Introduction to Aerosol Technology for Drug Delivery

Reinhard Vehring

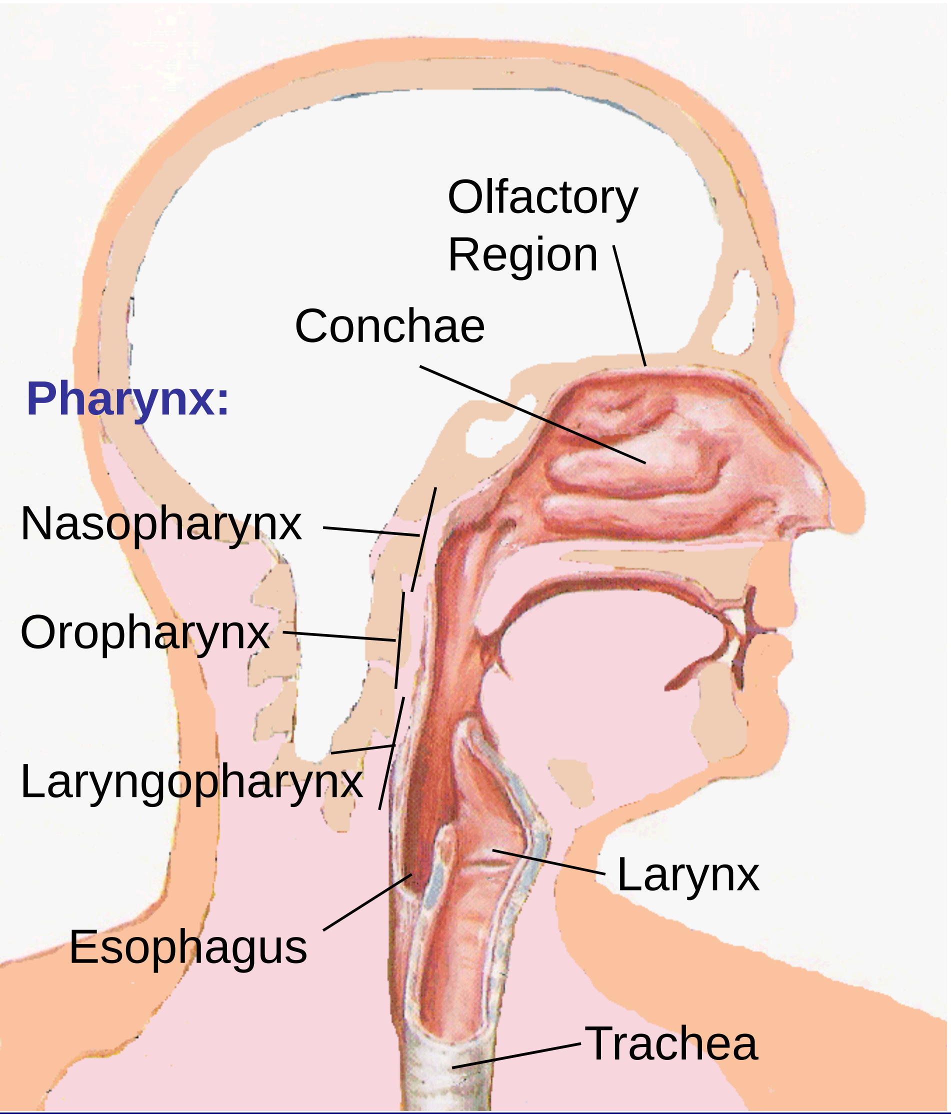
Pearl Therapeutics, Inc.
200 Saginaw Dr
Redwood City, CA 94063
650 305 2067
rvehring@pearltherapeutics.com

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 Devices
- Powder Manufacture
- Particle Engineering

The Portal: Nose or Mouth



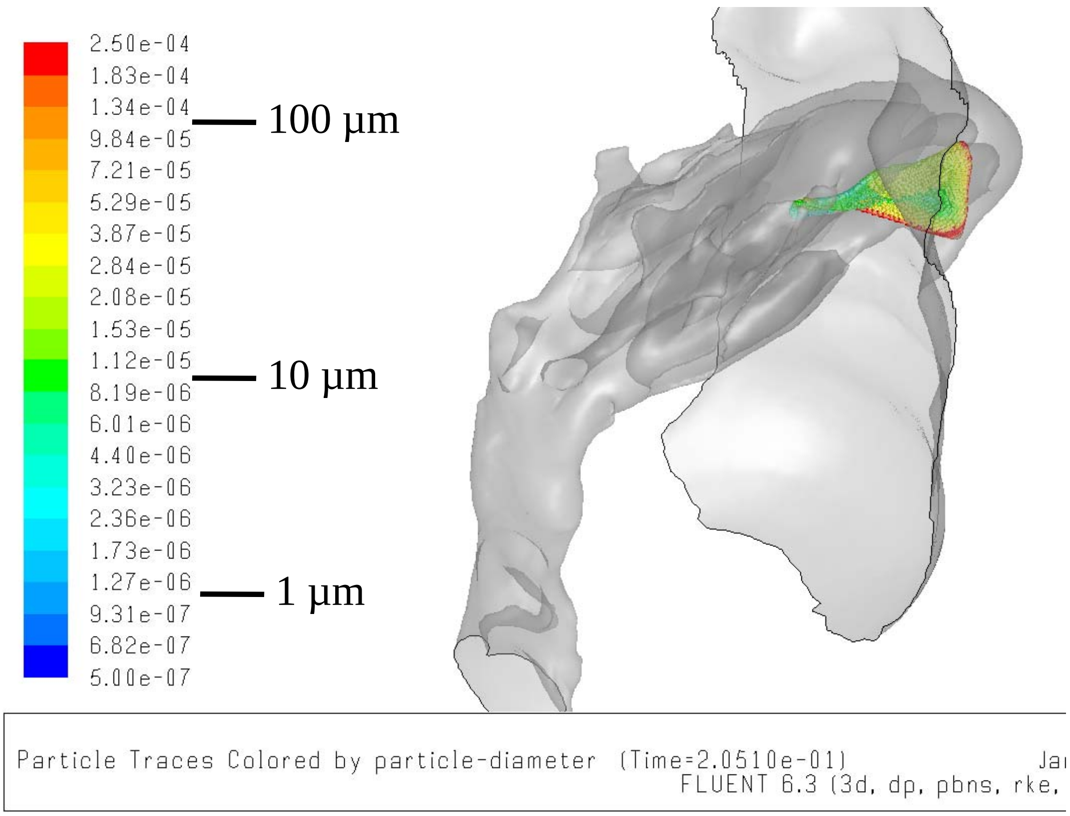
Nose

- 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.

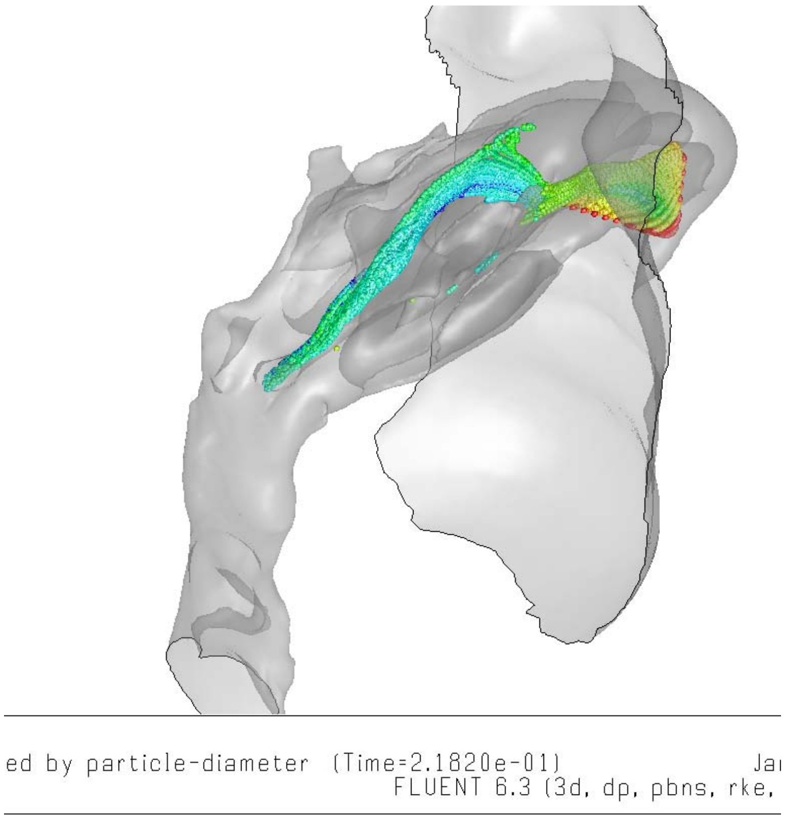
Mouth

- 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

Particle Tracking with Computational Fluid Dynamics

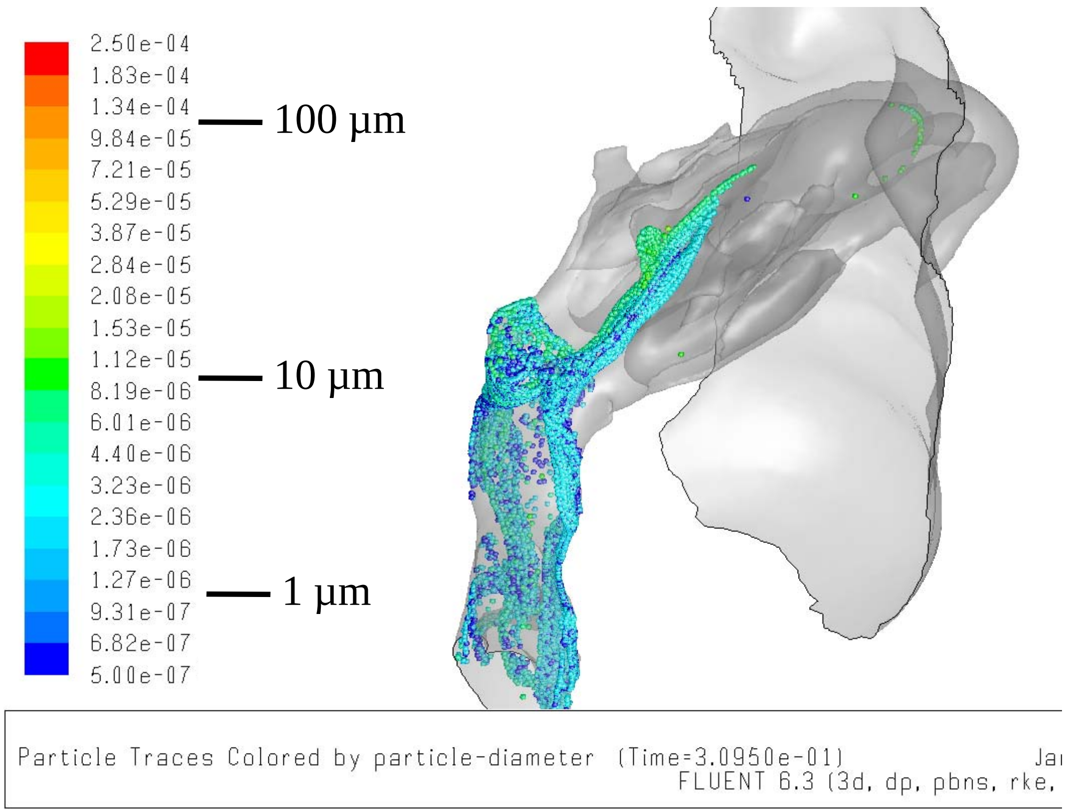


t = 205 ms

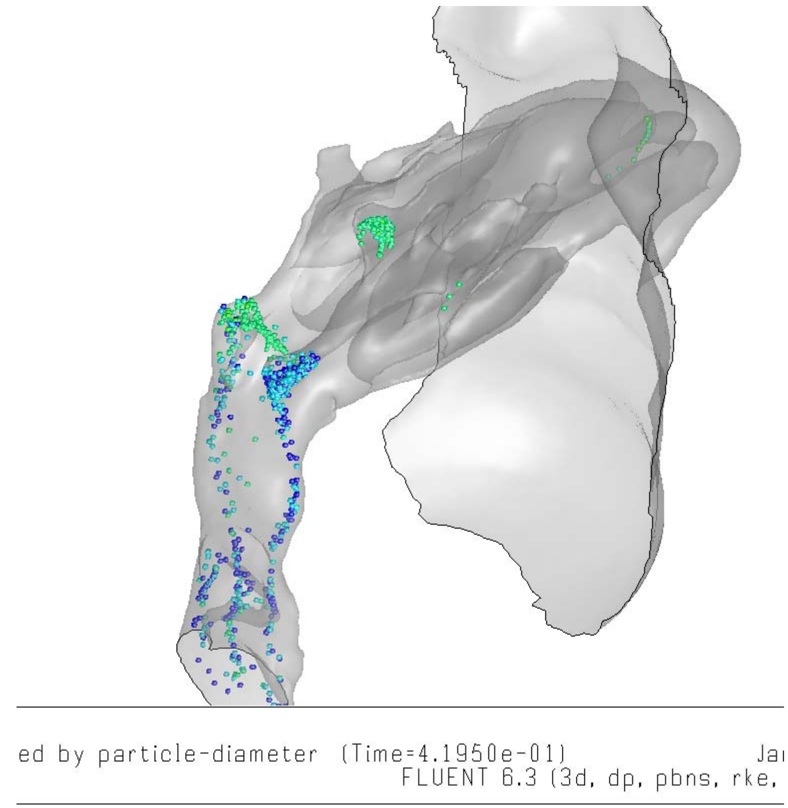


t = 218 ms

CFD Particle Tracking



t = 310 ms

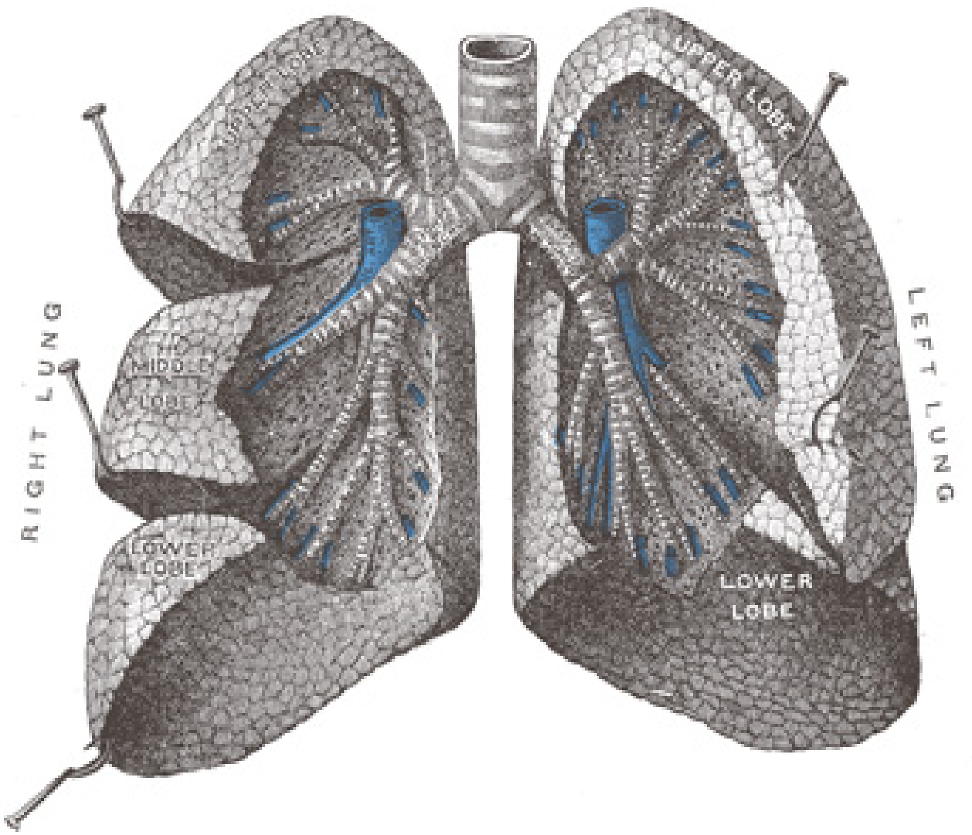


t = 420 ms

Lung Anatomy - Overview

3 lobes

2 lobes



Conducting Zone

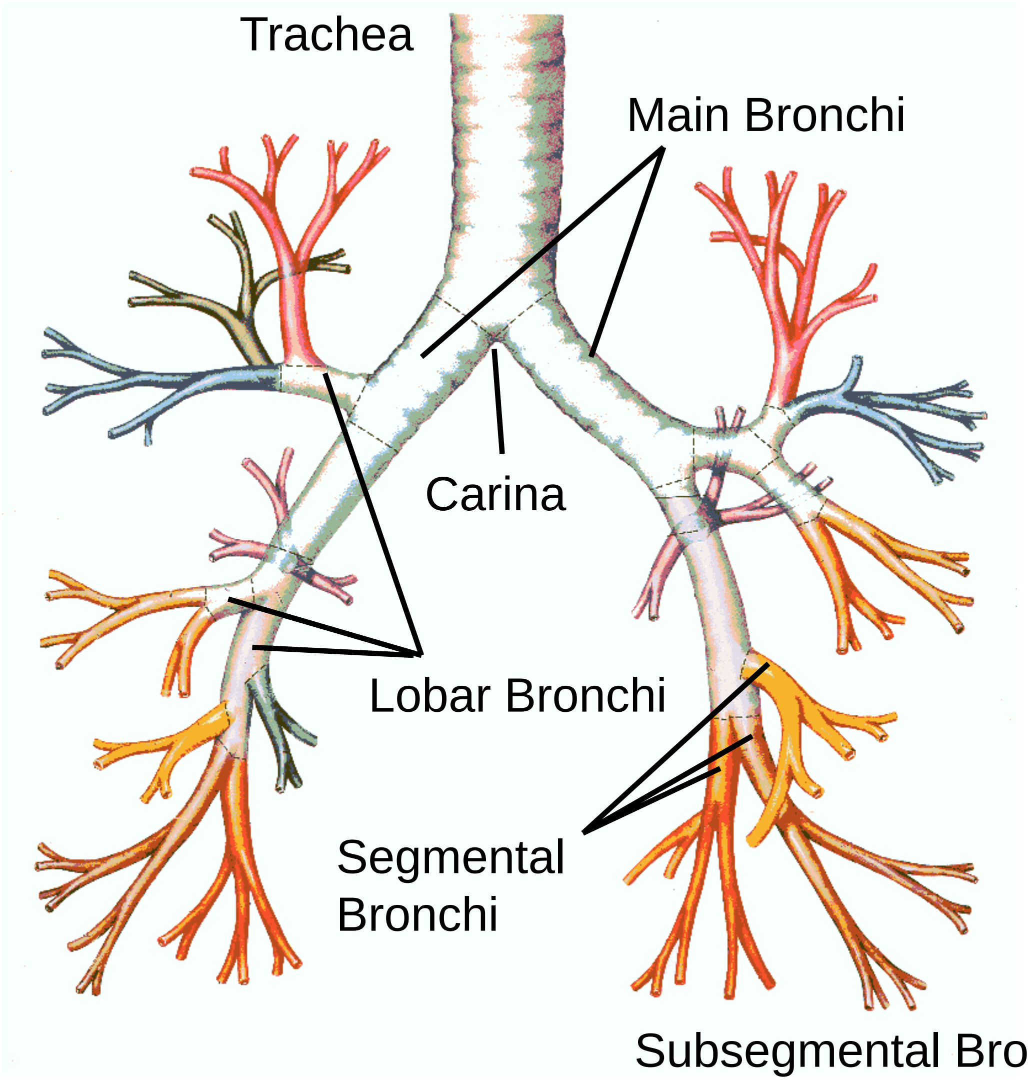
- Trachea
- Bronchi
- Bronchioles
- Terminal Bronchioles
- Volume: 175 cm^3
- Surface Area: 3500 cm^2

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

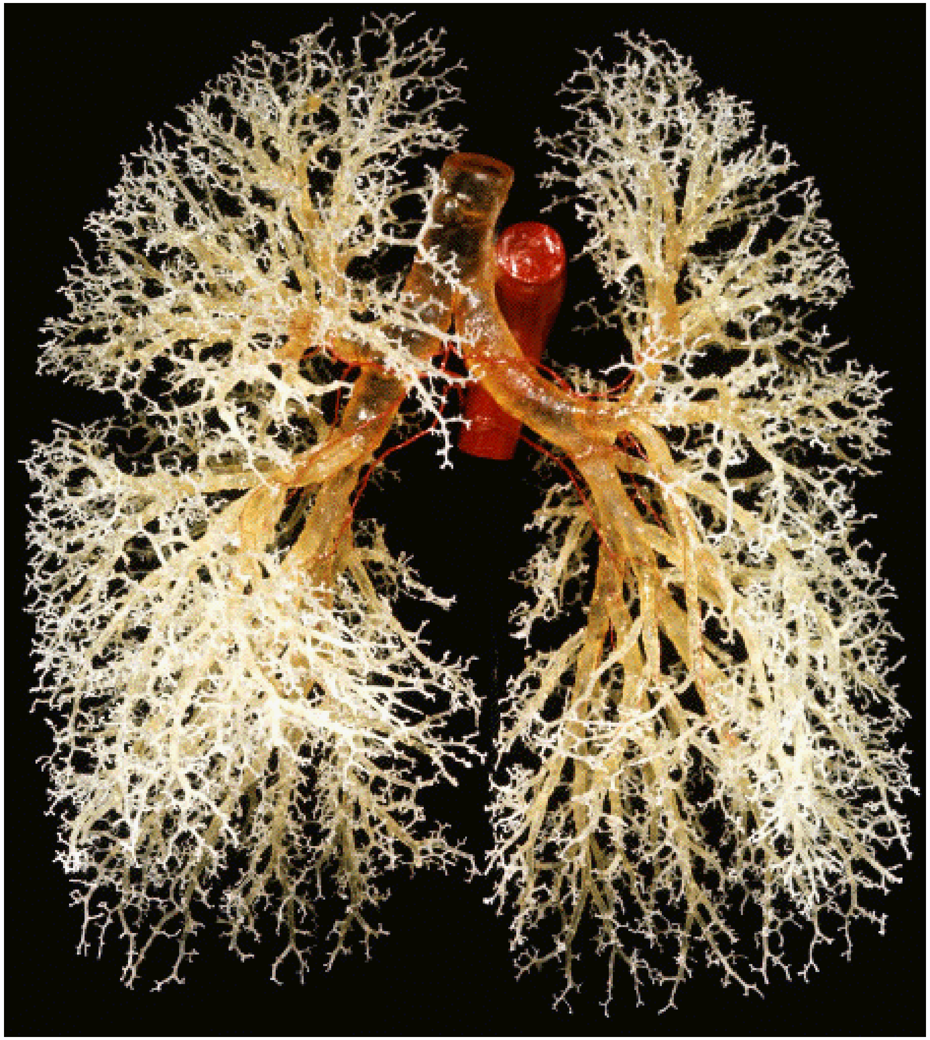
- Cartilaginous
- Longitudinal elastic fibers
- Smooth muscle
- Ciliated
- Mucus layer
- Branching with irregular dichotomy

