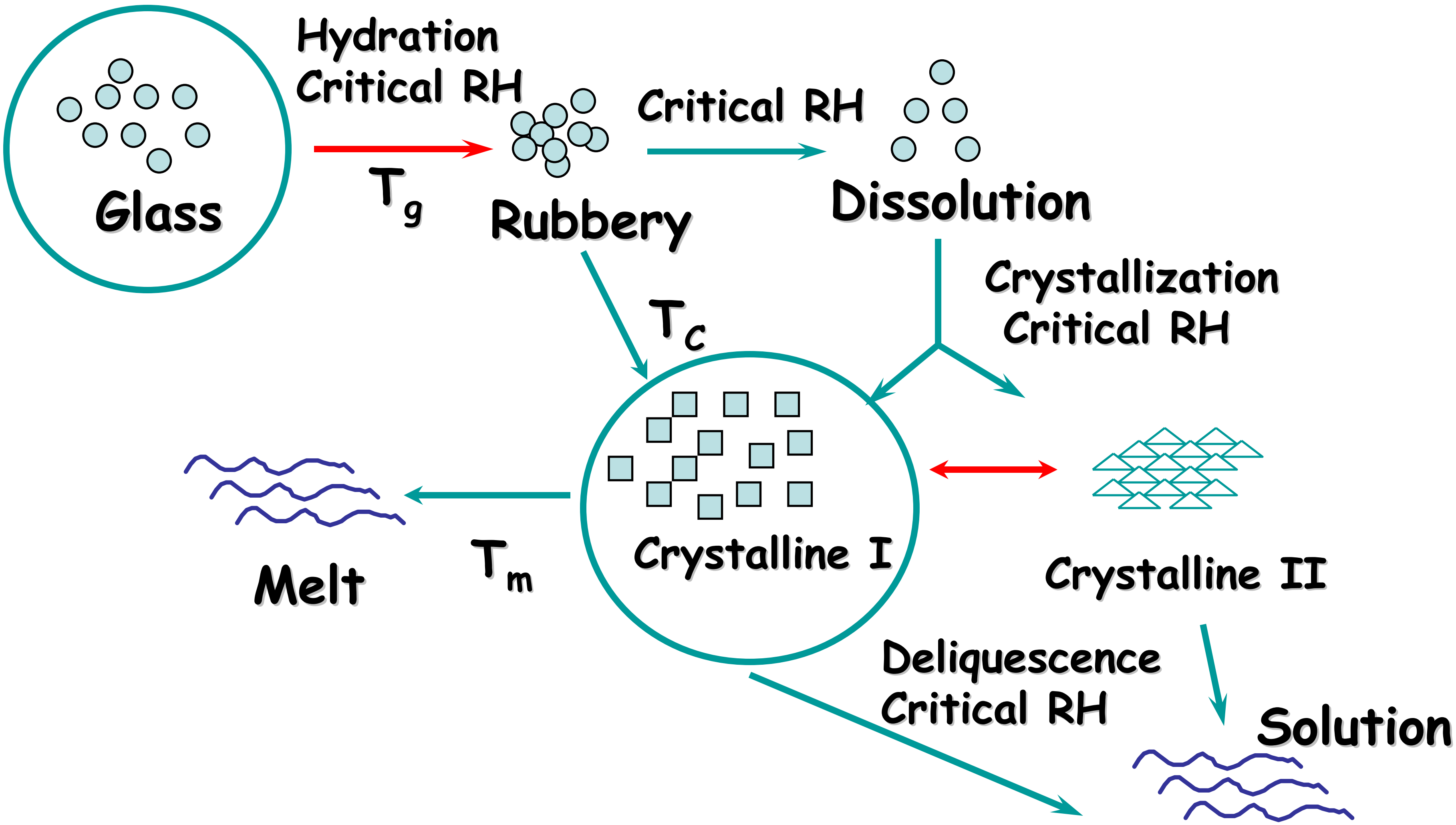
15 % Leu_3

Netilmicin Sulfate



Lechuga-Ballesteros, et al. 30th Annual Meeting Controlled Release Society, Glasgow, Scotland, 2003