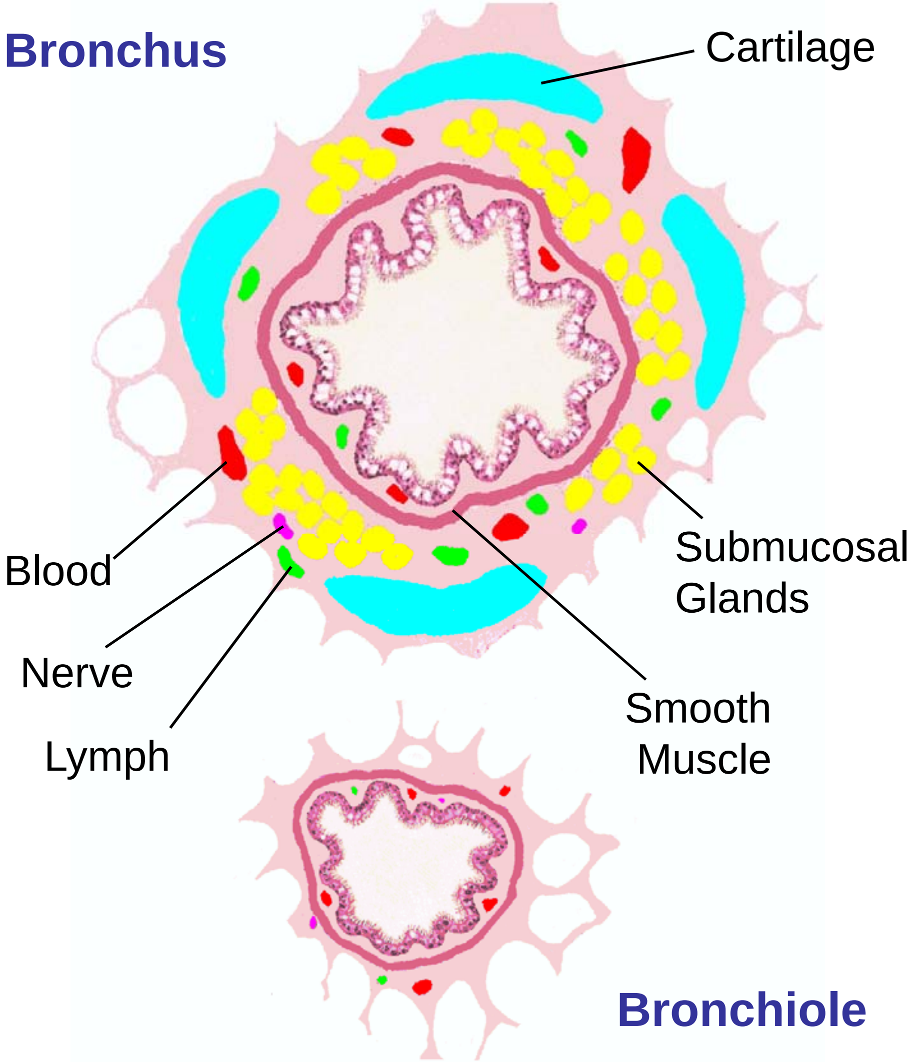
Physiology

- Contributes most of the airway resistance

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

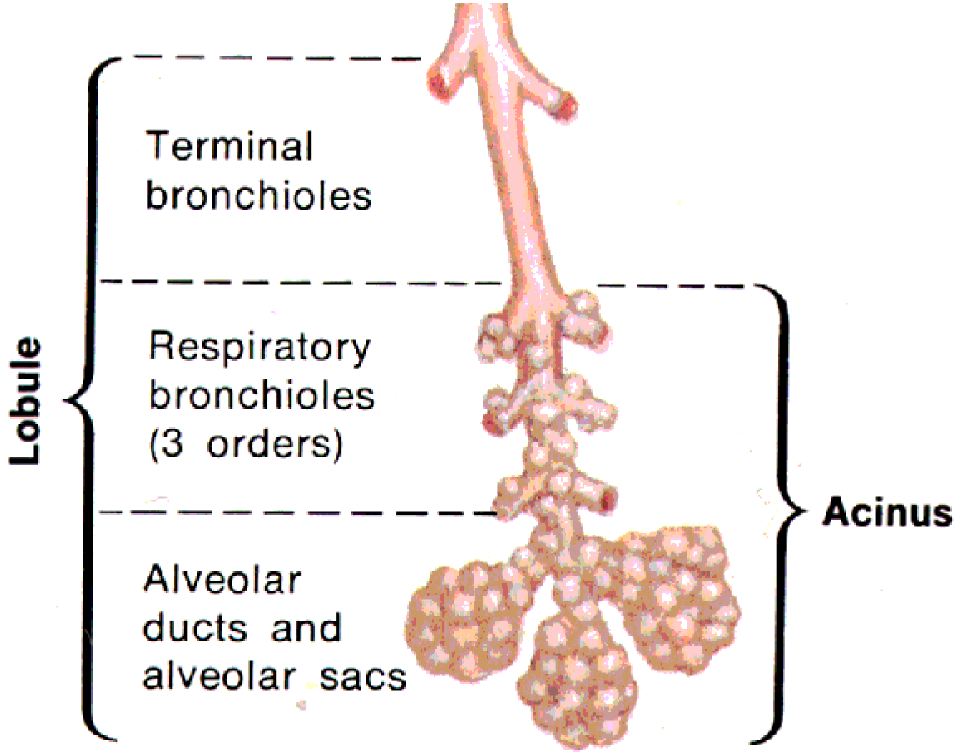
Conducting Airways - Bronchi and Bronchioles

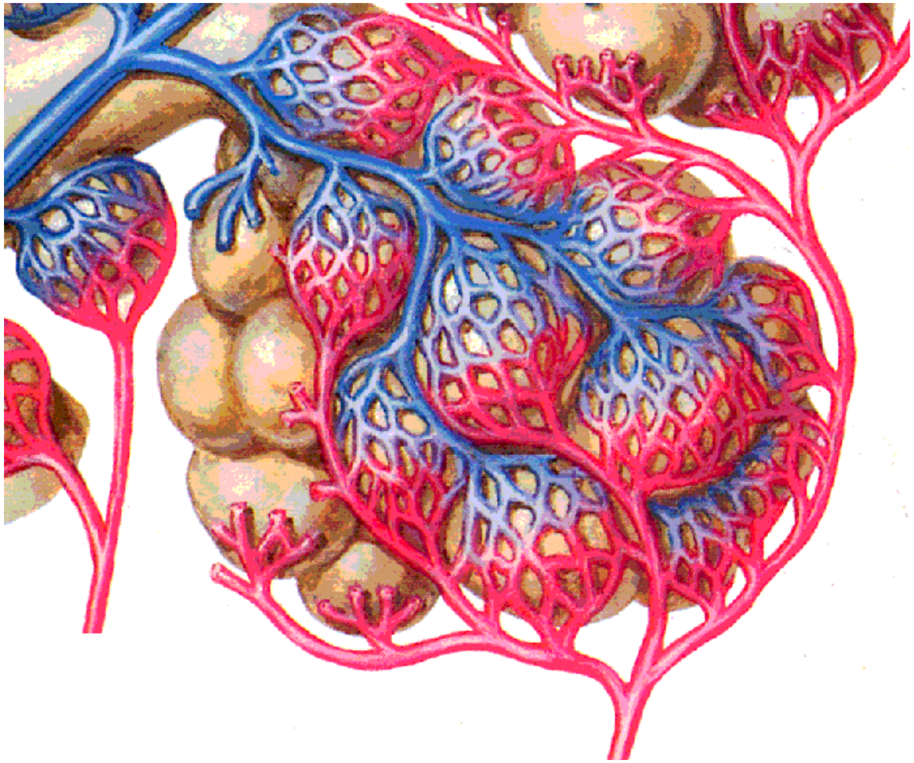




http://courses.washington.edu/envh515

Respiratory Zone

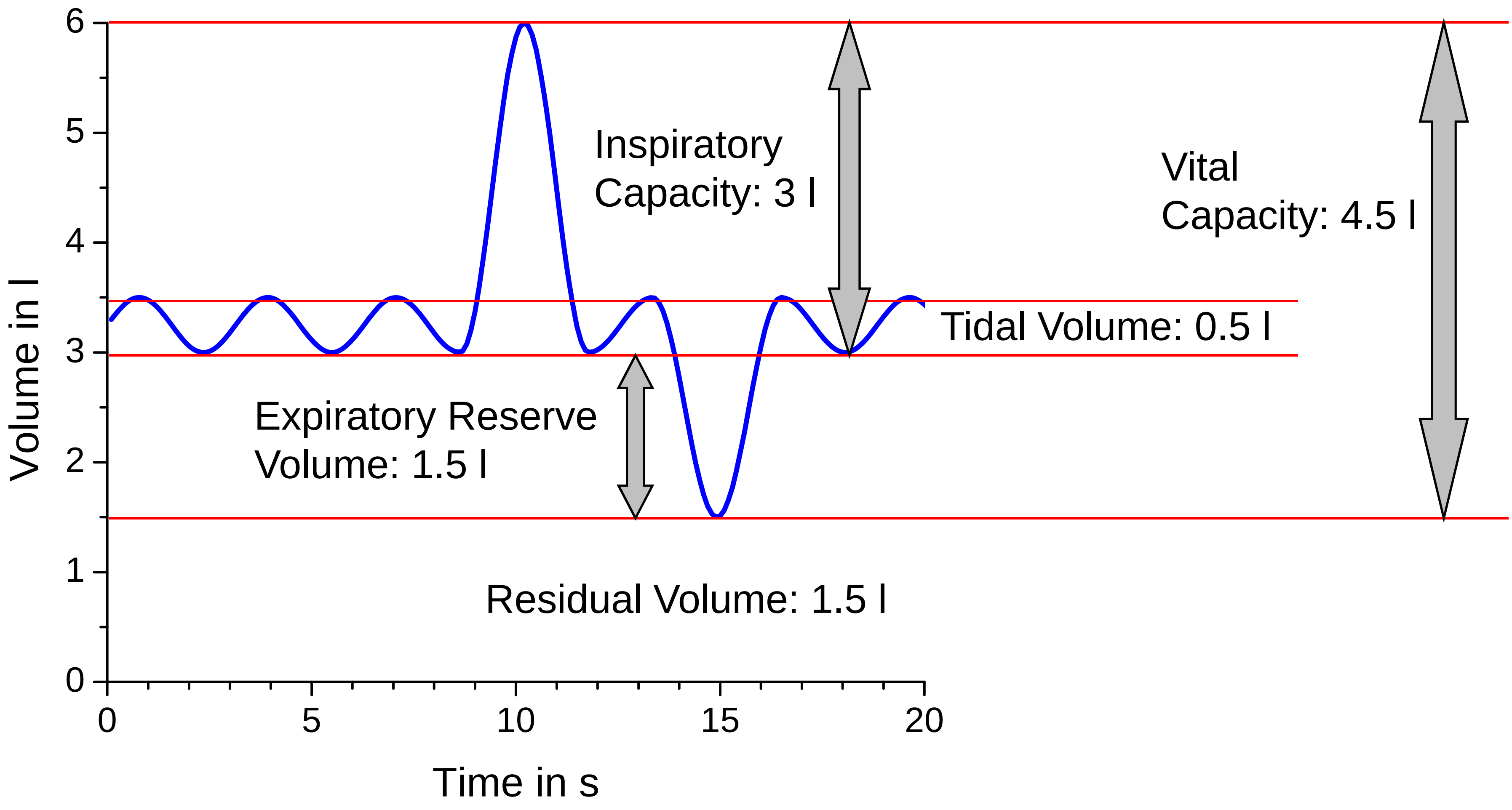




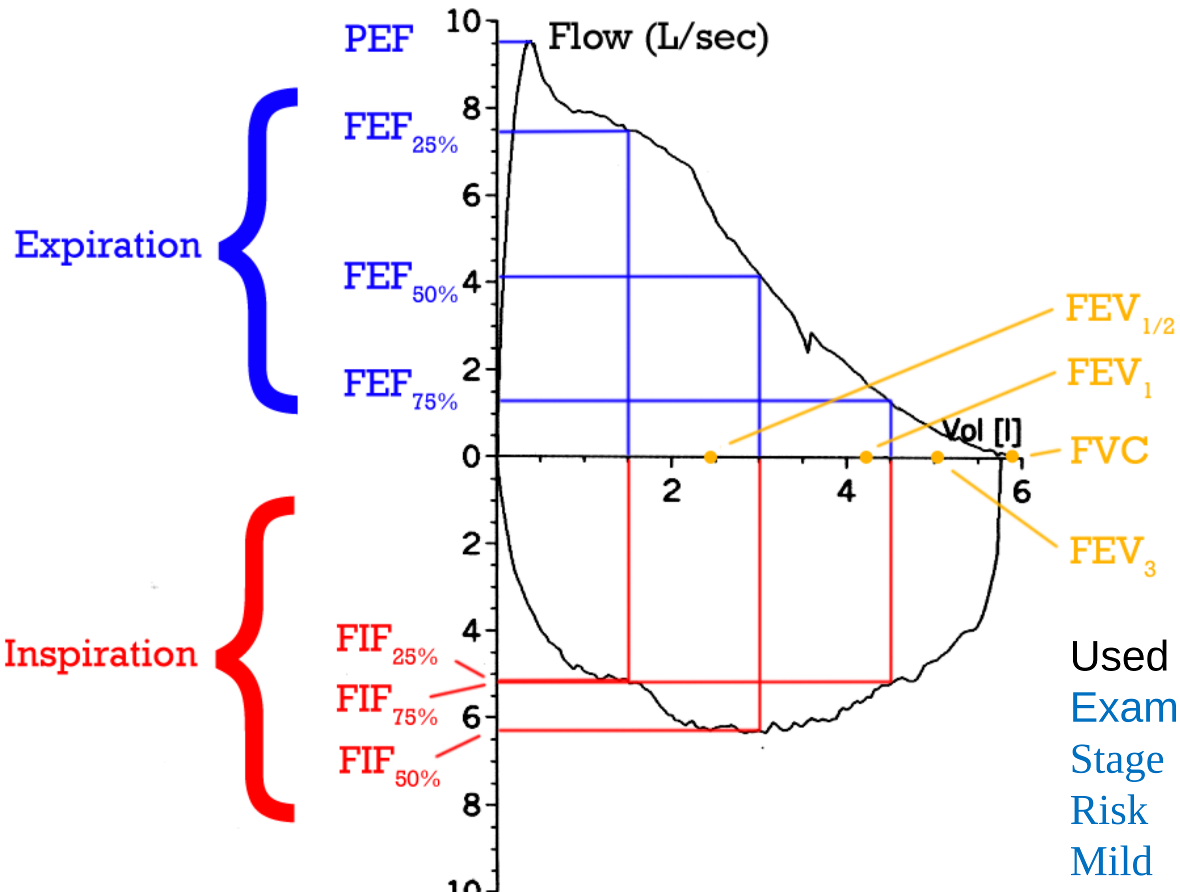
- No cartilage, cilia or mucus
- Few longitudinal elastic fibers and some smooth muscle
- 300 million alveoli provide a large surface area (100 m^2) separated from blood flow by a thin tissue layer.
- The entire blood volume of the body passes through the lungs each minute.

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

Lung Volumes



Lung Function Test / Spirometry



Flow-Volume Loop

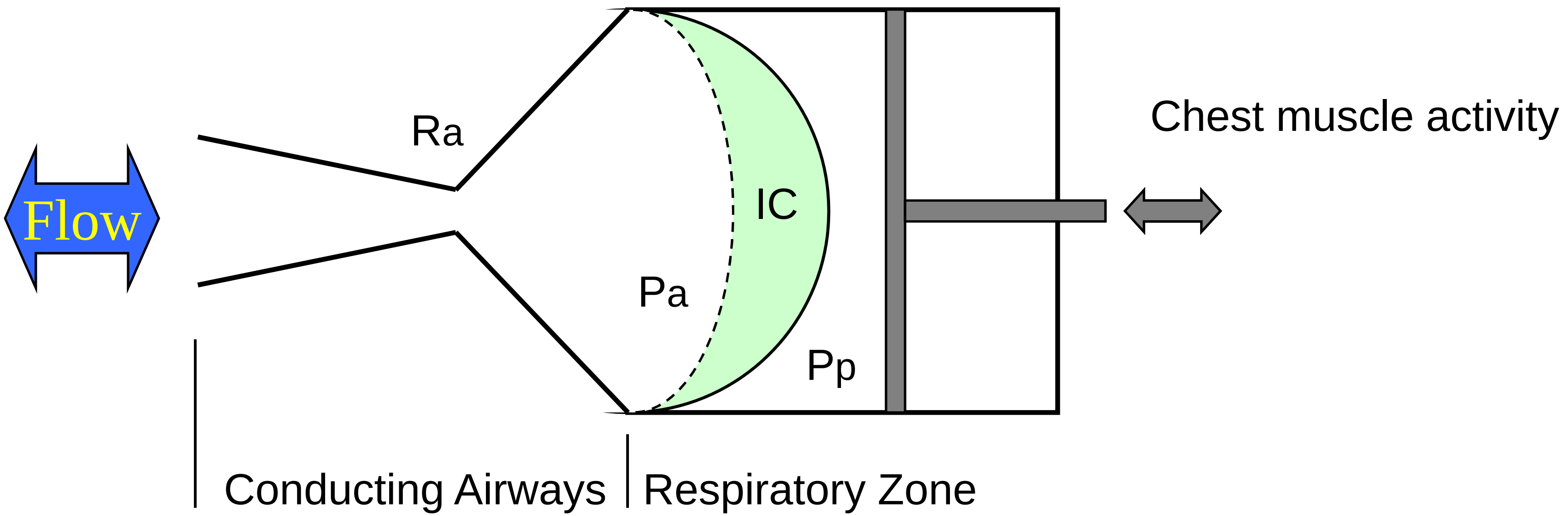
FEF: Forced expiratory flow
PEF: Peak expiratory flow
FEV: Forced expiratory volume
FVC: Forced vital capacity
FIF: Forced inspiratory flow
Ratios, e.g FEV_1 / FVC

Used for diagnosis and categorization

Example COPD:

Stage	FEV_1 / FVC, pd	FEV_1 % pred.
Risk	> 0.7	> 80 %
Mild	< 0.7	> 80 %
Moderate	< 0.7	50 – 80 %
Severe	< 0.7	30 – 50 %
Very Severe	< 0.7	< 30 %

Breathing - Mechanical Analogy

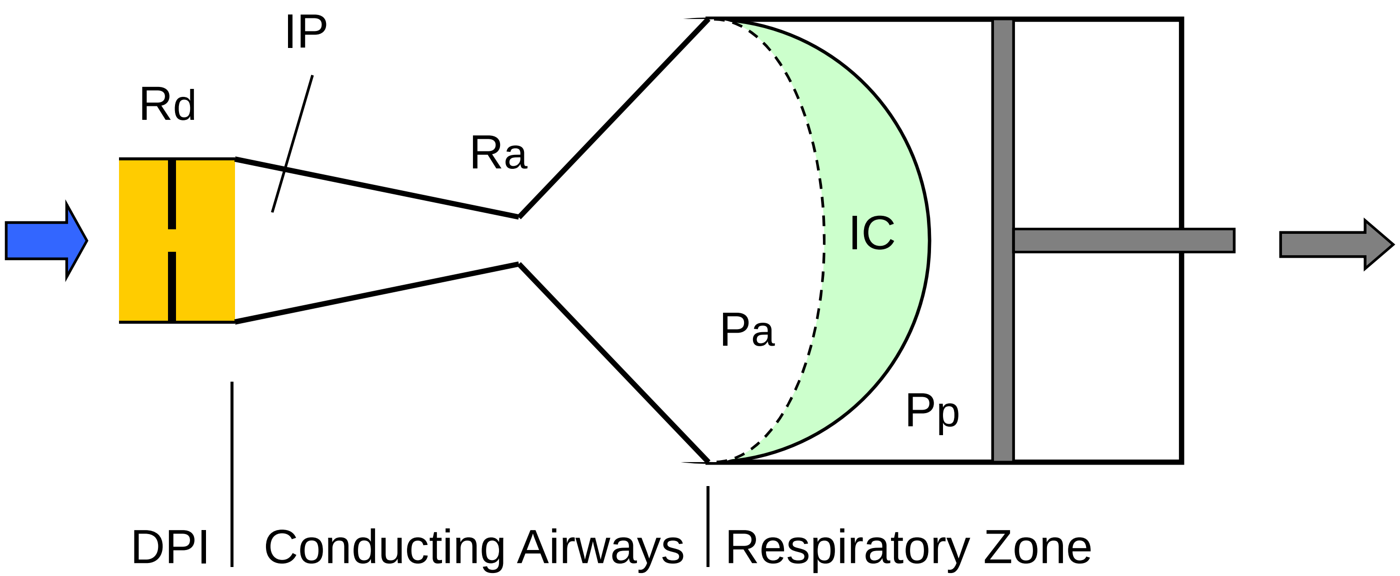


Flowrate: $$Q = \frac{\sqrt{Pa}}{R_a}$$

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

IC: Inspiratory Capacity

Inspiration through a DPI - Mechanical Analogy

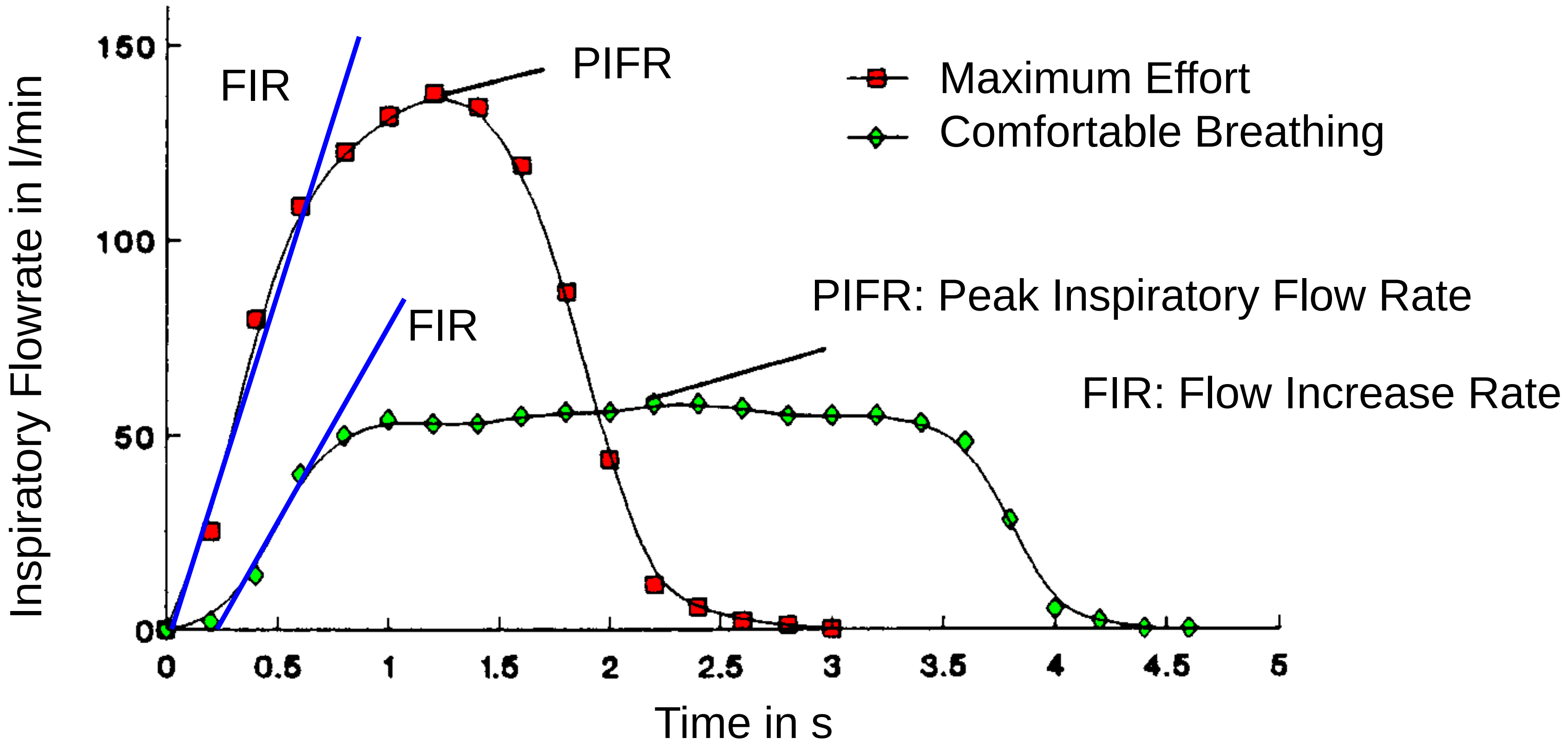


Flowrate: $$Q = \frac{\sqrt{IP}}{R_d}$$, Rd >> Ra

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

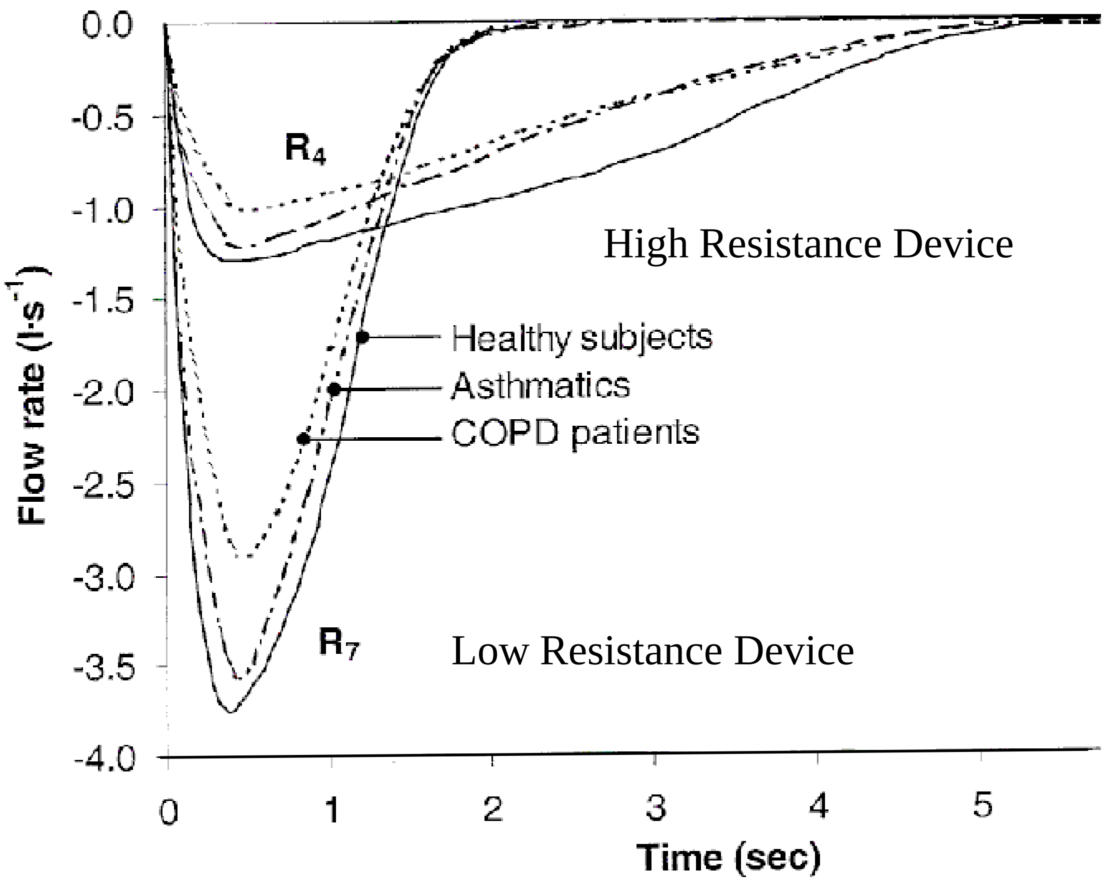
Breathing Profile, Flow Versus Time

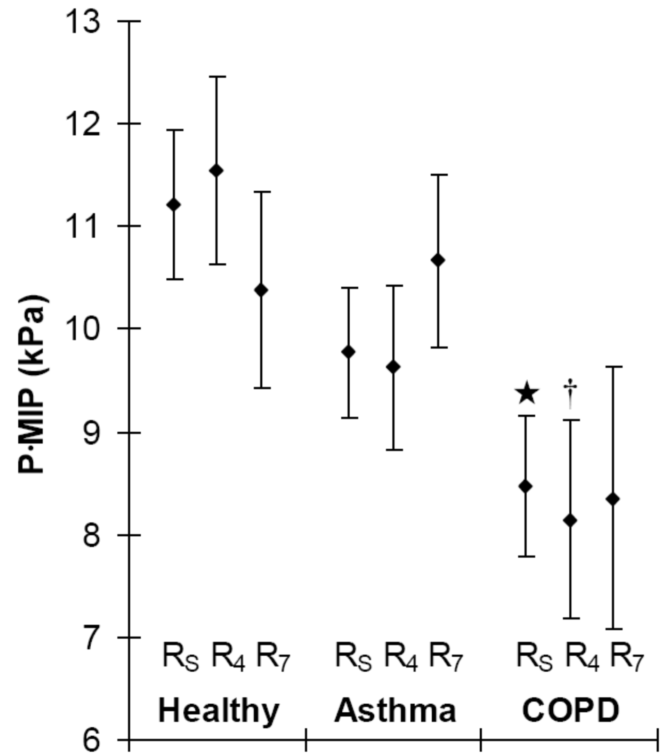
Device Resistance: 0.051 cm $H_2O^{1/2}$ / (l/min)



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

Breathing Profiles and Mouth Pressure in the Diseased Lung





J. P. de Koning, Dry Powder Inhalation, PhD Thesis, Rijkuniversiteit Groningen, 2001

Outline

- Anatomy and Physiology of the Respiratory System
- **Deposition and Pharmacology**
- Delivery and Dispersion Devices
- Powder Manufacture
- Particle Engineering

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.

$$Stk = \frac{s}{x} = \frac{v_0 \tau}{x}$$

$$\tau = \frac{d_a^2 C_C}{18\eta}$$

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

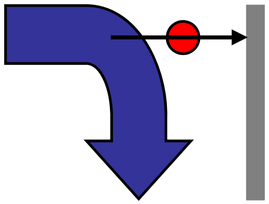
For the impaction of a gas jet onto a surface the characteristic dimension is the jet radius. The particle velocity is assumed to be the same as the gas velocity.

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

$$K = d_a^2 Q$$

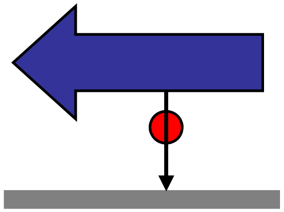
For lung deposition a related parameter, called impaction parameter or inertial parameter, is often used, where Q is the inspiratory flow rate. This is less accurate, because it assumes a fixed geometry.

Lung Deposition - Mechanisms



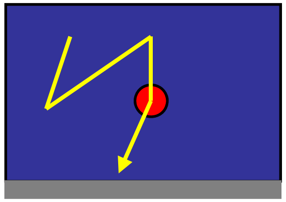
Impaction

Primary mechanism for big particles and upper airways



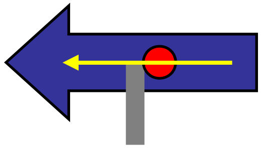
Sedimentation

More important in smaller airways and affected by breath-hold



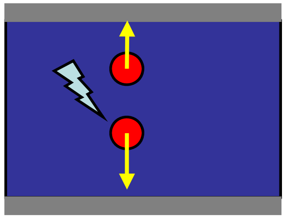
Diffusion

Primary mechanism for small particles in the respiratory zone



Interception

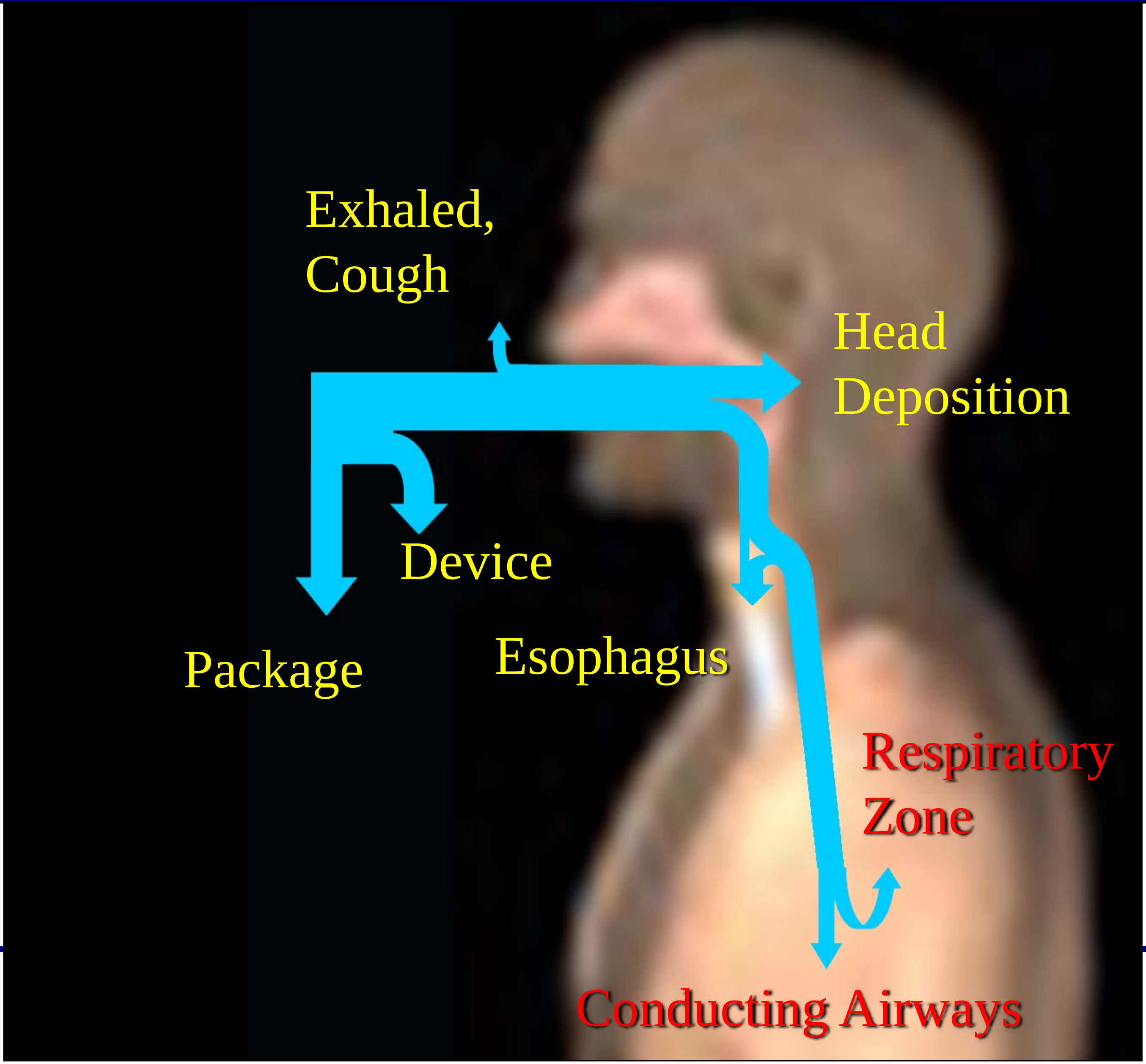
Important for non-spherical particles



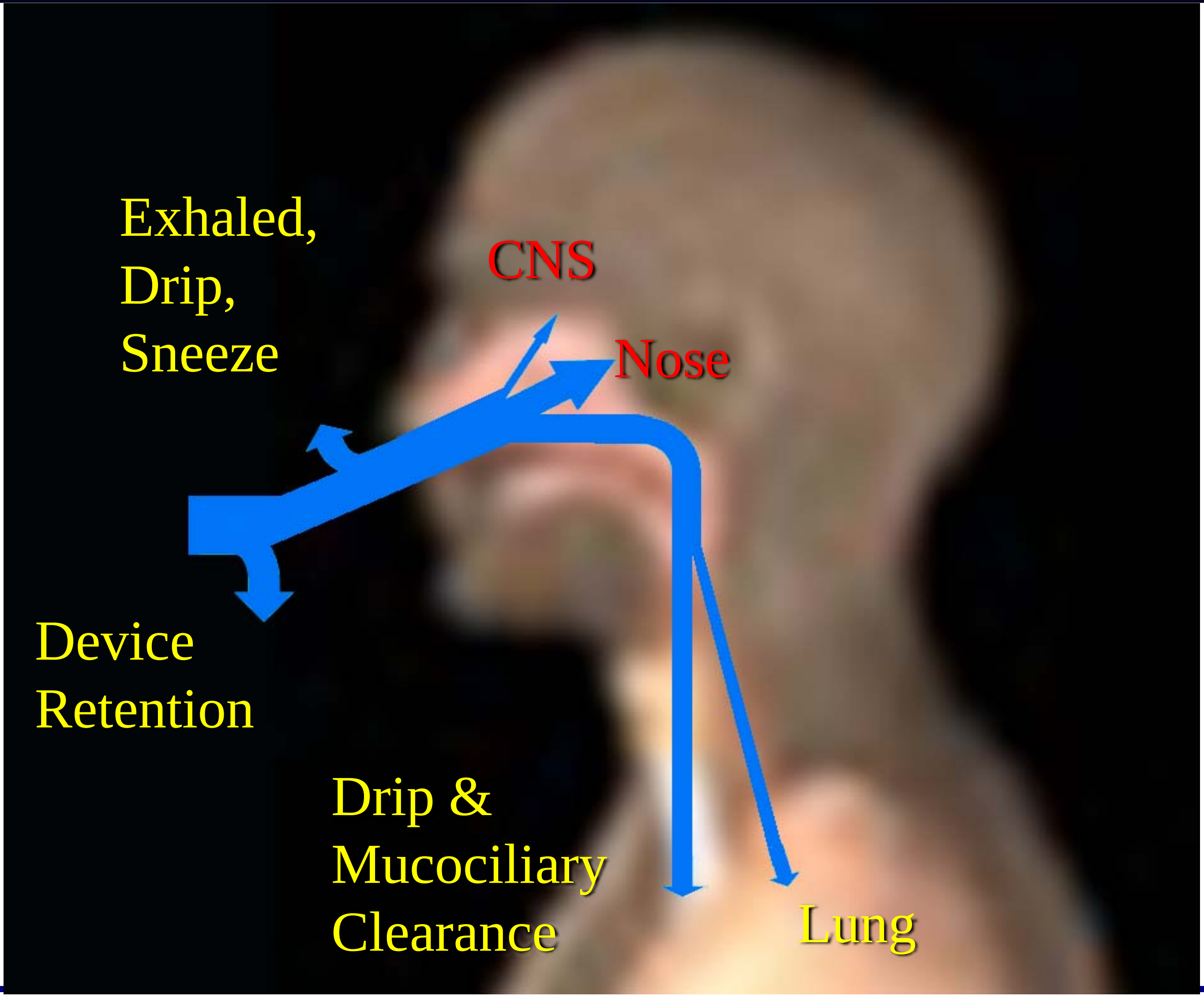
Electrostatic Precipitation

Plays a role in triboelectrically charged aerosol

Losses in Pulmonary Delivery



Losses in Nasal Delivery



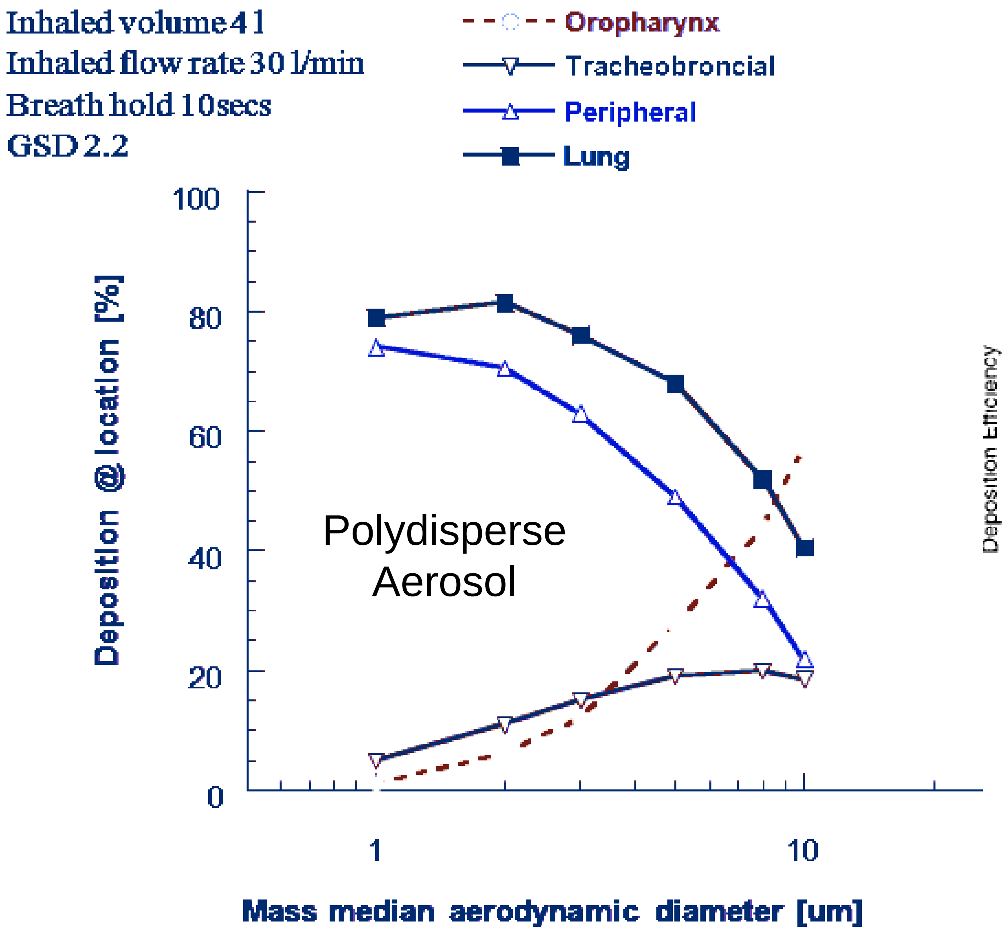
Factors Affecting Lung Deposition

- 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

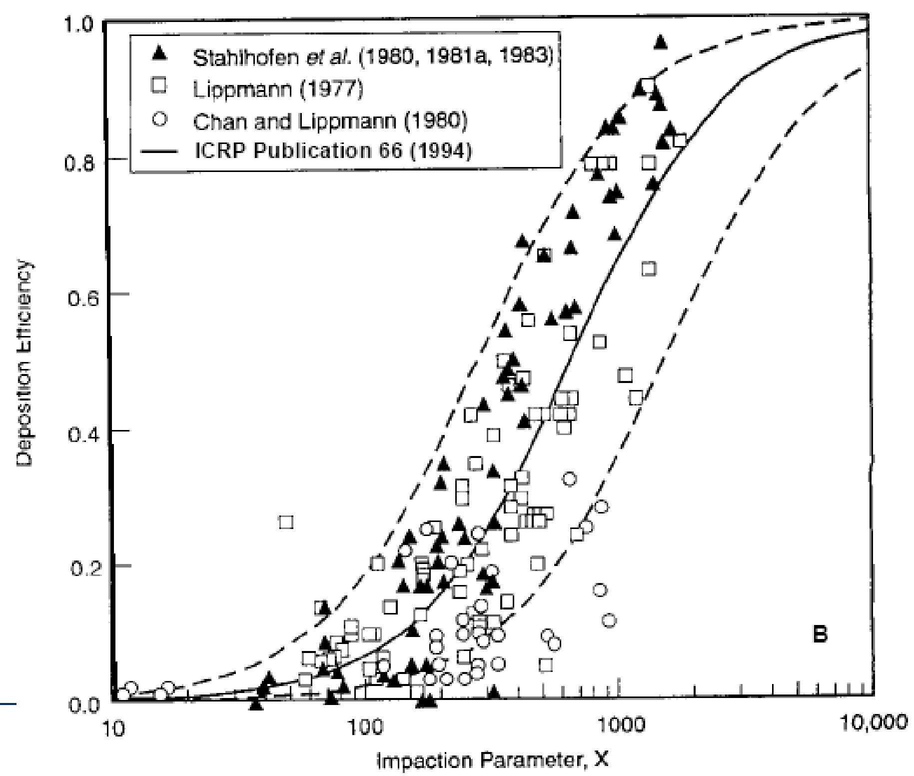
- Formulation
- Delivery Device
- Patient
  - Gender
  - Age
  - Training
  - Disease state
  - Inspiratory Effort

Deposition as a Function of Particle Size and Flow Rate



Extrathoracic Deposition

Particles inhaled through a mouthpiece

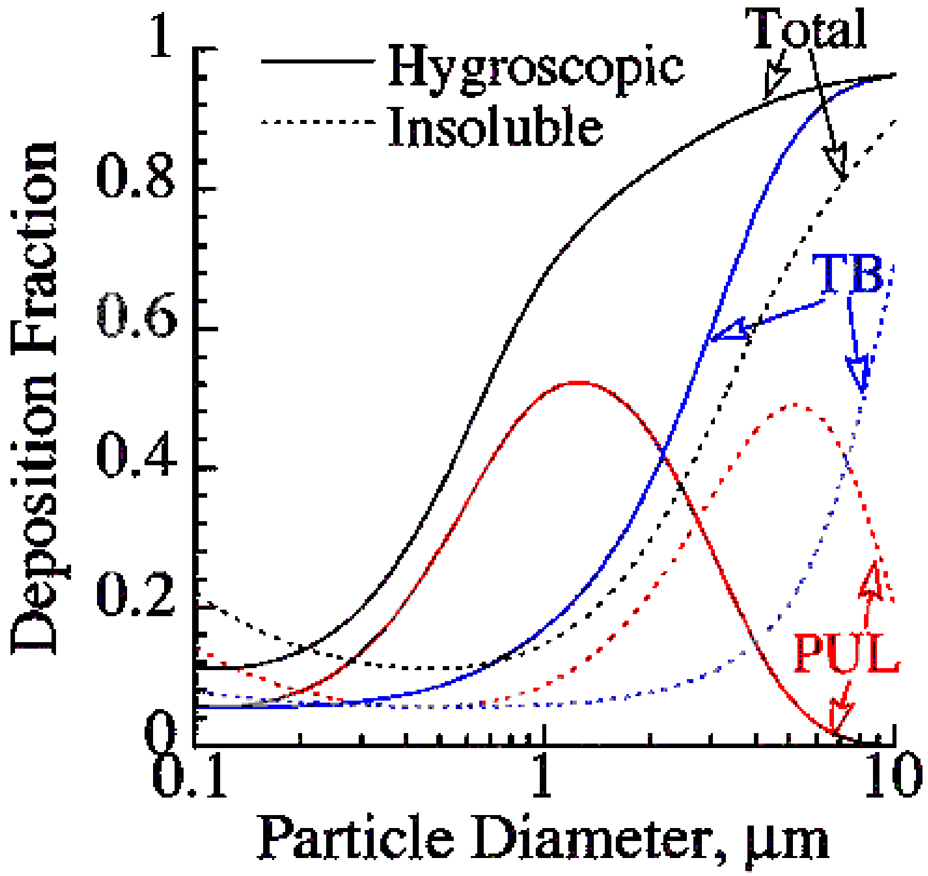


$X = d_a^2 Q^{0.6} V_T^{-0.2}$ [$\mu m^2 cm^{1.2} s^{0.6}$]