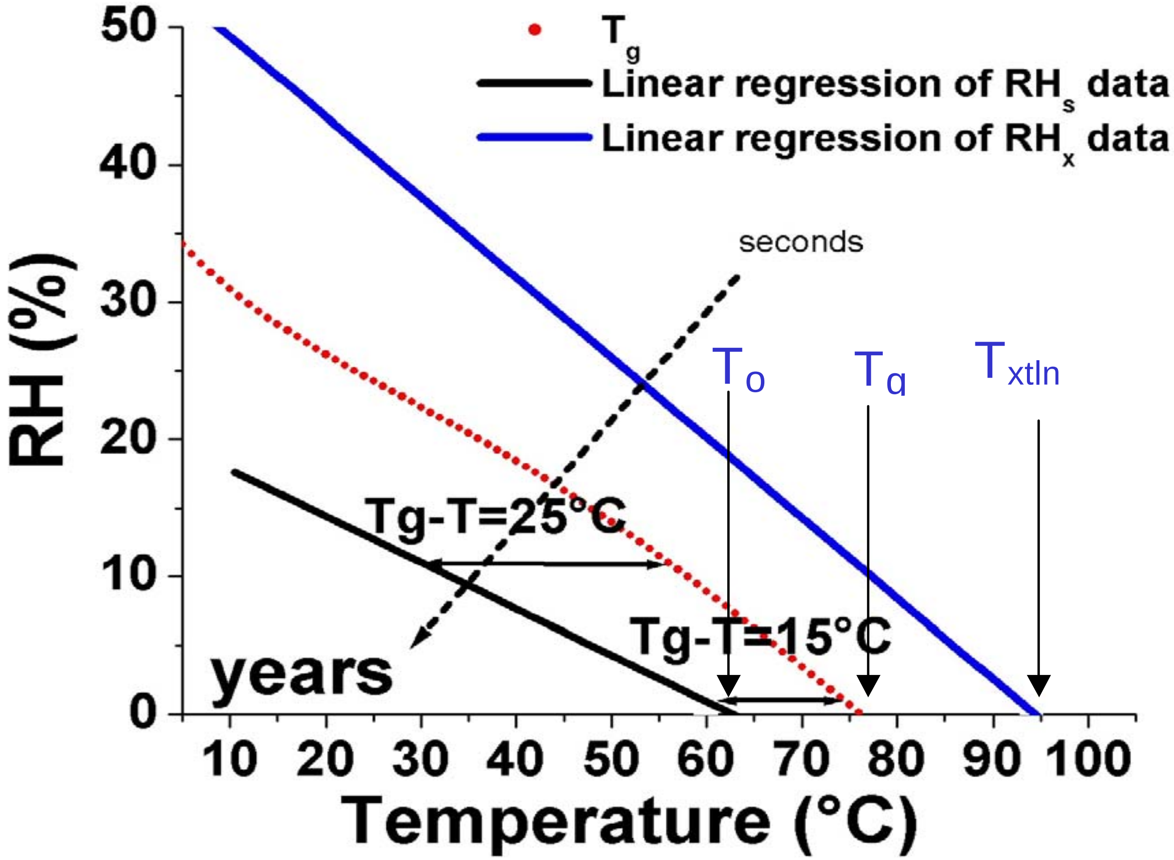
Stability Challenges for Spray-Dried Material



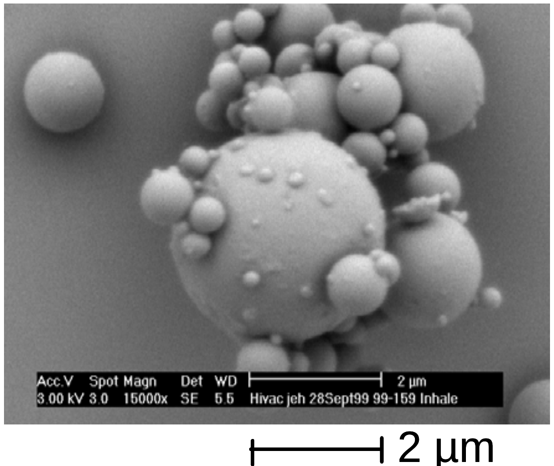
Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

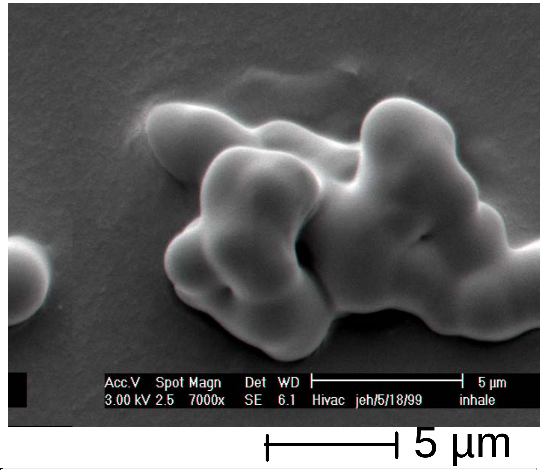
Key Stability Indicators

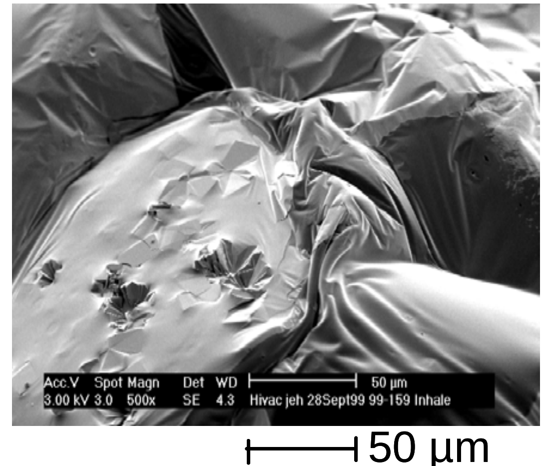
Glass Transition Temperature and Structural Relaxation Time