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

Hygroscopicity Influences Deposition

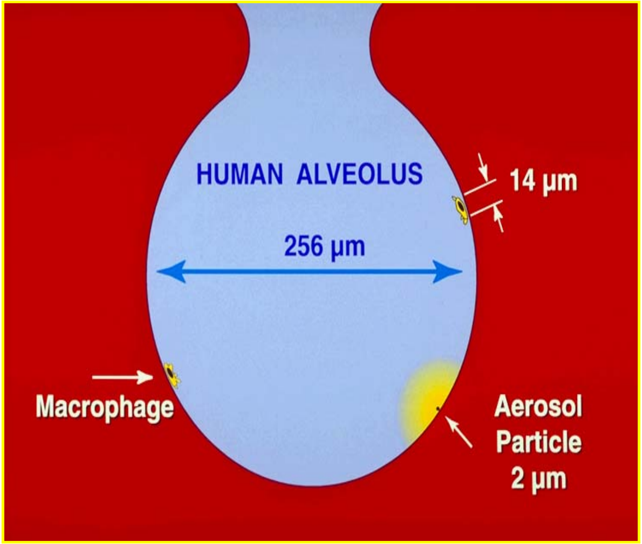
Regional and Total Deposition
Oral Breathing

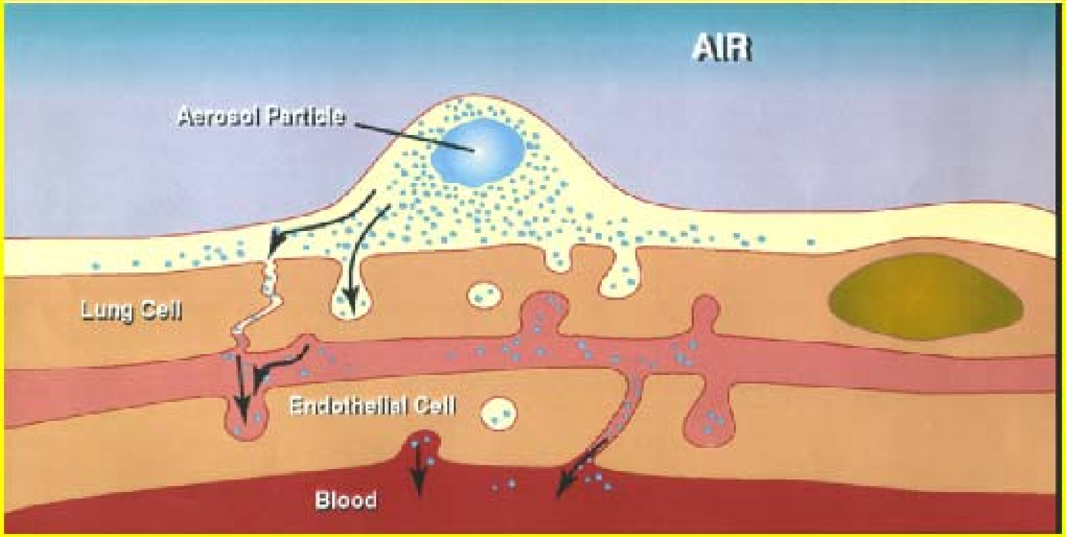


Numerical model results
Tidal volume: 625 ml
Breathing frequency: 15 / min
Monodisperse NaCl particles

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)

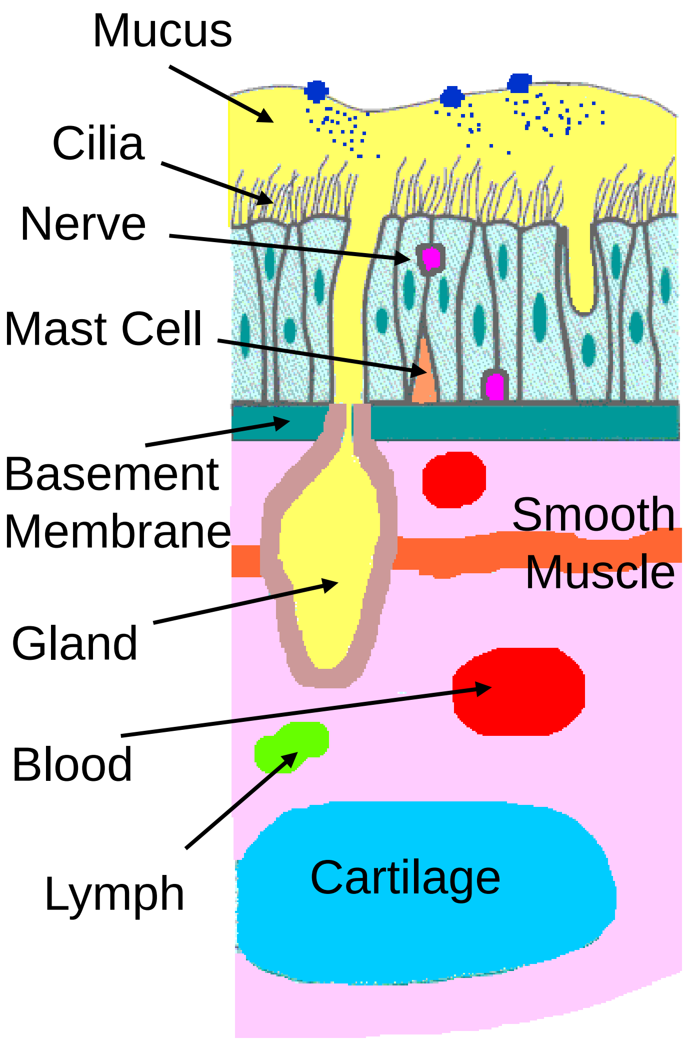
Transport mechanisms

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

Absorption kinetics are fast and depend on

- Molecular weight
- Solubility
- Partition coefficient.

Pharmacology - Local Drug Delivery



Across the Bronchiolar Epithelium

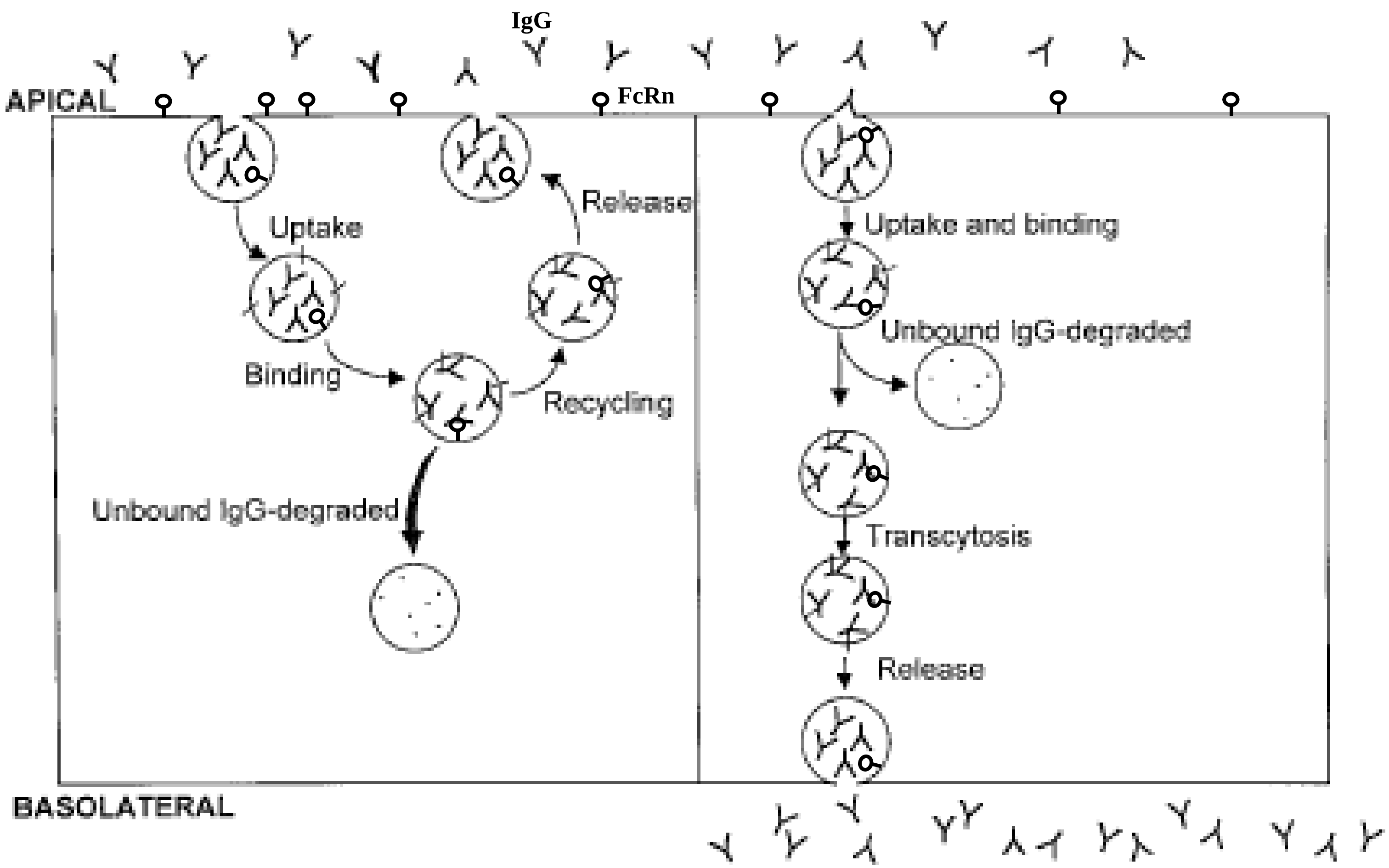
Transport mechanisms

- 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

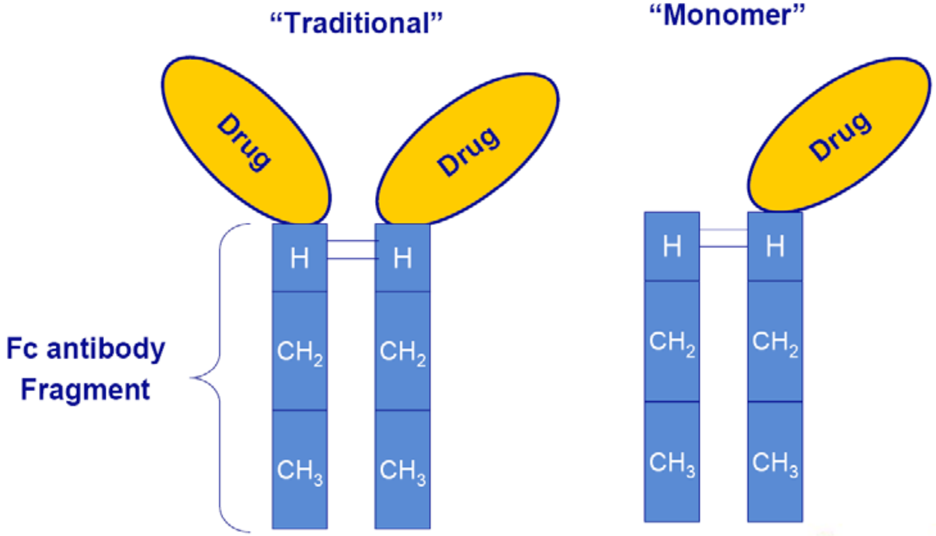
- Slower but targeting the conducting airways is difficult
- Interstitial tissue may act as reservoir

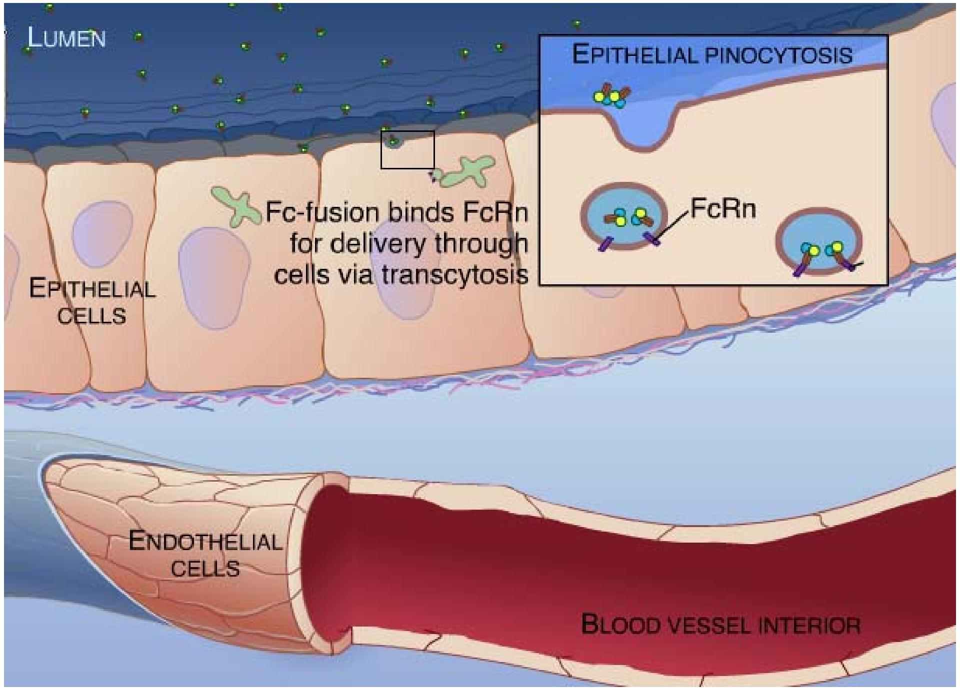
Active Transport Using FcRn Trafficking



Systemic Delivery of Fc-Fusion Molecules (Syntonix)

- Fc-fusion molecules: API attached to Fc fragment.
- 5 to 50 % bioavailability depends on type of fusion molecule, monomeric vs. dimeric.
- Receptor saturation limits capacity for systemic delivery

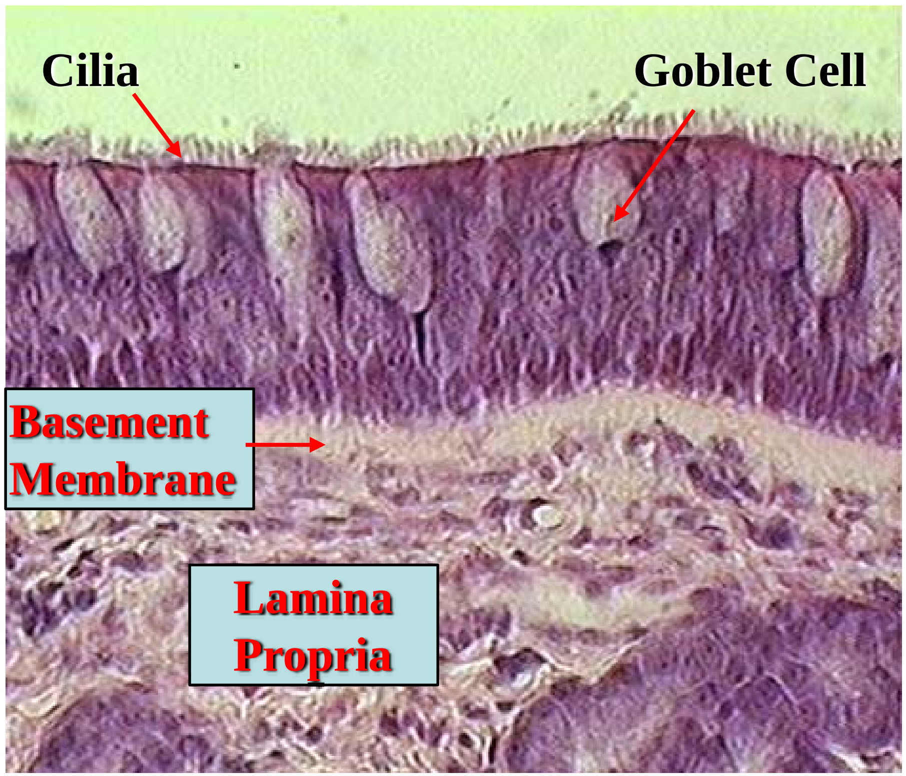




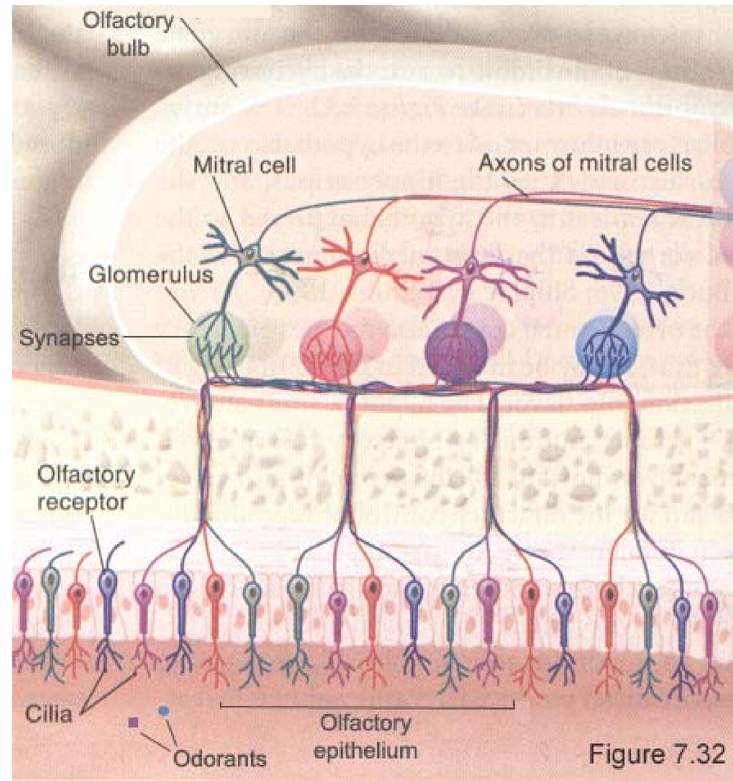
Nose Ultrastructure

- Cilia and mucus transport particles to the pharnyx.
- Mucociliary clearance takes 15 – 20 min
- High bioavailability only for small molecules (< 1 kDa) with rapid uptake (1 - 5 min)

3 – 5 % of total nasal surface



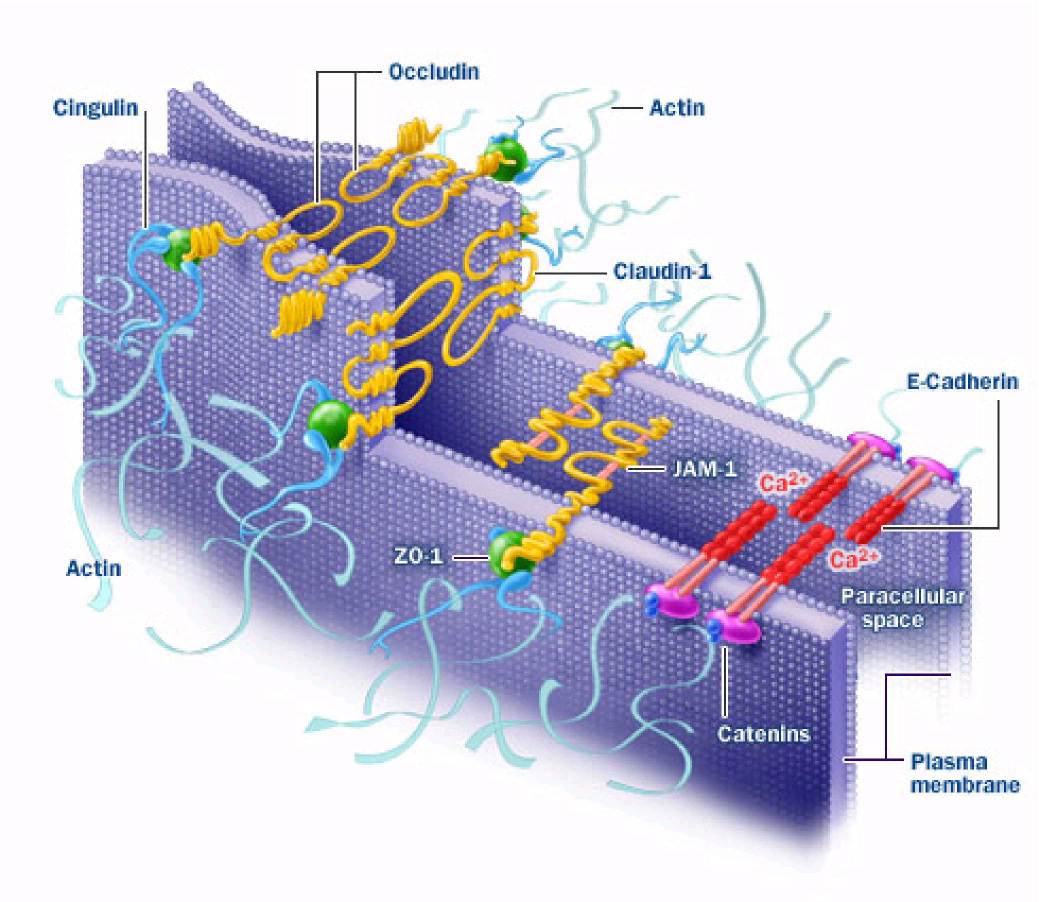
Columnar ciliated epithelium

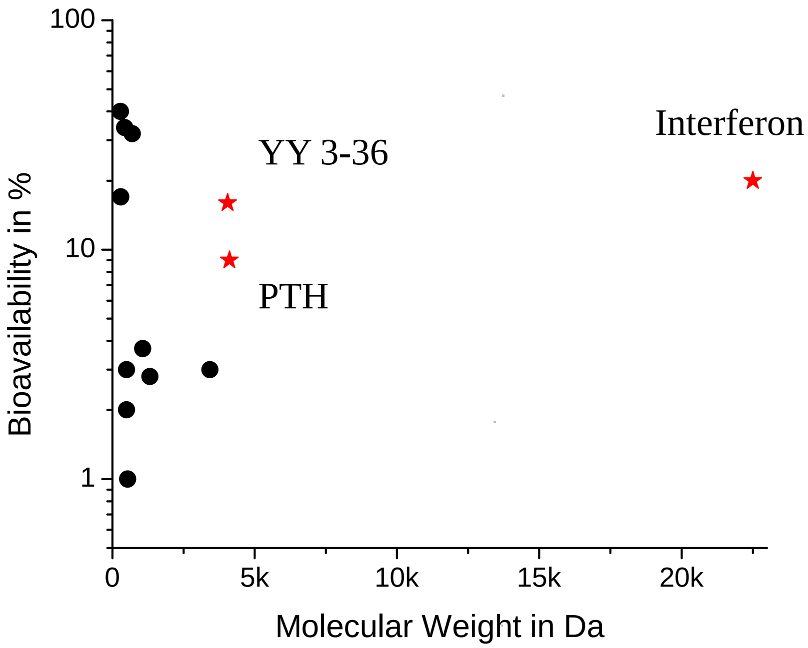


Olfactory Region

casweb.cas.ou.edu/pbell/Histology/Captions/Respiratory/106.nasal.epithel.40x.html
www.colorado.edu/epob/epob3730rlynch/image/figure8-18.jpg

Tight Junction Modulation (Nastech)





http://www.nastech.com/nastech/junctions_biology

Defense Mechanisms and Ways to Beat Them

- **Mucus / Mucociliary Clearance**
- **Phagocytosis**
- **Cellular Barrier**
  - Tight Junctions
  - Cell Wall
- **Lysosomal Proteases**
- **Filter Function**

- Bioadhesives
- Rapidly dissolving particles

- Large particles
- Trojan Horses

- Tight junction modulation
- Transporter, viral vectors
- Molecular carriers, active transport
- Bioactive particle surfaces

- pH sensitive release

- Particle & Device Engineering

Outline

- Anatomy and Physiology of the Respiratory System
- Deposition and Pharmacology
- **Delivery and Dispersion Devices**
- Powder Manufacture
- Particle Engineering

Delivery Devices – Classification

By actuation

- Passive – uses breathing maneuver to administer or disperse dose
- Active – uses external energy source to administer dose
  - Active coordinated – requires cooperation of patient
  - Active uncoordinated – no patient cooperation

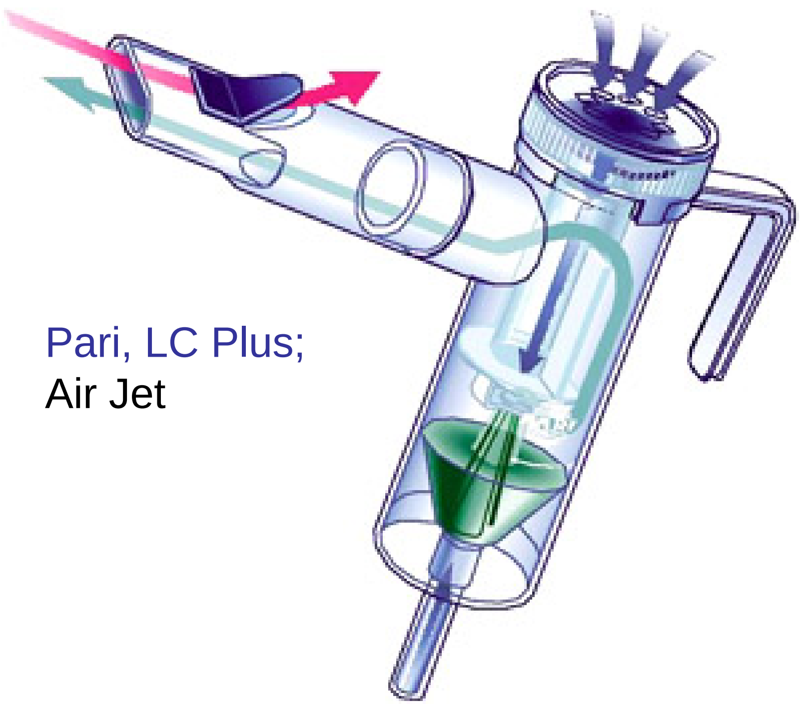
By dosage form

- Liquid (drops, jet, spray, aerosol)
- Suspension
- Dry (homogeneous powder, blend, on carrier)

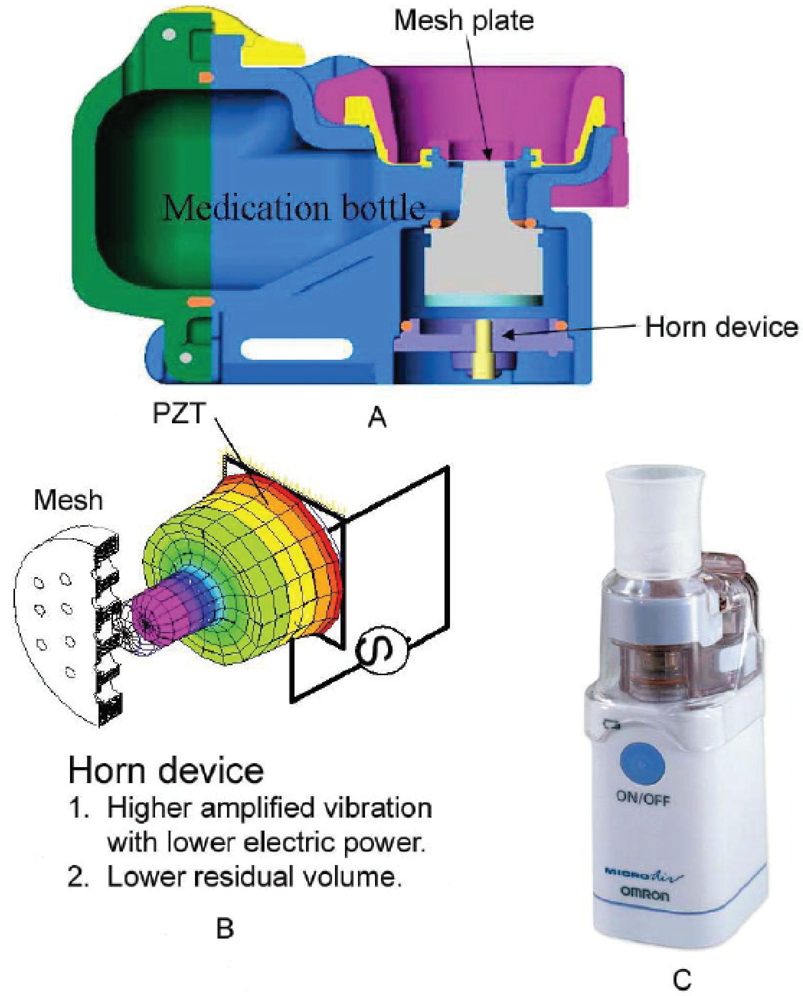
By dosing type

- Single dose
- Multi dose
  - Reservoir
  - Unit packaged (single course, refillable)
- Metered versus unmetered
- Administration to a single patient versus multiple patients

Nebulizer Types



Pari, LC Plus;
Air Jet



Omron, MicroAir; Ultrasonic / Vibrating Mesh

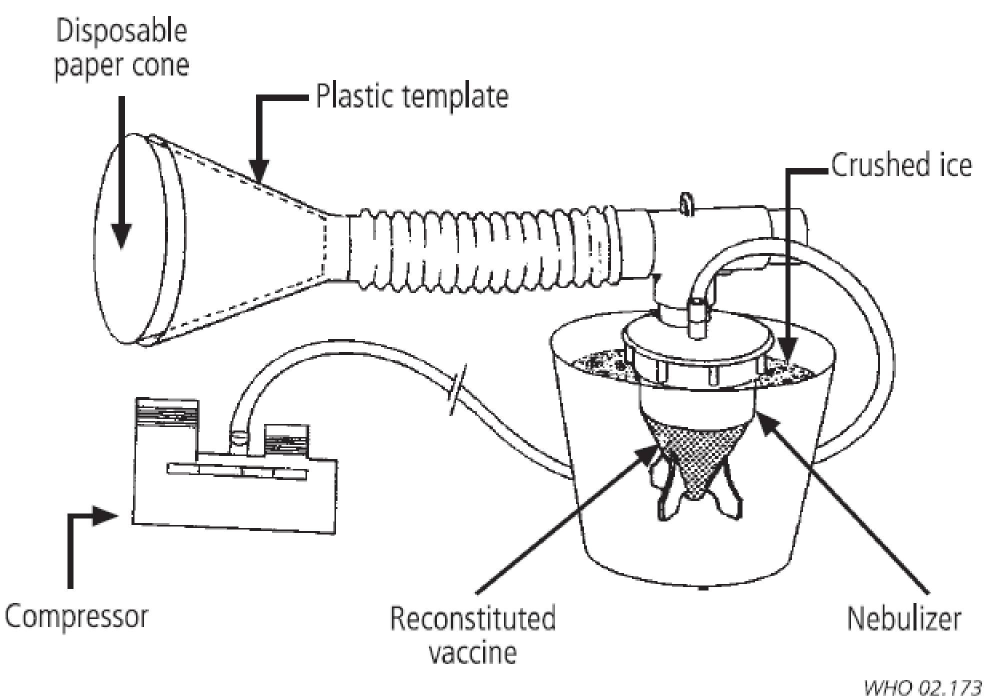
Business Briefings Ltd.: Long-Term Healthcare Strategies 2003; www.pari.com/products/index.html

Pulmonary Mass Inoculation Systems

Used by WHO for measles mass immunization
Multi patient delivery with disposable patient interface.

Attack rates during the 1988-90 measles outbreak in Mexico:
Not vaccinated: 26 %
Vaccinated SC: 14 %
Vaccinated pulmonary: 0.8 %

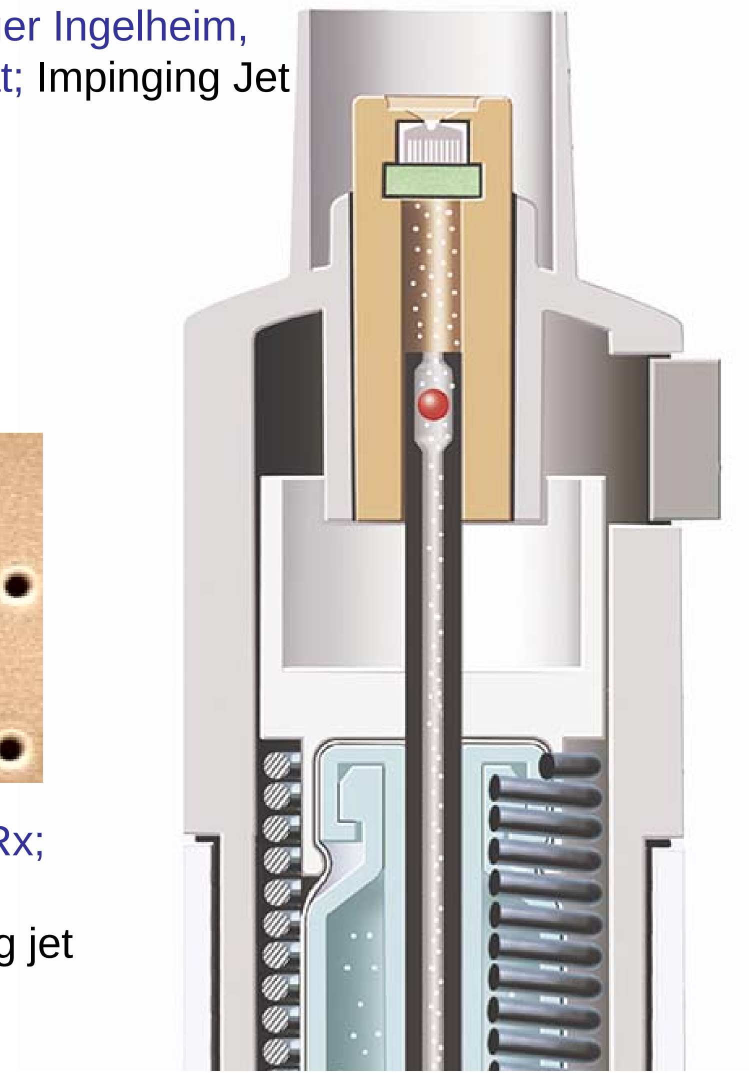
Fig. 1. Diagram of equipment used to aerosolize vaccines



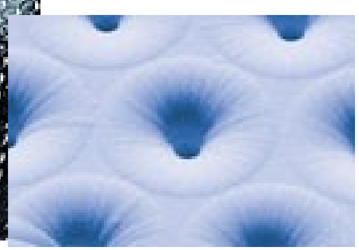
http://www.who.int/vaccine_research/diseases/measles/en/aerosol.pdf

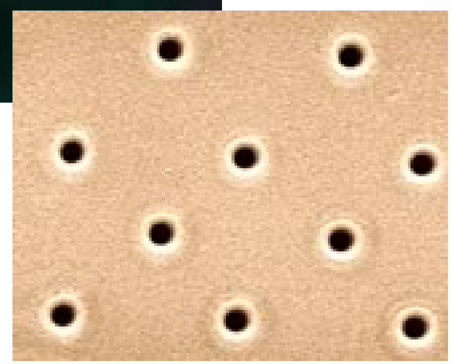
New Nebulizer Developments

Boehringer Ingelheim,
Respimat; Impinging Jet



Aerogen / Nektar,
OnQ; Micropump,
Vibrating mesh

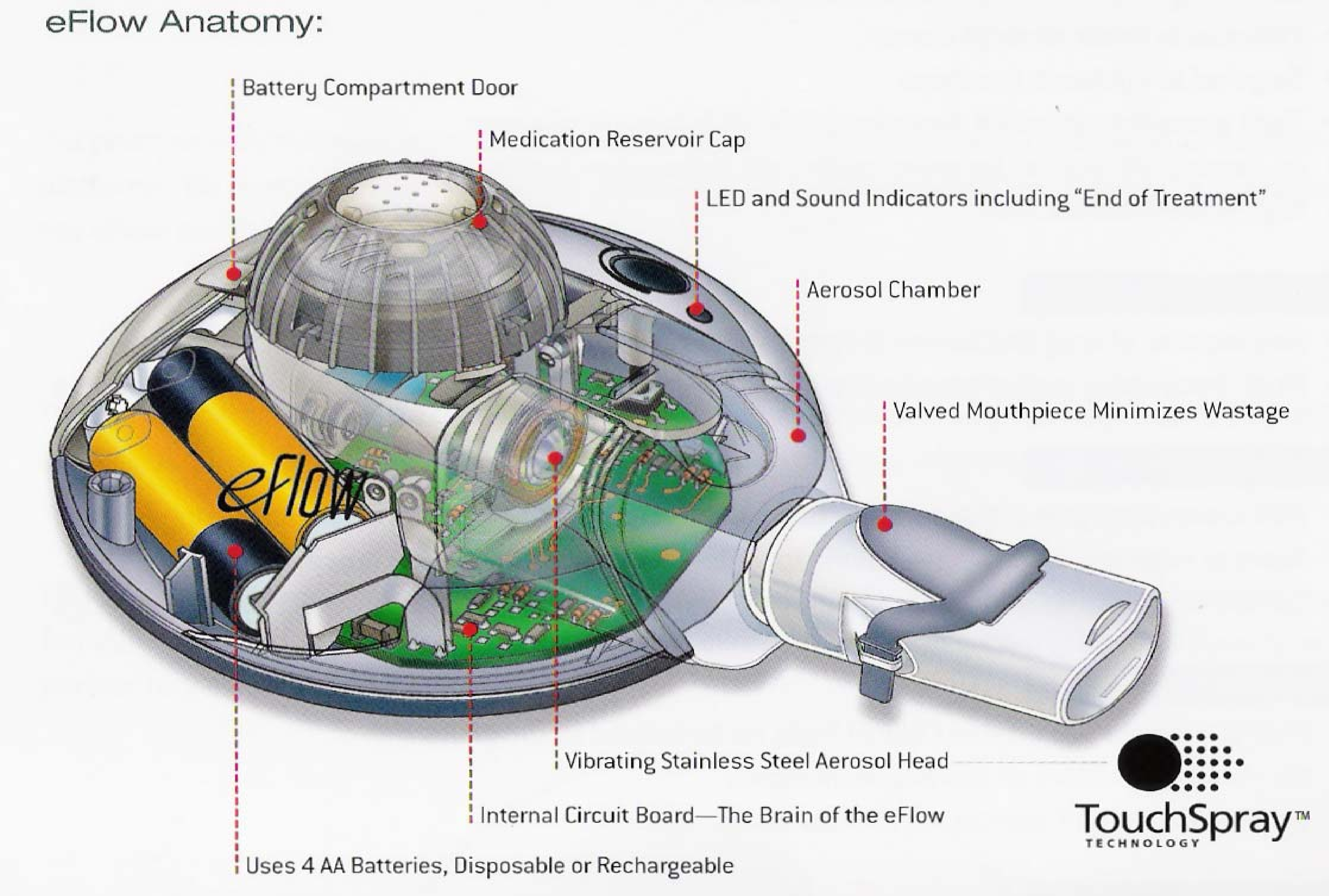




Aradigm AERx;
Microorifice /
Disintegrating jet

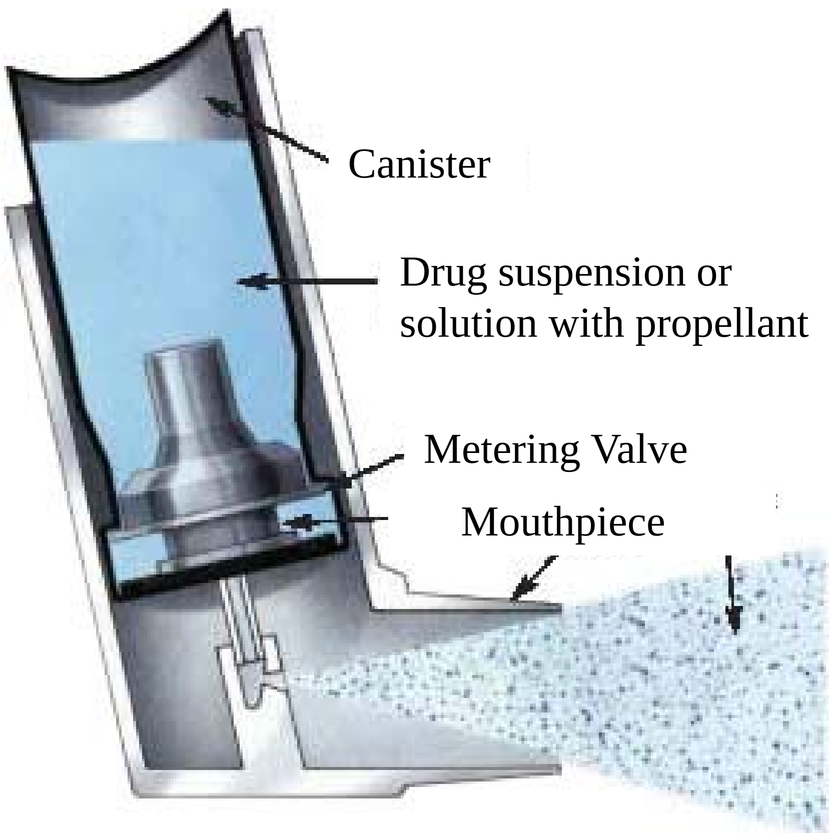
www.respimat.com; www.aradigm.com/tech/aerx_tech.html; www.aerogen.com/onq/index.htm

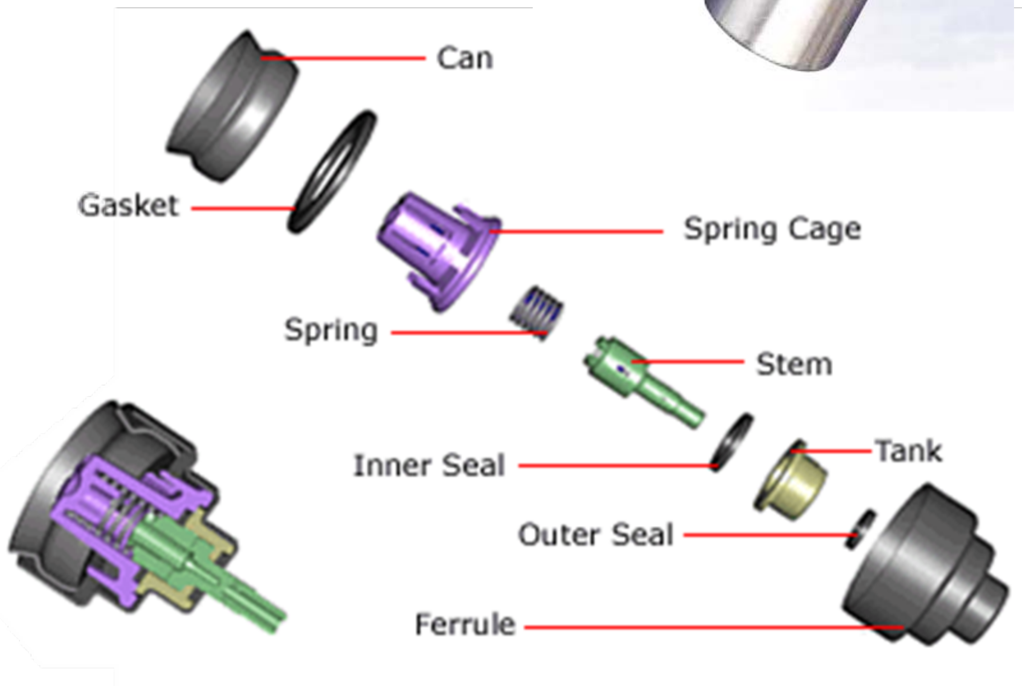
Stand-Alone, Hand-Held Nebulizer (Pari)



Pressurized Metered Dose Inhalers

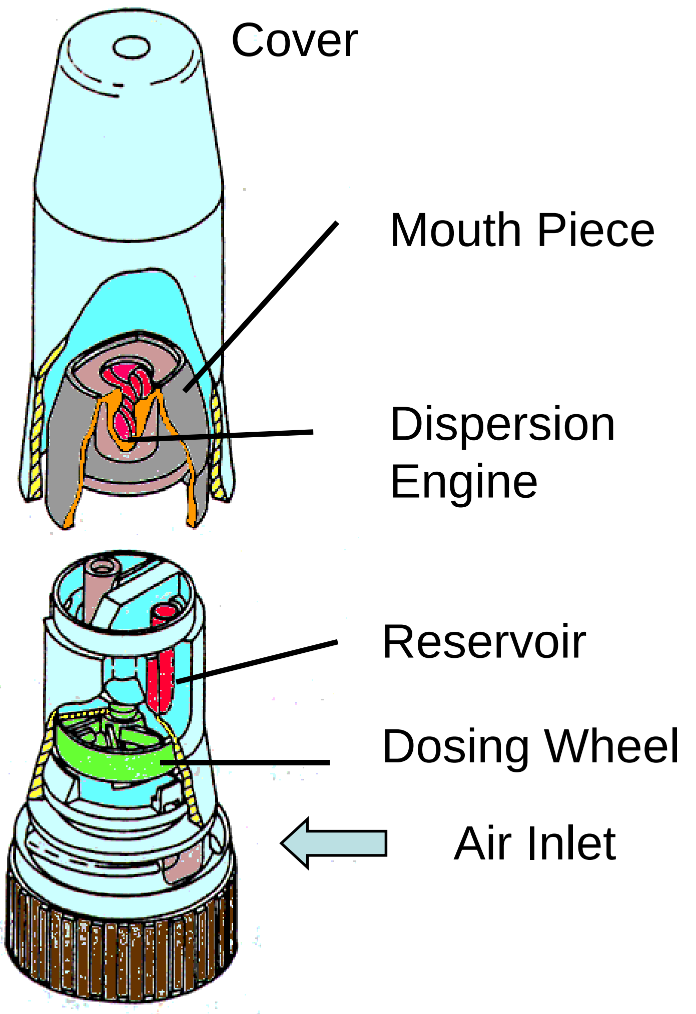
Propellant driven spray (solution or suspension).
Multi-dose, metered.
Active (coordinated) device





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

Multi-Dose Dry Powder Inhaler - Reservoir



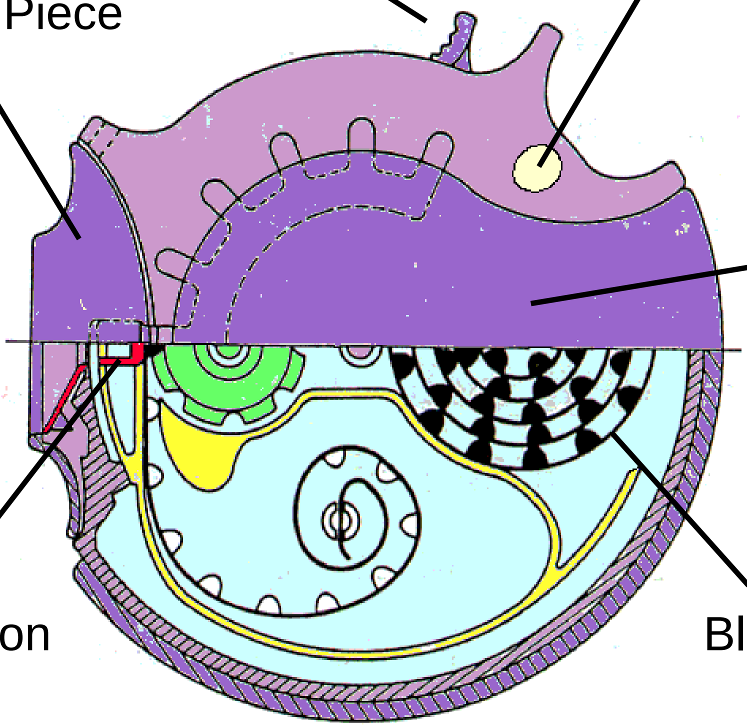
Example:

Turbuhaler (Astra Zeneca)

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

Dry powder aerosol.
Multi-dose, reservoir metered.
Passive device

Multi-Dose (Maintenance) Dry Powder Inhaler - Blister



Example:

Diskus (GSK)

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

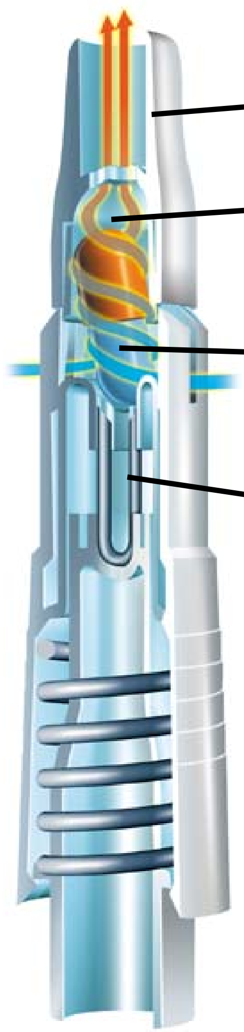
Multi-Dose (Therapy) Dry Powder Inhaler - Blister

Example:

DiskHaler / Relenza (GSK)
Antiviral therapy

- Uses 20 mg lactose carrier + 5 mg of active
- Daily dose in blister disk
- Room temperature storage
- 13 ! steps to administer

Single-Dose Passive 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

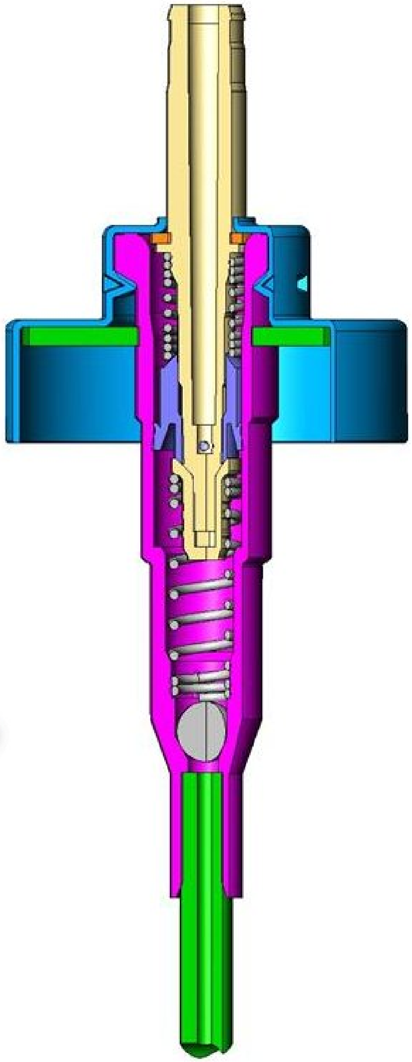
Single-Dose Active Dry Powder Inhaler - Blister

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

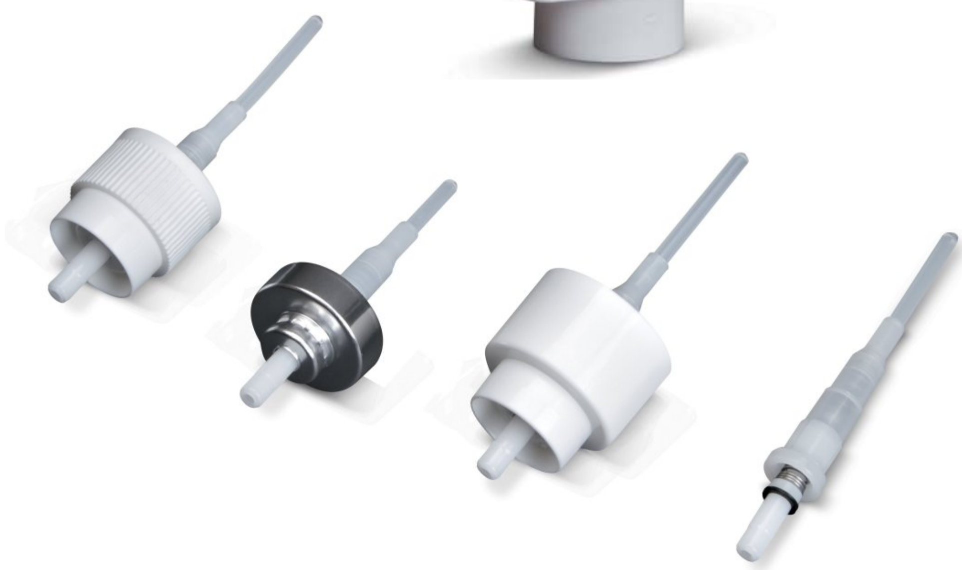
Nasal Delivery Devices – Spray Bottles

Pump



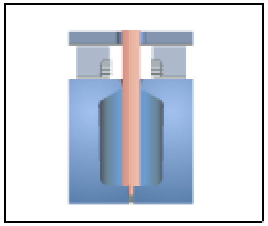
Applicator

Squeeze
bottle



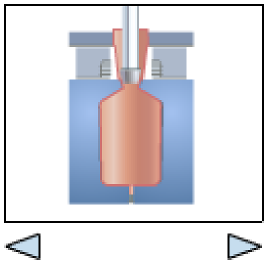
Drops, jet or spray.
Multi-dose.
Unmetered or coarse
Metering.

Blow-Fill-Seal Technology



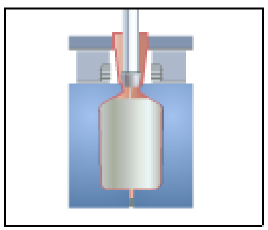
Extruding

The plastic parison, extruded from polymer, is accepted by the opened blow mould and cut below the die of the parison head.



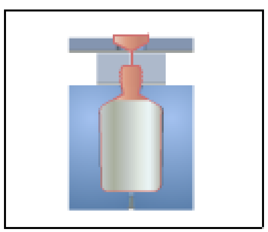
Moulding

The main mould closes and simultaneously seals the bottom. The special mandrel unit settles onto the neck area and forms the parison into a container using compressed air or vacuum.



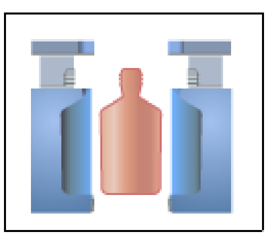
Filling

By the way of the special mandrel unit, the product precisely measured by the dosing unit is filled into the container.



Sealing

After the special mandrel unit retracts, the head mould closes and forms the required seal by vacuum.

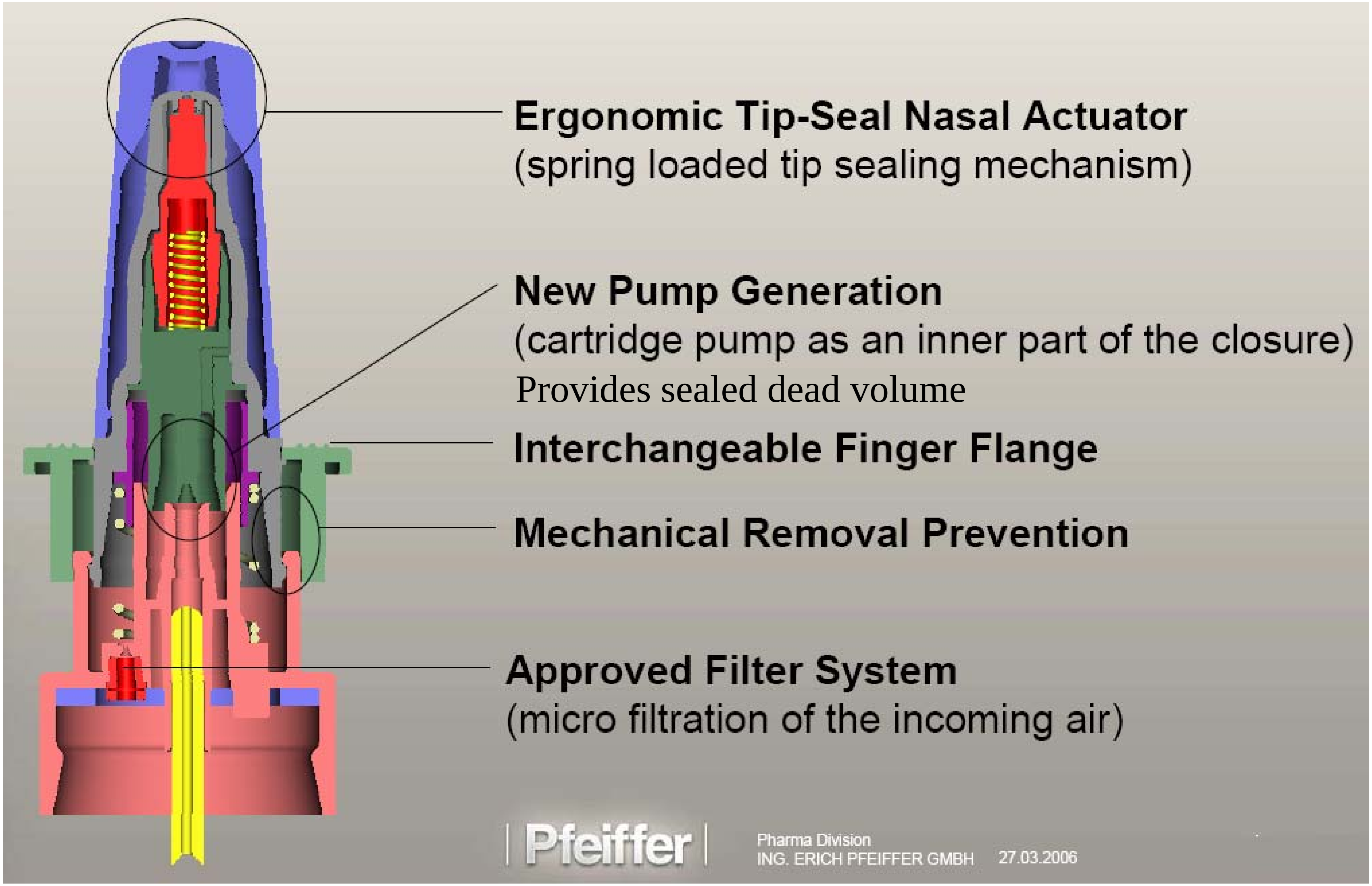


Mould opening

With the opening of the blow mould, the containers exits from the machine and the cycle repeats itself.

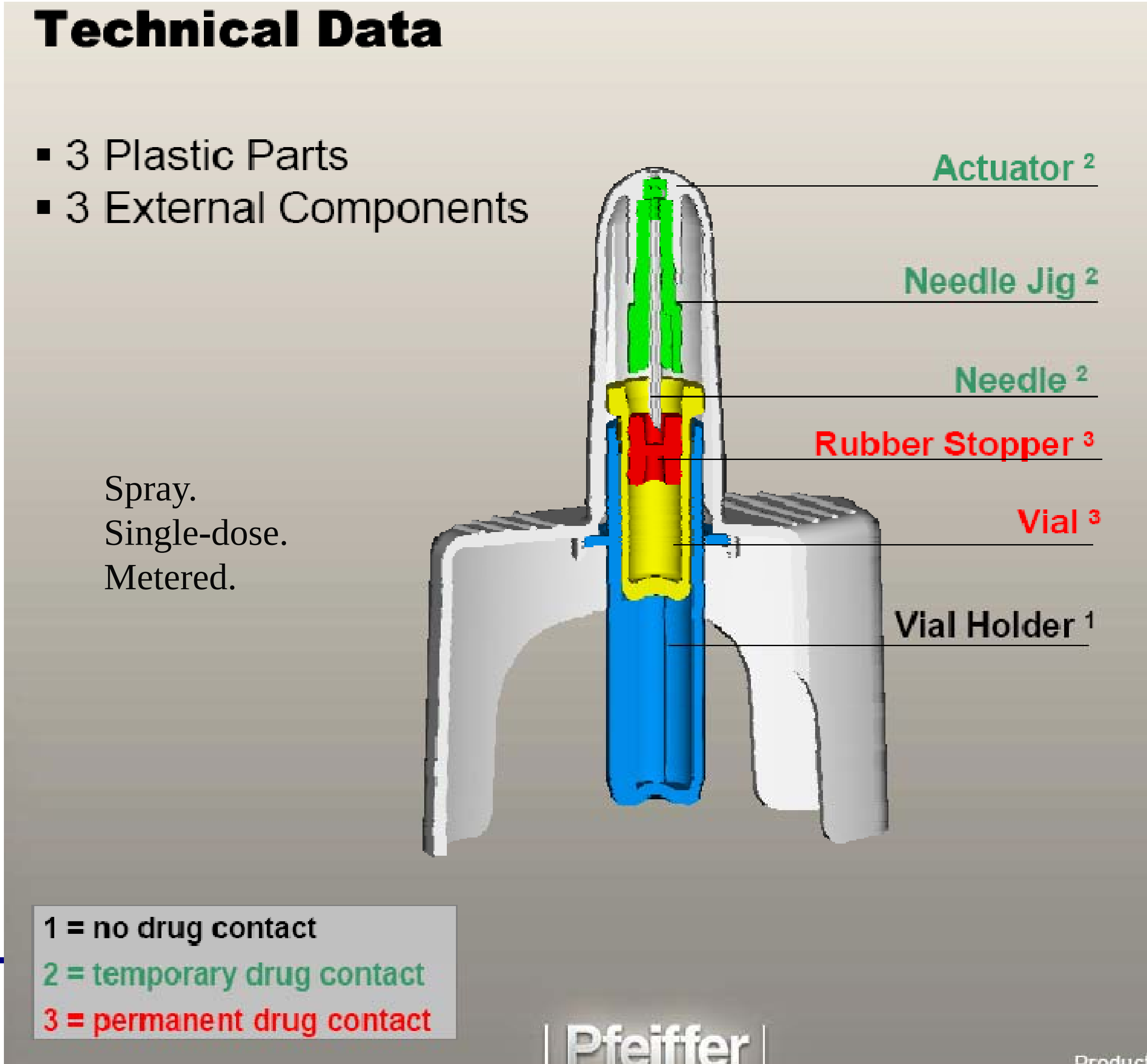
Drops, jet, spray?
Single-dose.
Metered.

Preservative Free Spray Bottle



Metering Spray Pump working as a closed system: (Aerodiol® from Servier, Nezeril® from Astra Zeneca, and Otrivin® from Novartis)

Nasal Delivery Devices – Metered Sprays



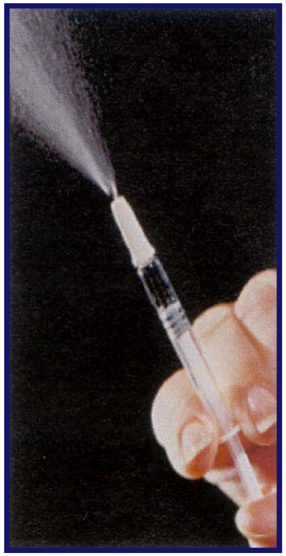
Spray.
Single-dose.
Metered.

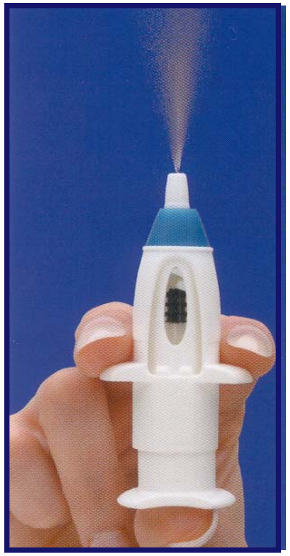
Used in

- ➢ Hormone replacement therapy (Oestradiol),
- ➢ Osteoporosis (Calcitonin),
- ➢ Pain management (Butorphanol, Sumatriptan, and Zomitriptan),
- ➢ Smoking cessation (Nicotine),
- ➢ Enuresis (Desmopressin),
- ➢ Motion sickness (Metoclopramide)

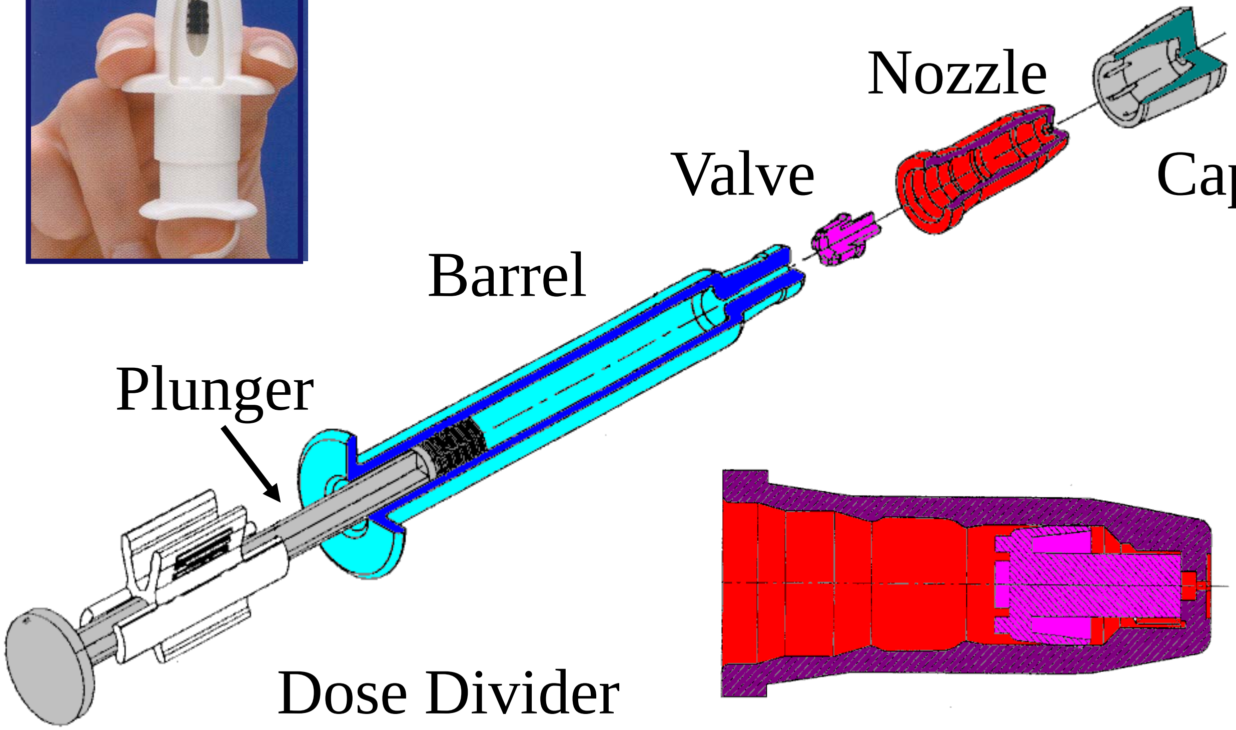
Nasal Delivery Devices – Metered Sprays

BD - Accuspray





Vaccine Delivery

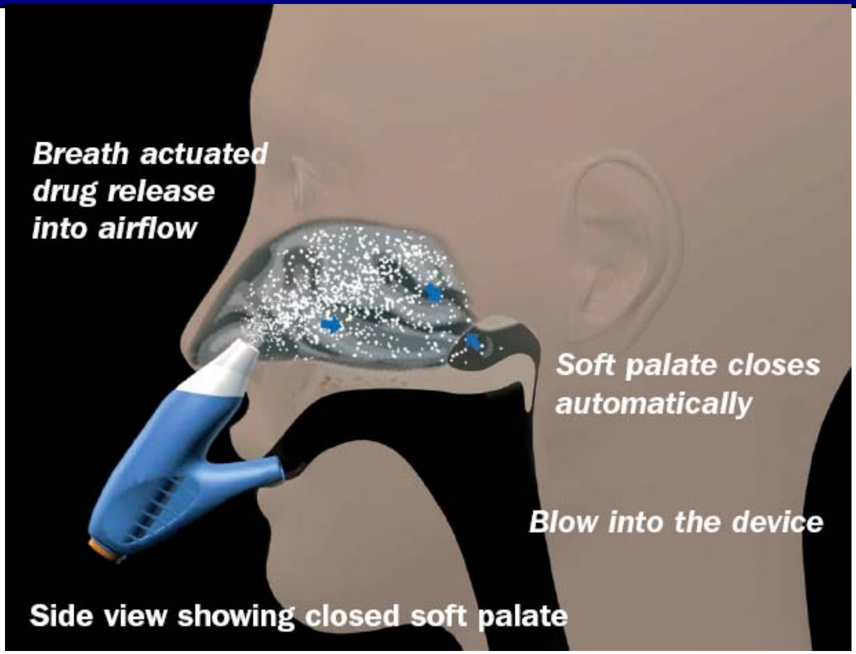


Spray.
Bi-dose.
Metered.

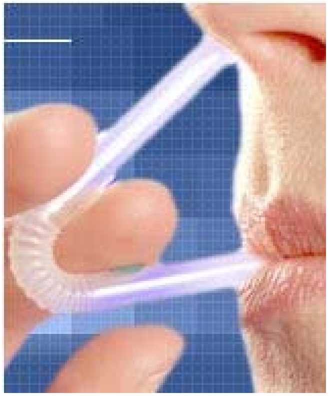
MedImmune, Inc., FluMist

Nasal Delivery Devices – Bidirectional

OptiNose



Spray.
Multi-dose.
Metered
Breath actuated
Active coordinated.



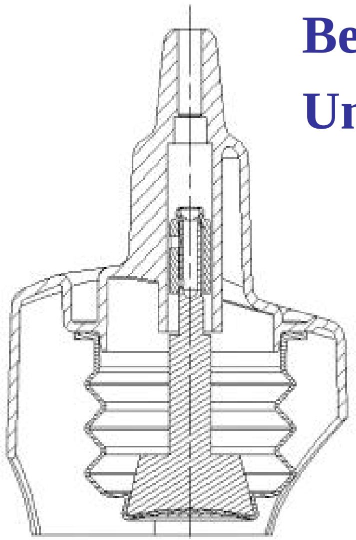
DirectHaler

Dry powder

Dry powder.
Single dose.
Passive.

http://www.optinose.no/publications/files/20051010171411_OptiNose_OnDrugDelivery_2005.pdf

Nasal Powder Delivery Devices – Active



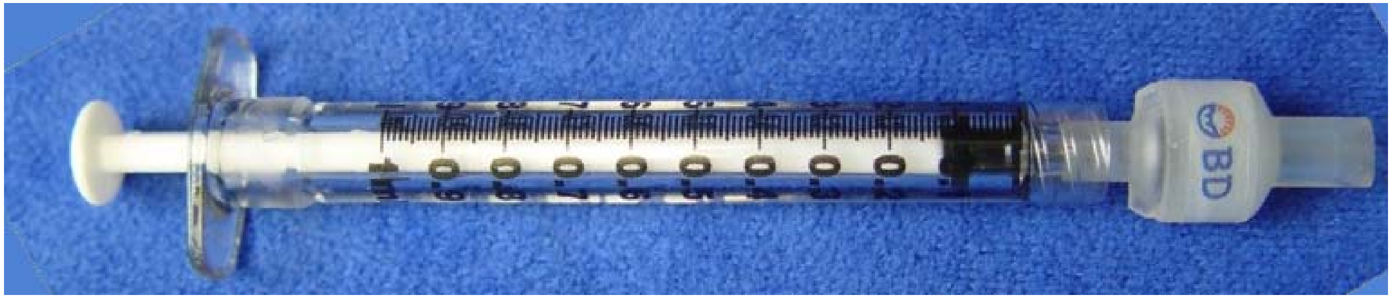
Bespak

Unidose DP

Valois Monopowder

Dry powder.
Active uncoordinated.
Single dose.