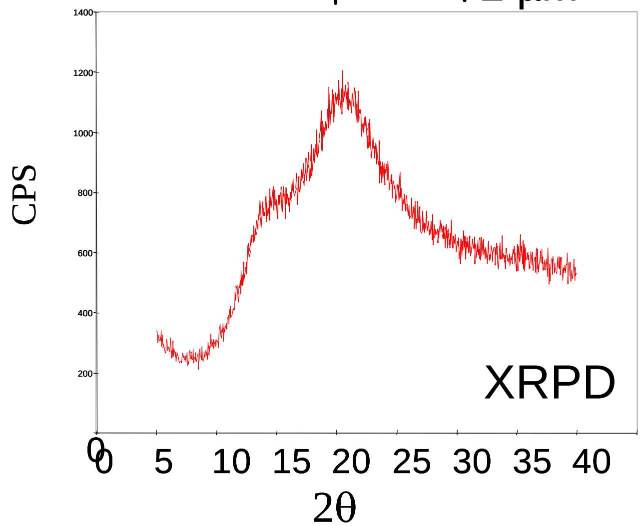


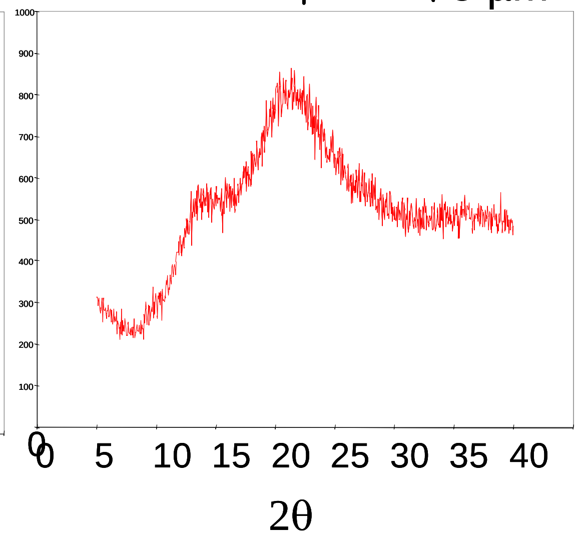
Moisture Induced Failure: Sucrose

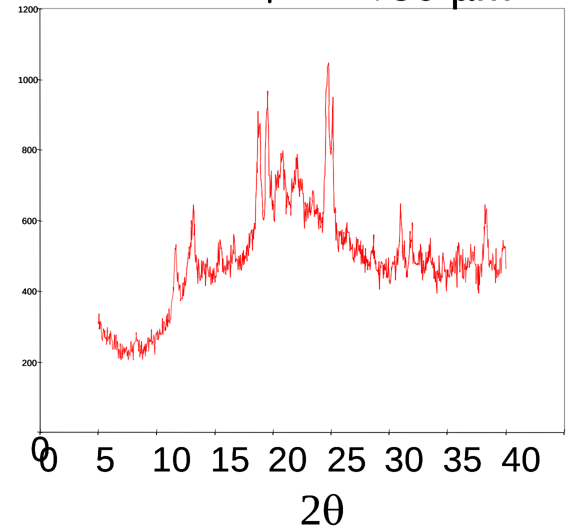












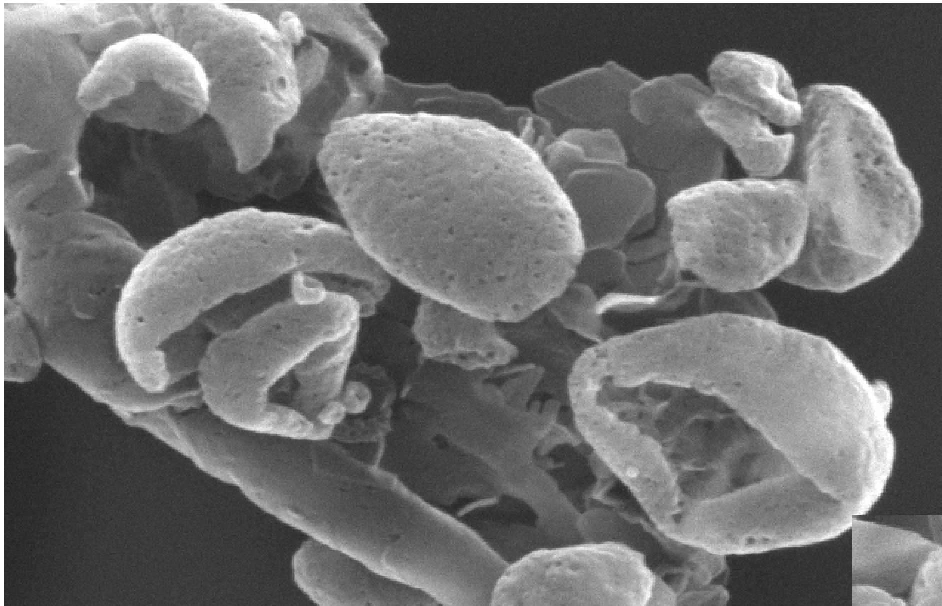
RH < 10 %, years

RH 33 %, hours