BD SoloVent



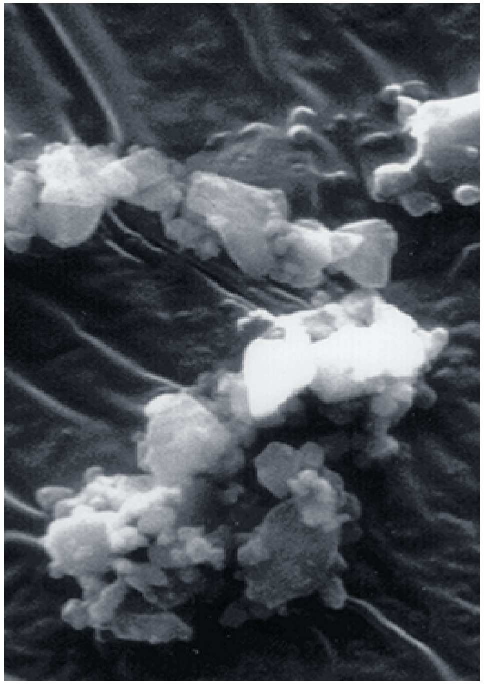
Outline

- Anatomy and Physiology of the Respiratory System
- Deposition and Pharmacology
- Delivery and Dispersion Devices
- **Powder Manufacture**
- Particle Engineering

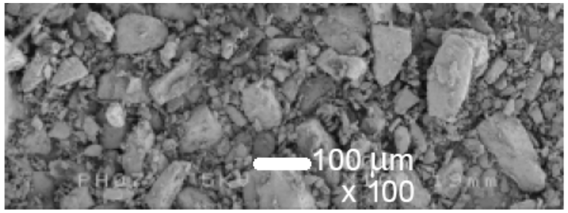
Powder Manufacturing Methods – Milling and Blending

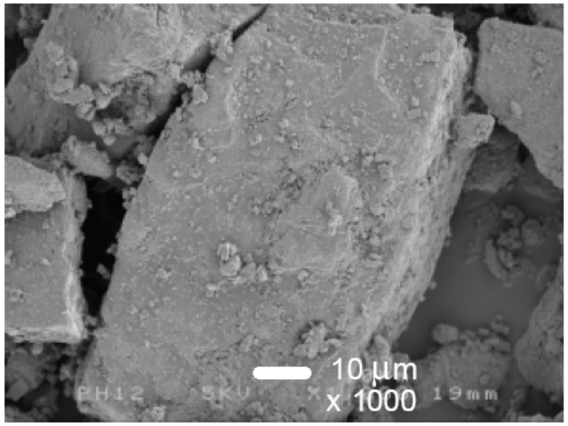
Milling
- Jet-milling (dry)
- Homogenization (wet)
- Cryo-milling (cold)

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



Micronized Budesonide

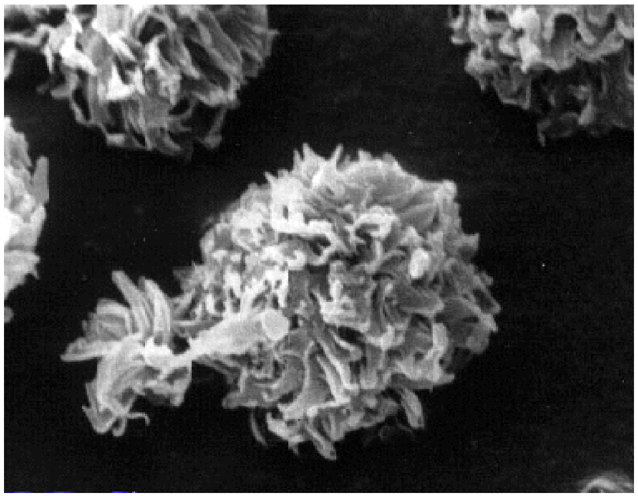




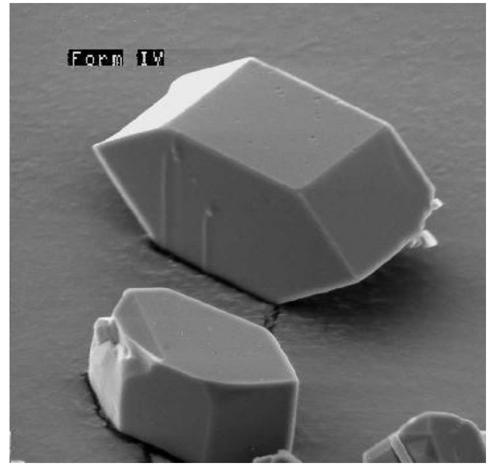
Lactose Blend

Powder Manufacturing Methods – Precipitation and SCF

Precipitation

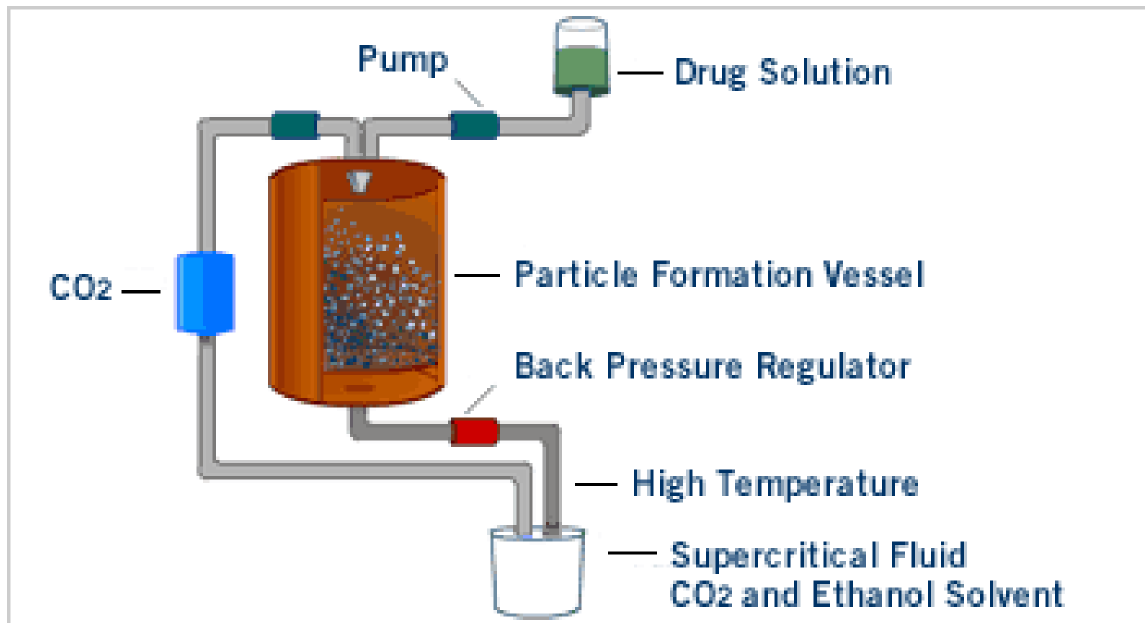


Example:
Mannkind Technospheres:
Self Assembling Particles
Precipitation induced by pH shift



Supercritical Fluid Particle Technology

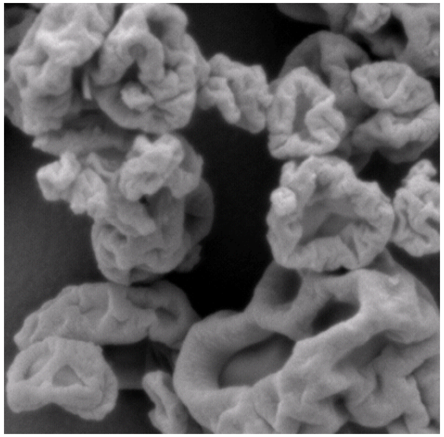
Dispersion and solvent extraction by supercritical fluids



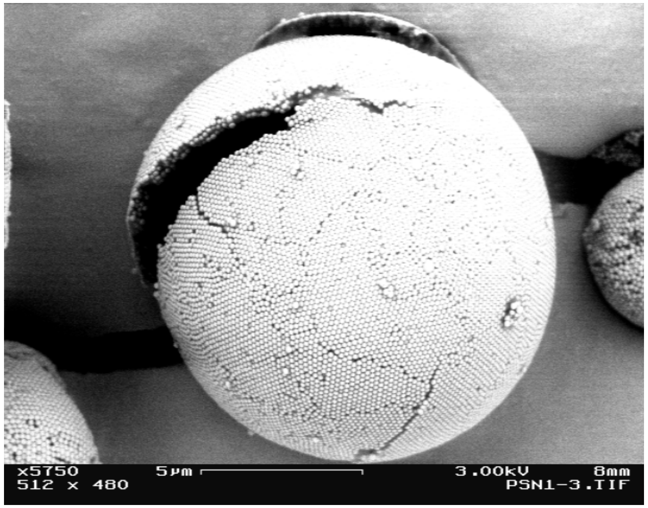
Powder Manufacturing Methods – Spray Drying

Spray Drying

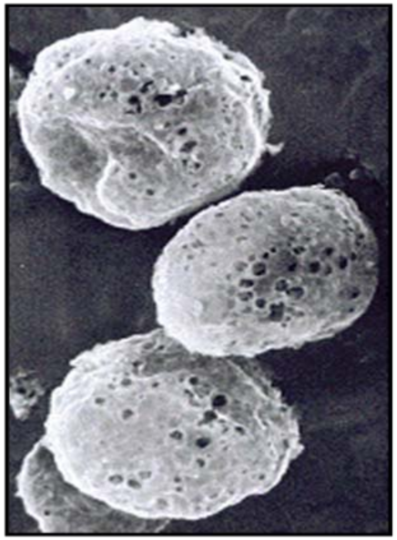
- Solutions
- Suspensions, dispersions
- Emulsions
- Co-solvent
- With pore-forming agent



Protein solution



Nanoparticle suspension



Pore-forming Agent

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 by Spray Drying**

Particle Engineering Basics

- Particle design requires a good understanding of the particle formation process
- Particle formation is determined by formulation *and* process
- The balance between material properties (solubility, diffusion coefficient, solid state properties) and process parameters (droplet size, evaporation rate, droplet temperature) is key to designing the desired particle morphology

Studying the Particle Formation Process

Problem:

The two phase flow in an actual spray dryer is difficult to model.

Heat and mass transfer processes are difficult to study *in situ*.

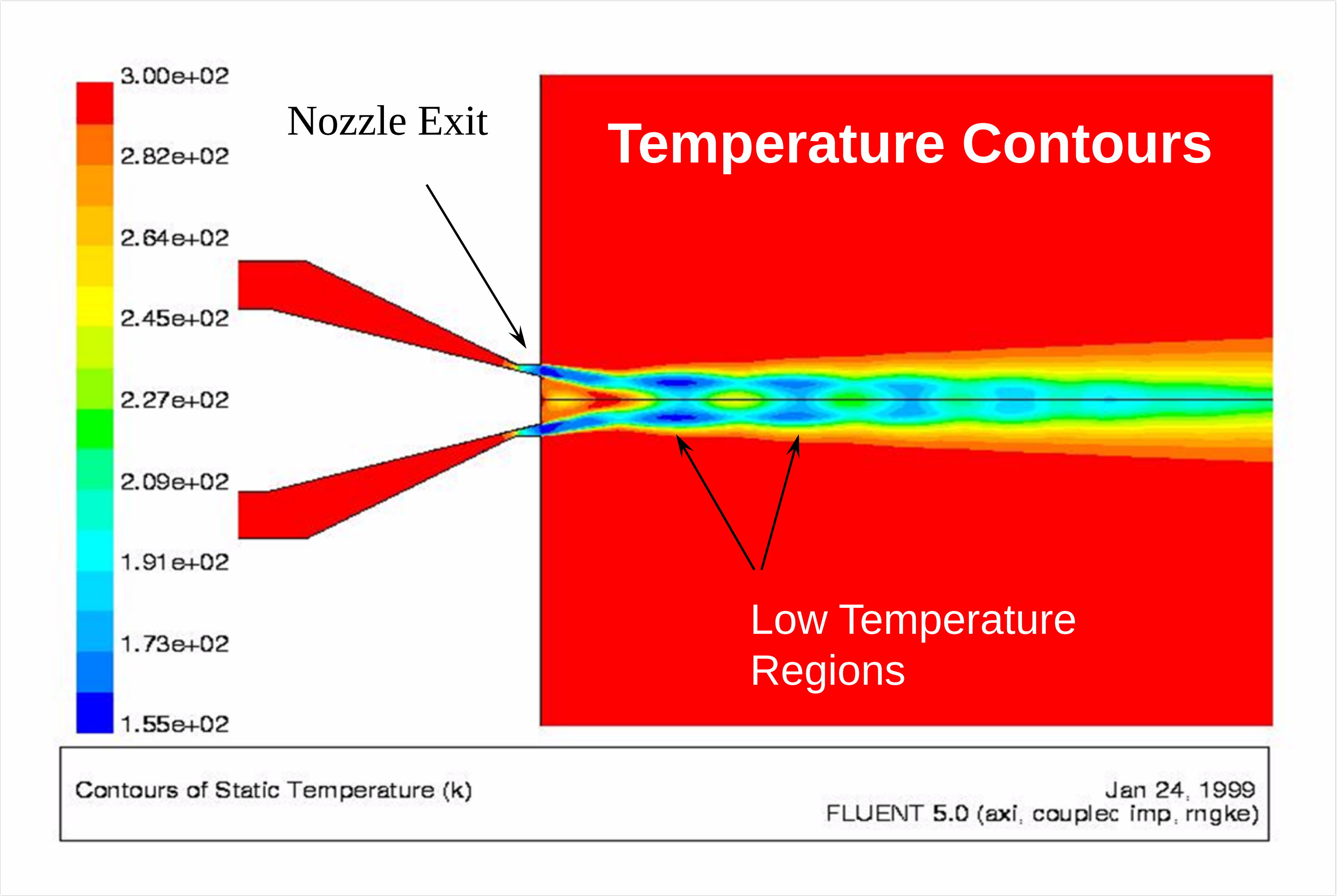
Comprehensive numerical models of evaporation and particle formation are very complex and of limited use due to missing material properties

Approach:

Isolate and study relevant sub-processes in idealized environments

- *Single droplets* (acoustic, electrodynamic, optical levitation, concave hot plate, filament technique)
- *Droplet chains* (vibrating orifice, droplet-on-demand)
- *Research spray dryers* (highly instrumented, monodisperse)
- Approximate analytical model for particle formation
- CFD models for sub-processes with simplified two-phase conditions

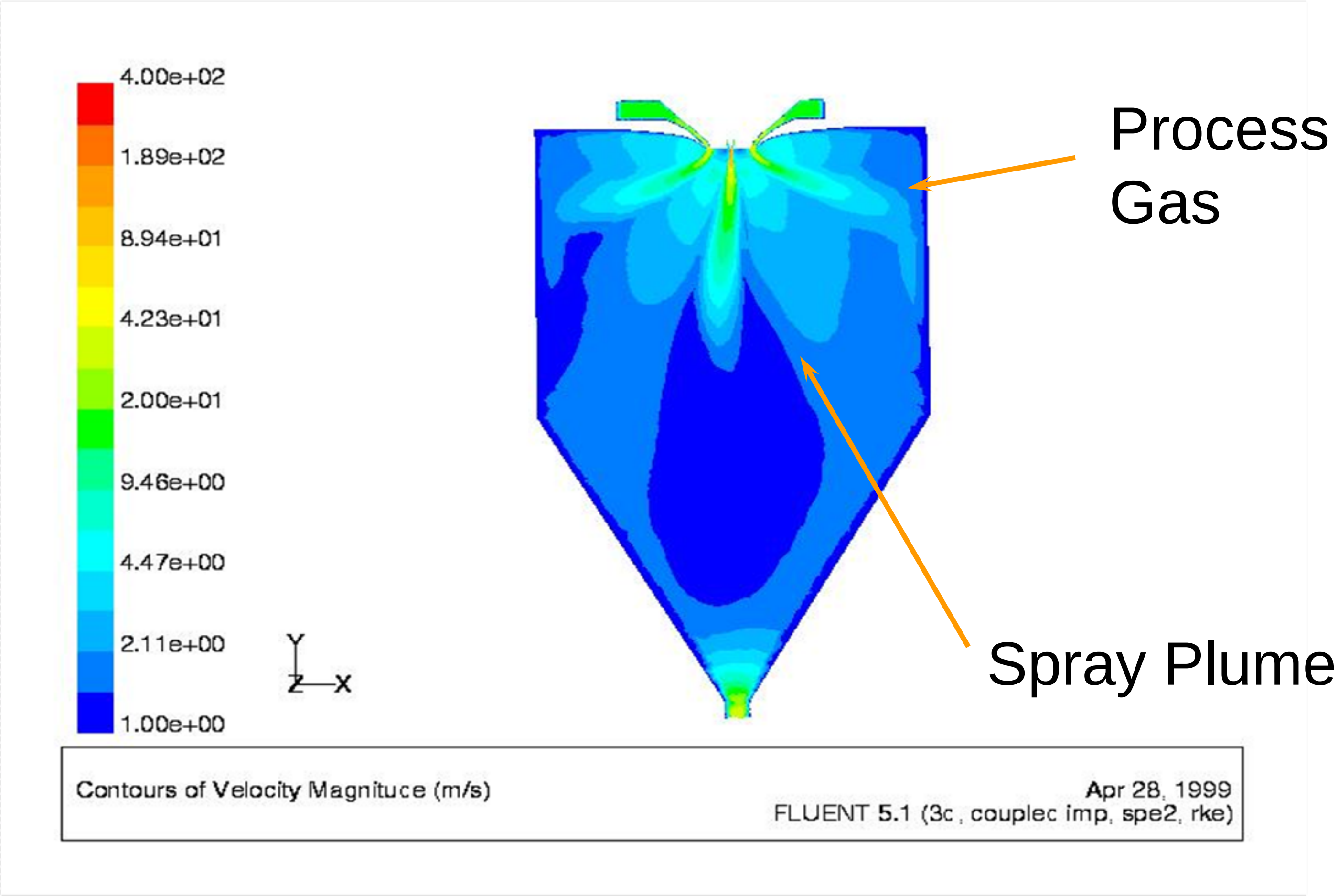
Example: CFD Model of the Atomization Process



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

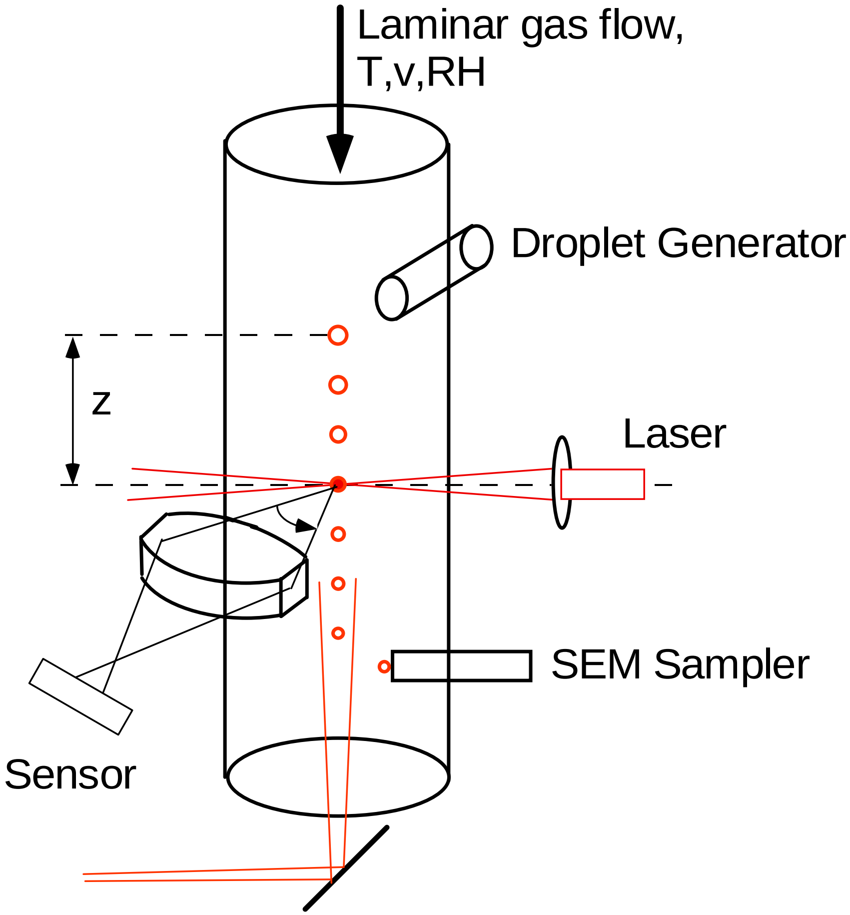
Example: Spray Dryer Internal Gas Flow Field

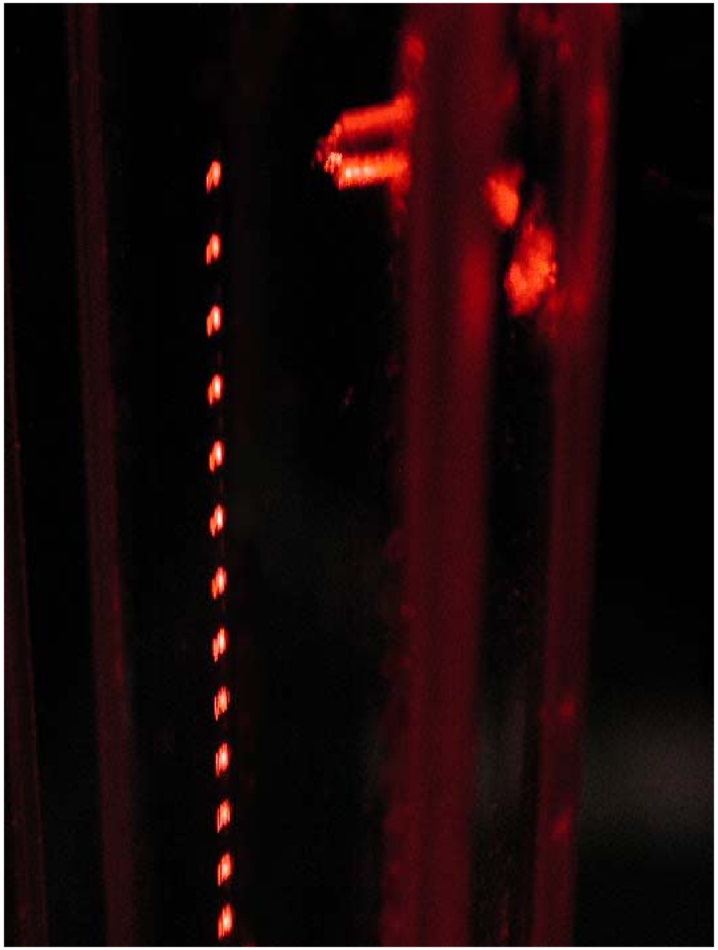


The flow field in the spray dryer is inhomogeneous.