RH 75 %, minutes

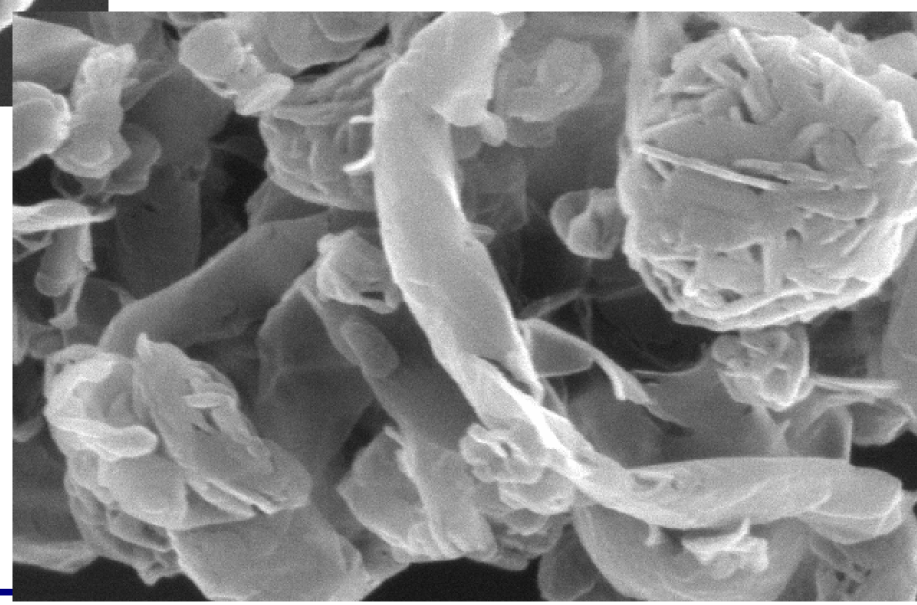
Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

Failure Mode - Recrystallization



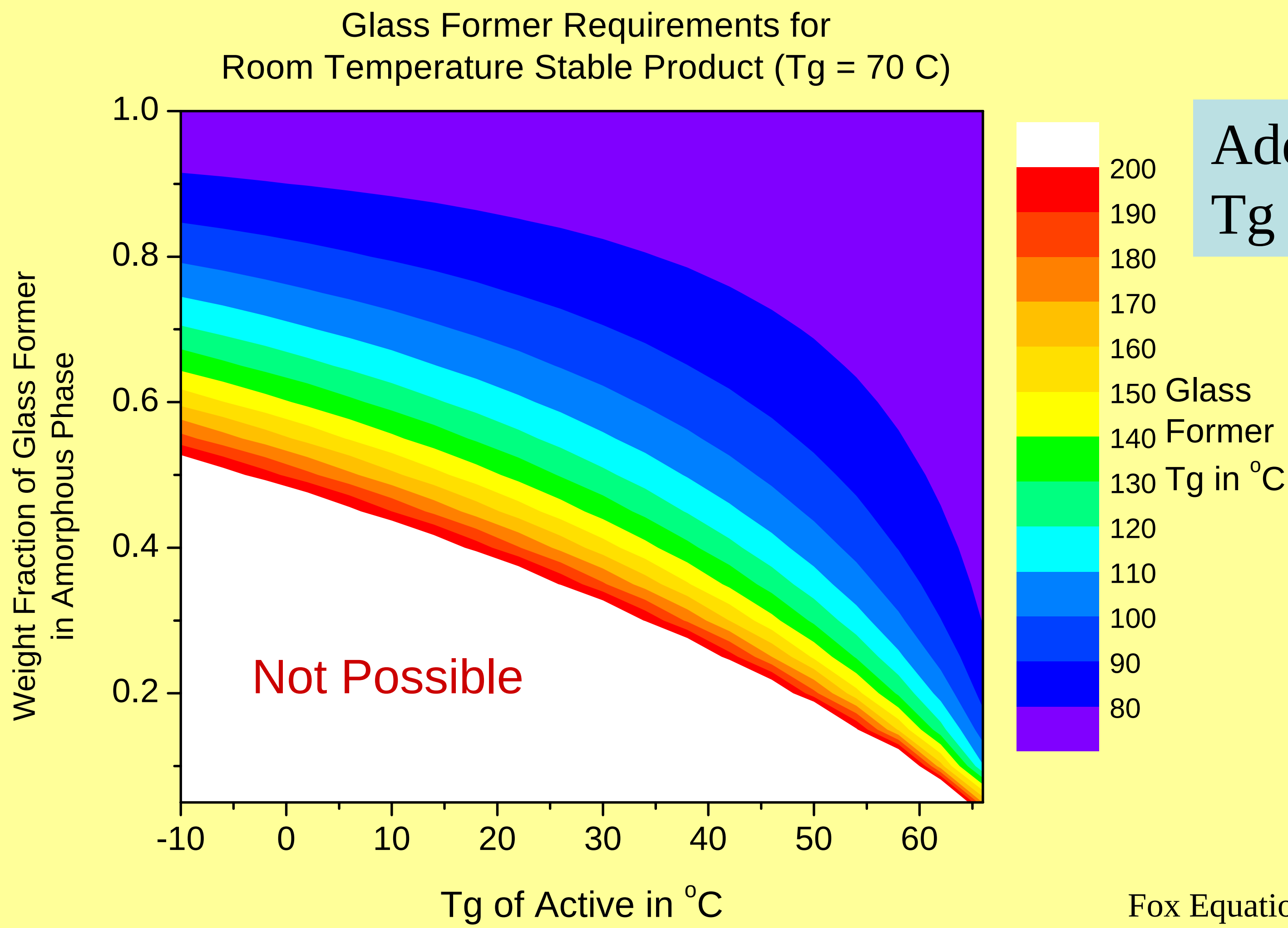
Spray-dried amino acid
95 % very small crystals

After storage at 40˚C for 2 weeks
100 % crystalline



Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

Increasing the Glass Transition Temperature

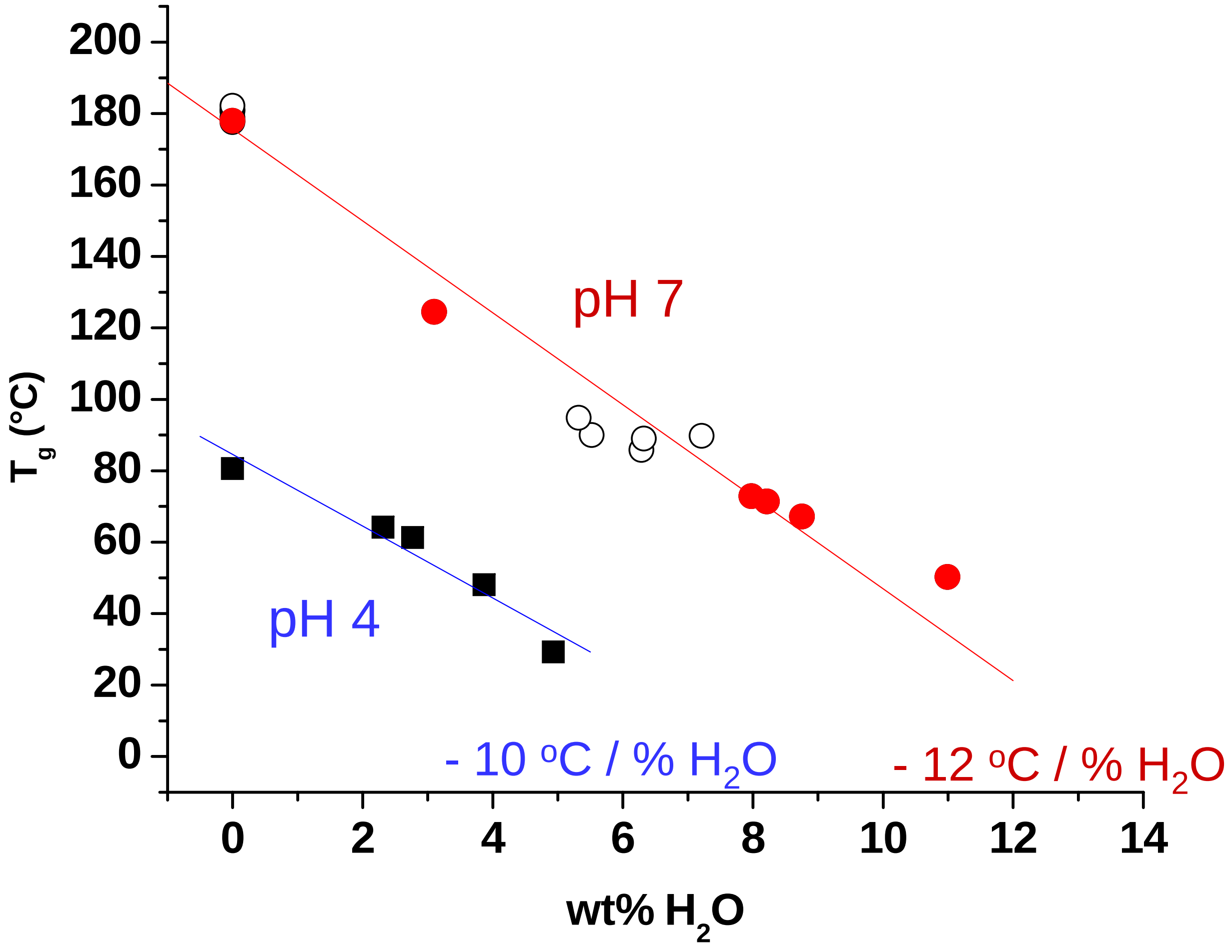


Fox Equation

Addition of a high Tg glass former

$$\frac{1}{T_g} = \sum_i \frac{Y_i}{T_{g,i}}$$

Increasing Water Content Depresses the Tg

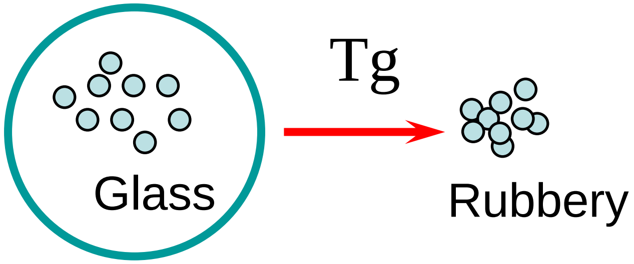


Example: Plasticization of amorphous sodium citrate.

Predictive Tool Assists Glass Stabilization

Glass Stabilization:

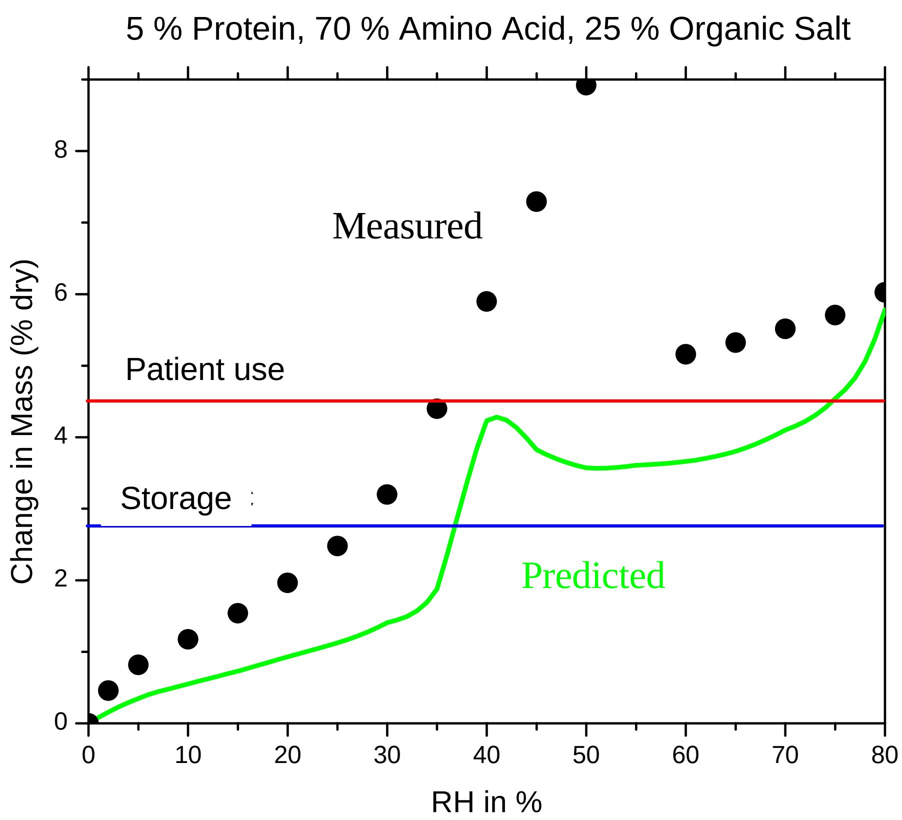
- Increase glass transition temperature
- Improve plasticization properties



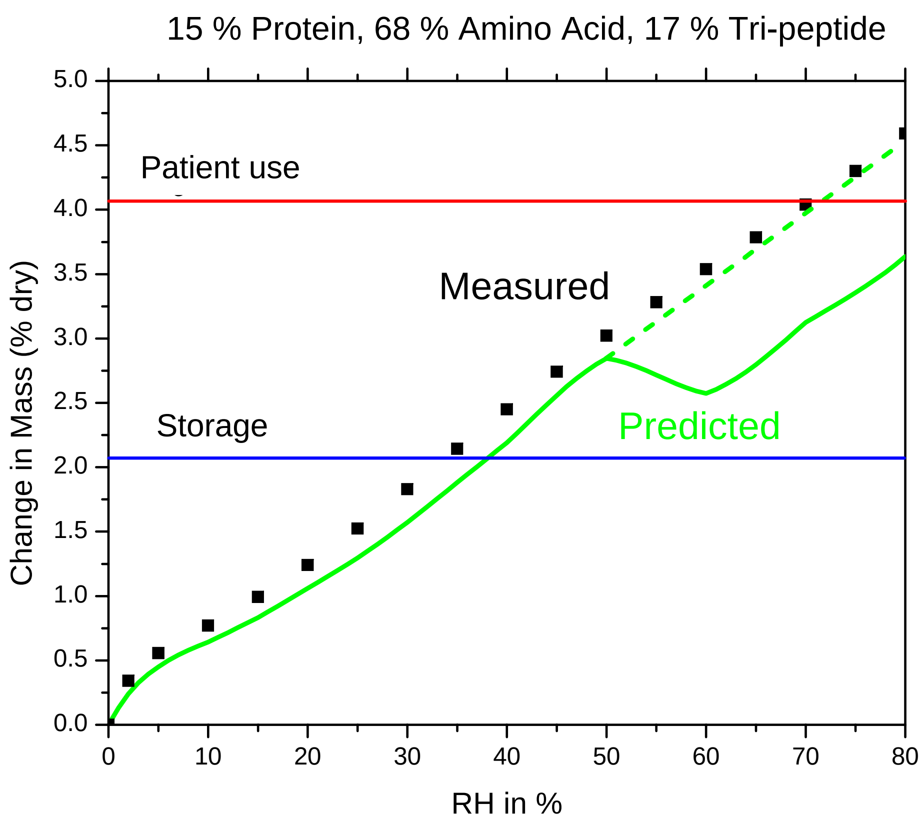
It is possible to develop a predictive tool for moisture sorption behavior and Tg of formulations as a function of excipient ratios and pH.

- Requires a database of excipient properties and excipient interactions.
- Coefficients for Tg models must be determined for typical formulation systems.

Designing the Amorphous Phase



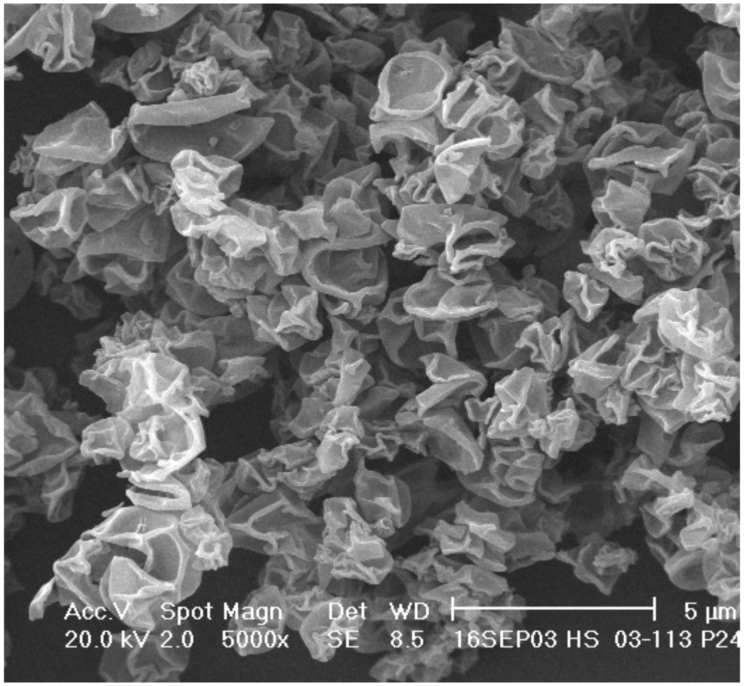
Crystallization at moderate RH

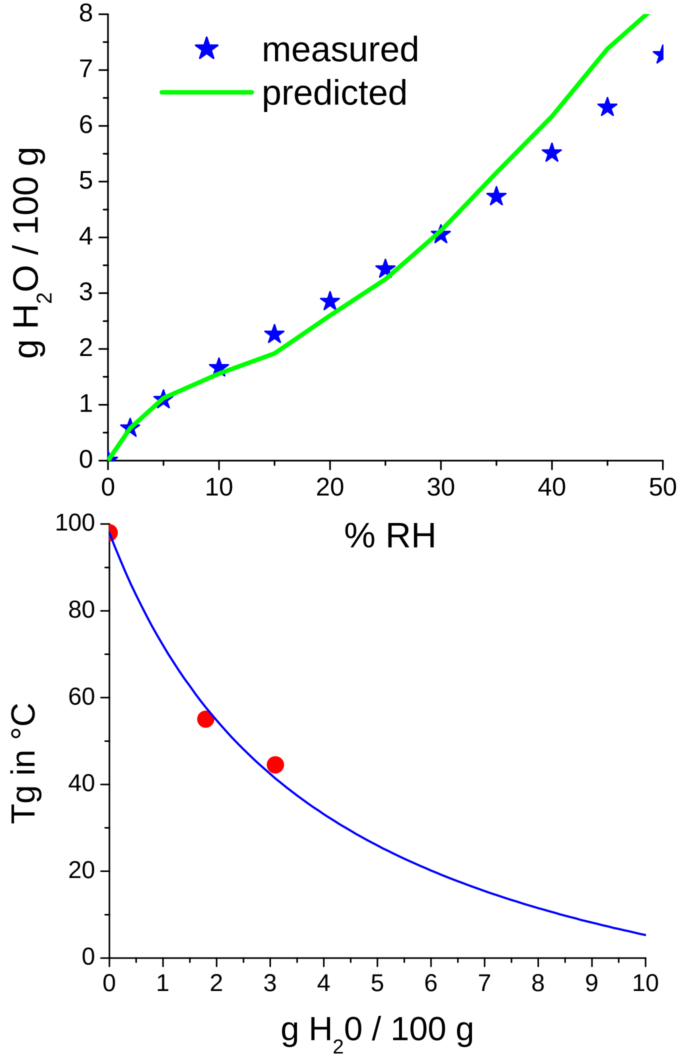


Much improved out-of-package stability

Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

Exceeding the Limits of Glass Stabilization

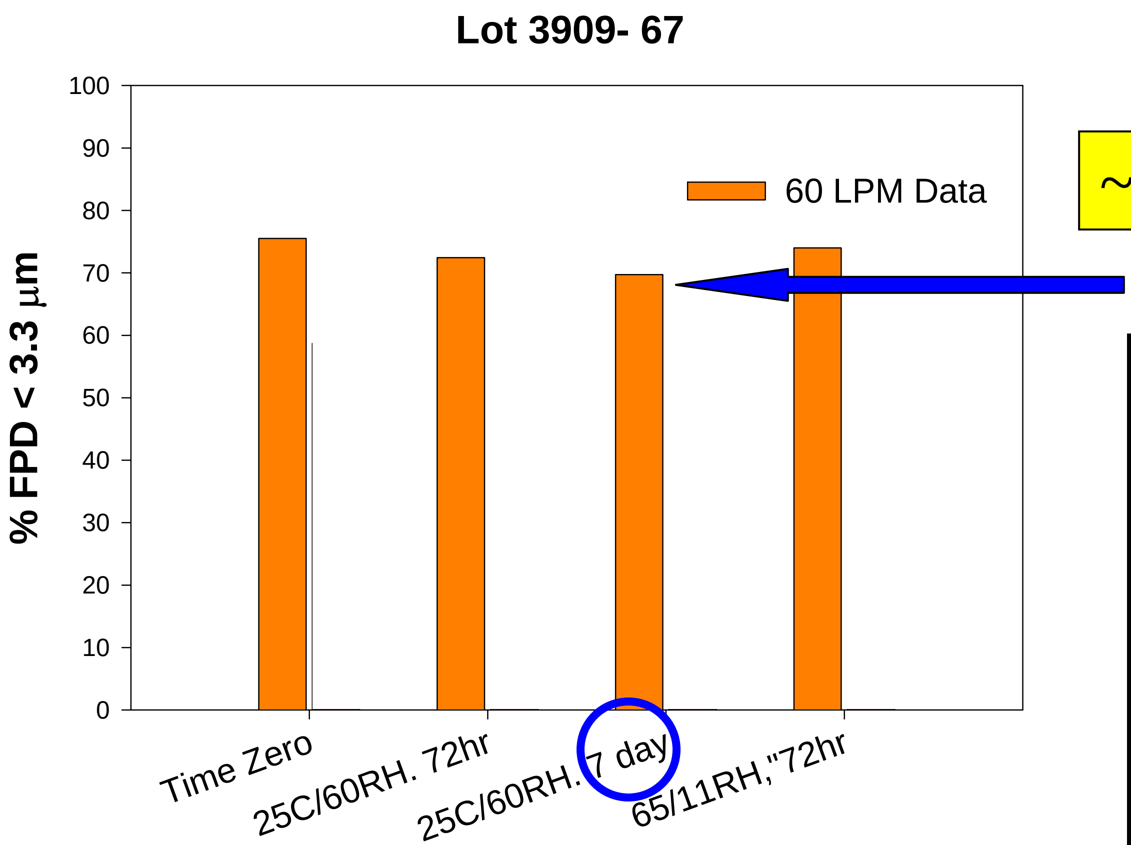


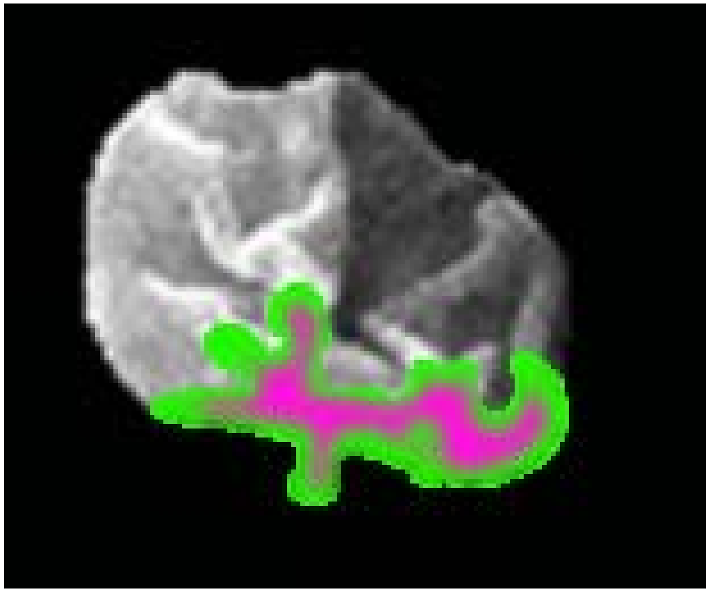


Plasticized core protected by a high Tg shell

Excellent Out-of-Package Stability

56 % Encapsulation excipient, 20 % Saccharide
20 % low Tg API, 4 % organic salt





Particle Engineering - Conclusion

- Aerosol science, process development and formulation are linked and form a new discipline: Particle Engineering.
- Understanding of the underlying physics and physical chemistry of the evaporation and particle formation processes has led to the development of predictive particle engineering tools.
- Predictive tools for the design of packaging configurations, processing conditions, and formulation compositions allow rapid development and optimal product performance
- Spray drying is capable of economical manufacture of sophisticated particles which have the potential to enable and improve therapeutics in the future for the benefit of patients