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

Idealized Environment: Droplet Chain Technique

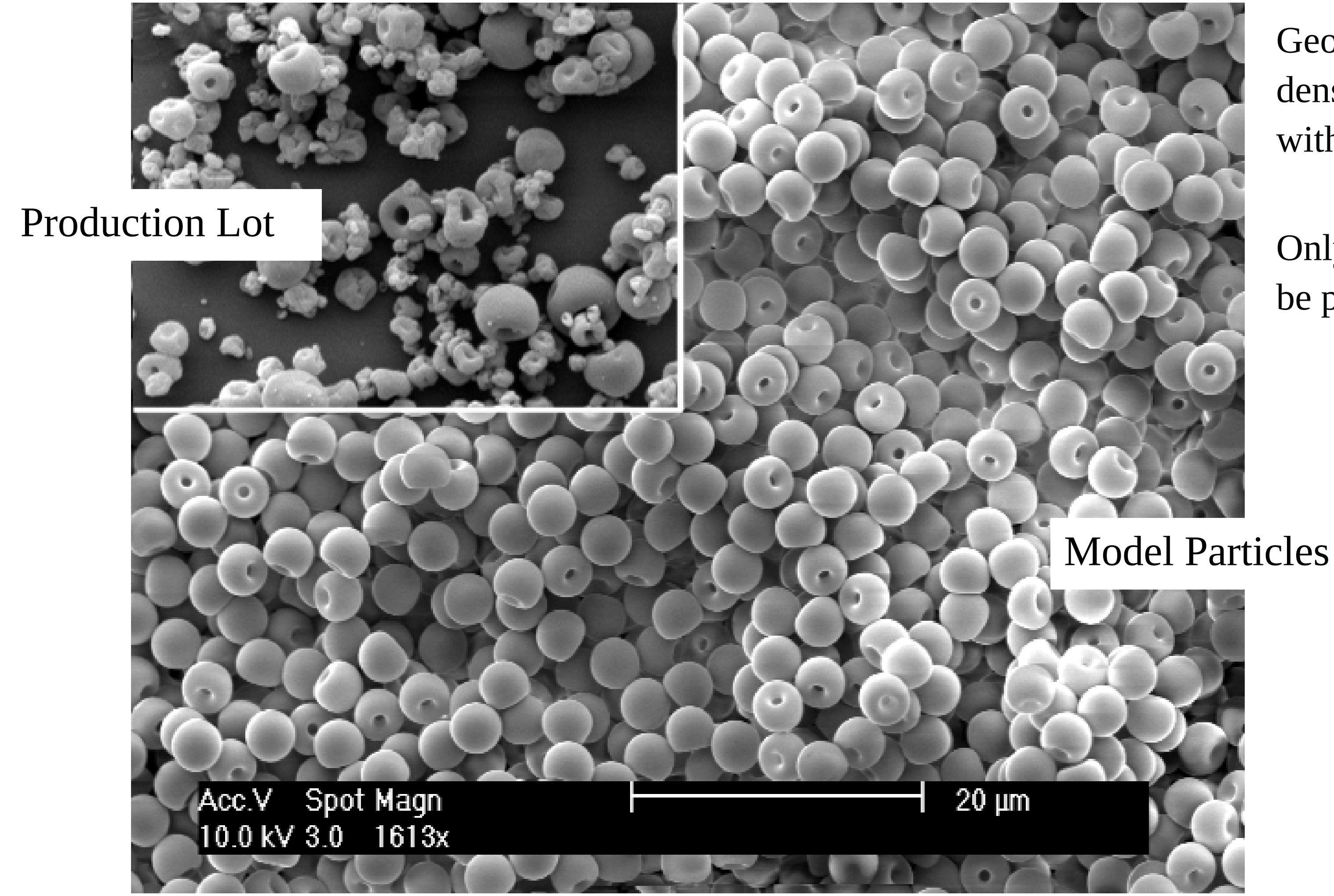




Droplets do not influence gas phase or each other. Allows measurement of evaporation rates.

Vehring, R. et al. Journal of Aerosol Science, **38**, 728, (2007)

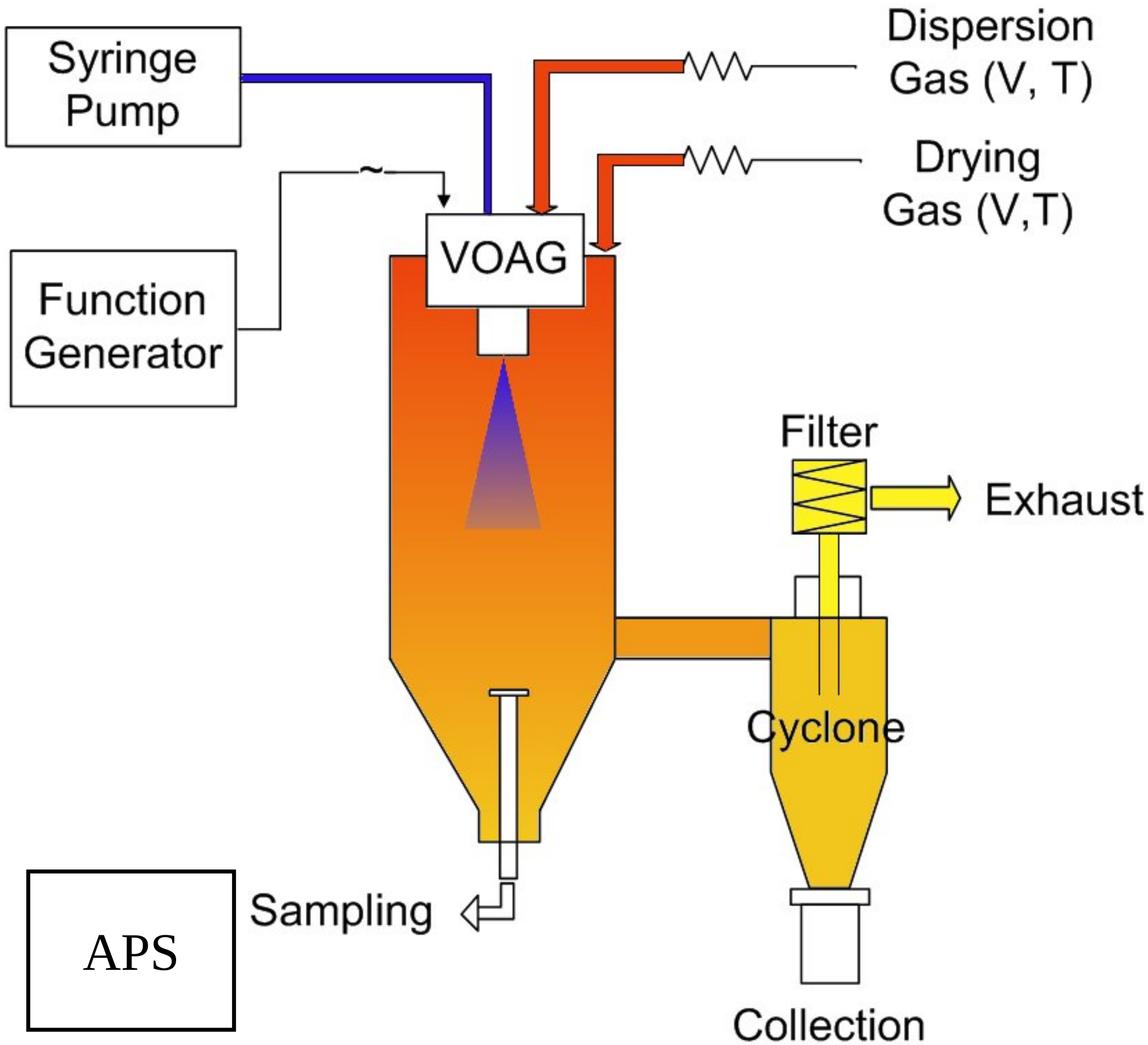
Monodisperse, Monomorph Particles



Geometric diameter and density can be correlated with drying rate.

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

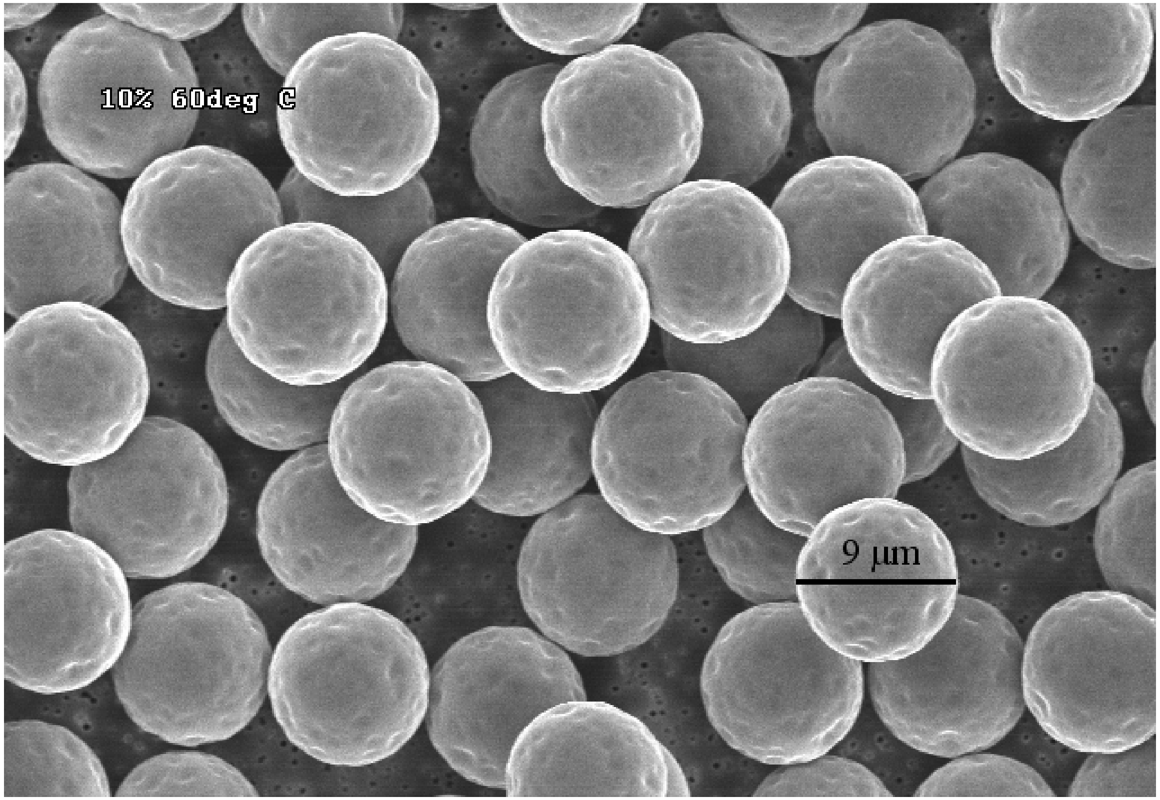
Idealized Environment: Monodisperse Spray Dryer



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

Grainger, C. et al. 26th Ann. AAAR Meeting, Reno, NV (2007) 9B.5

Particles from Monodisperse Spray Dryer

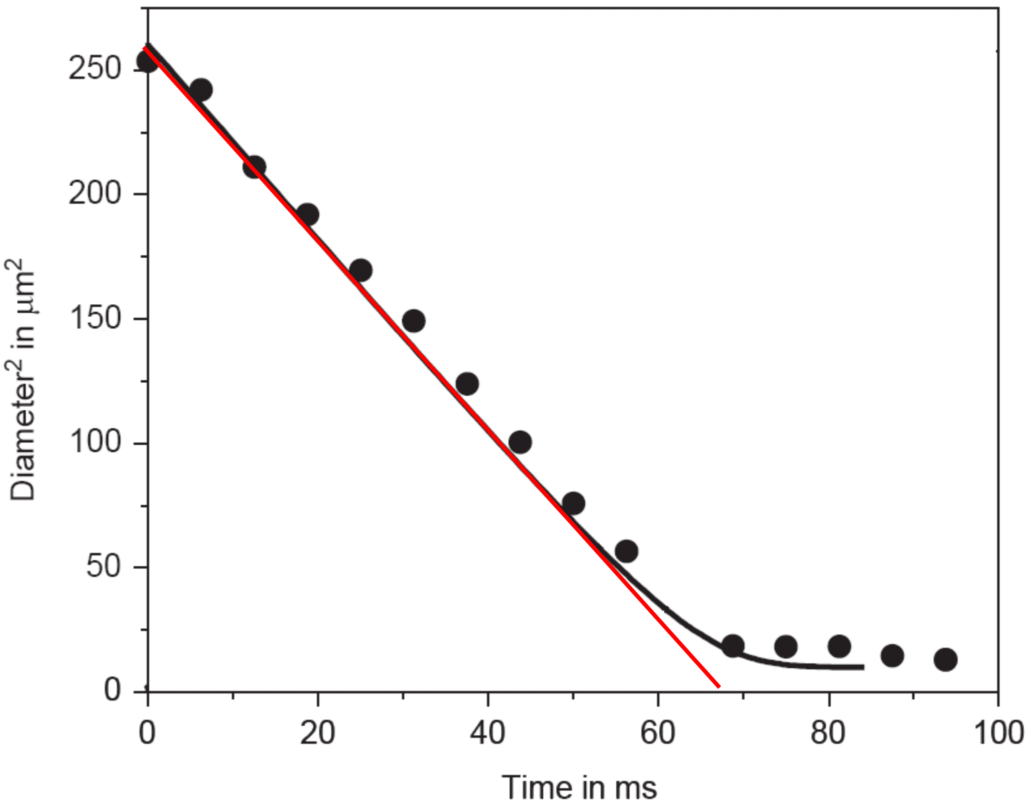


Consistent morphology

Density of main population can be determined

Constant Evaporation Rate Simplification

Definition: $$d^2(t) = d_0^2 - \kappa t$$



How to Estimate Evaporation Rate

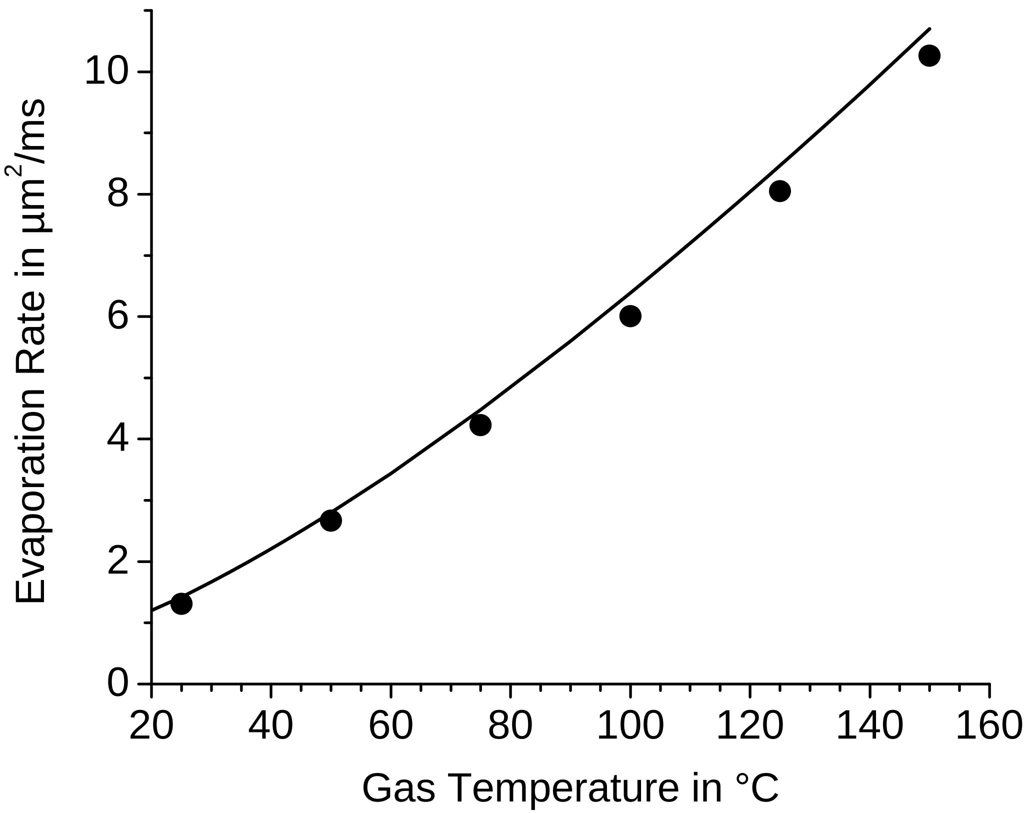
Approximation: $$\kappa = 8D_g \frac{\rho_g}{\rho_l}\left(Y_s\left(T_e\right) - Y_\infty\right)$$

Vapor Pressure: $$\log P_{sat} = A - \frac{B}{T + C}$$

A = 10.113
B = 1685.6
C = - 43.154
T in K, P in Pa

Wet bulb temperature: $$T_{\mathrm{wb}} = 137\left(\frac{T_{\mathrm{b}}}{373.15}\right)^{0.68} \log\left(T_{\mathrm{G}}\right) - 45$$

Water Evaporation Rates



Theoretical and measured evaporation rates for pure water droplets in dry air at gas conditions typical for spray drying applications .

Constant Rate Assumption Allows Analytical Solution

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

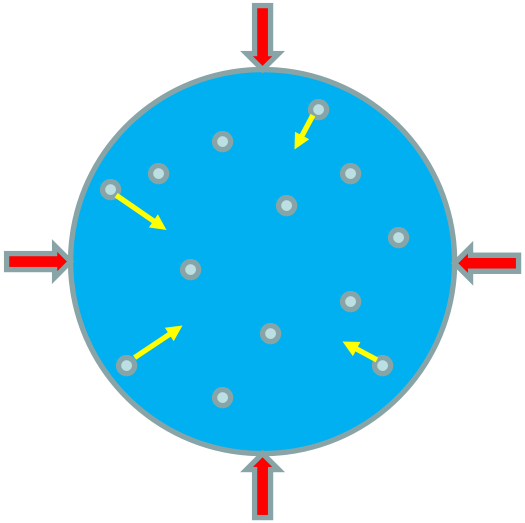
$$c = c_m \frac{\exp\left(-0.5\mathrm{Pe}R^2\right)}{3\int_0^1 R^2 \exp\left(-0.5\mathrm{Pe}R^2\right)\mathrm{d}R} \quad , \qquad \mathrm{Pe} = -\frac{r_s\partial r_s}{D\partial t} = \frac{\kappa}{8D}$$

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)

Peclet Number and Surface Enrichment

Definition: $$\mathrm{Pe}_i = \frac{\kappa}{8D_i}$$



Describes balance between velocity of surface recession and diffusion

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

Ratio of surface concentration to average concentration

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

Vehring, R. et al. Journal of Aerosol Science, **38**, 728, (2007)

Initial Saturation

Definition: $$S_{0,i} = \frac{c_{0,i}}{c_{sol,i}}$$

Ratio of initial concentration to solubility (for solutes)

Dimensionless initial density,

Definition: $$P_{0,i} = \frac{c_{0,i}}{\rho_{t,i}}$$

Ratio of initial concentration to true density
(for suspended material or high solubility solutes)

Characteristic Times

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

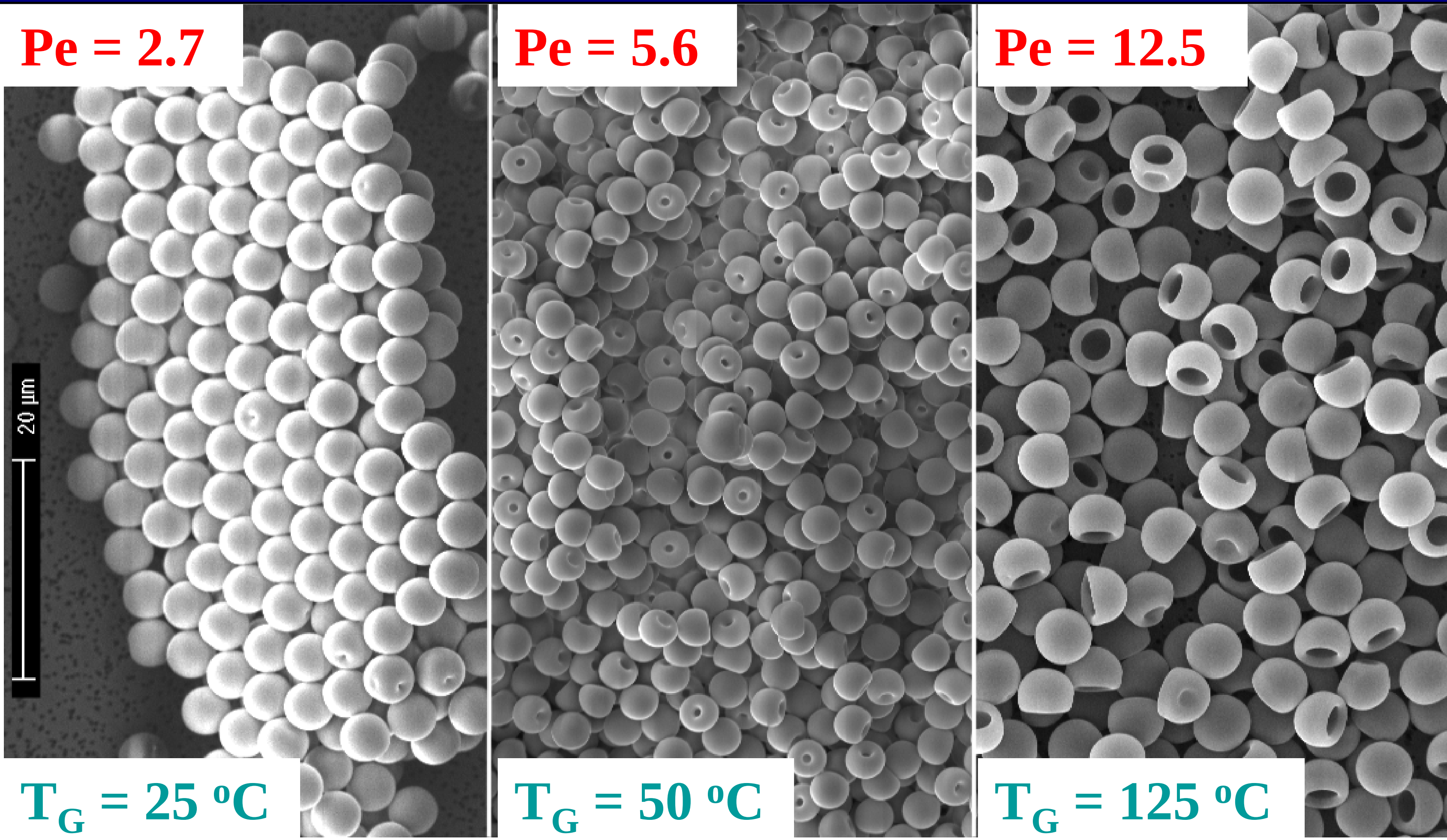
Time to saturation: $$\tau_{sat,i} = \tau_D \left(1 - \left(S_{0,i} \cdot E_i \right)^{\frac{2}{3}} \right)$$

Time to true density: $$\tau_{t,i} = \tau_D \left(1 - \left(P_{0,i} \cdot E_i \right)^{\frac{2}{3}} \right)$$

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

Particle morphology is determined by the components with the shortest τ_{sat} or τ_t. The precipitation window needs to be long enough or dried solutes will be amorphous.

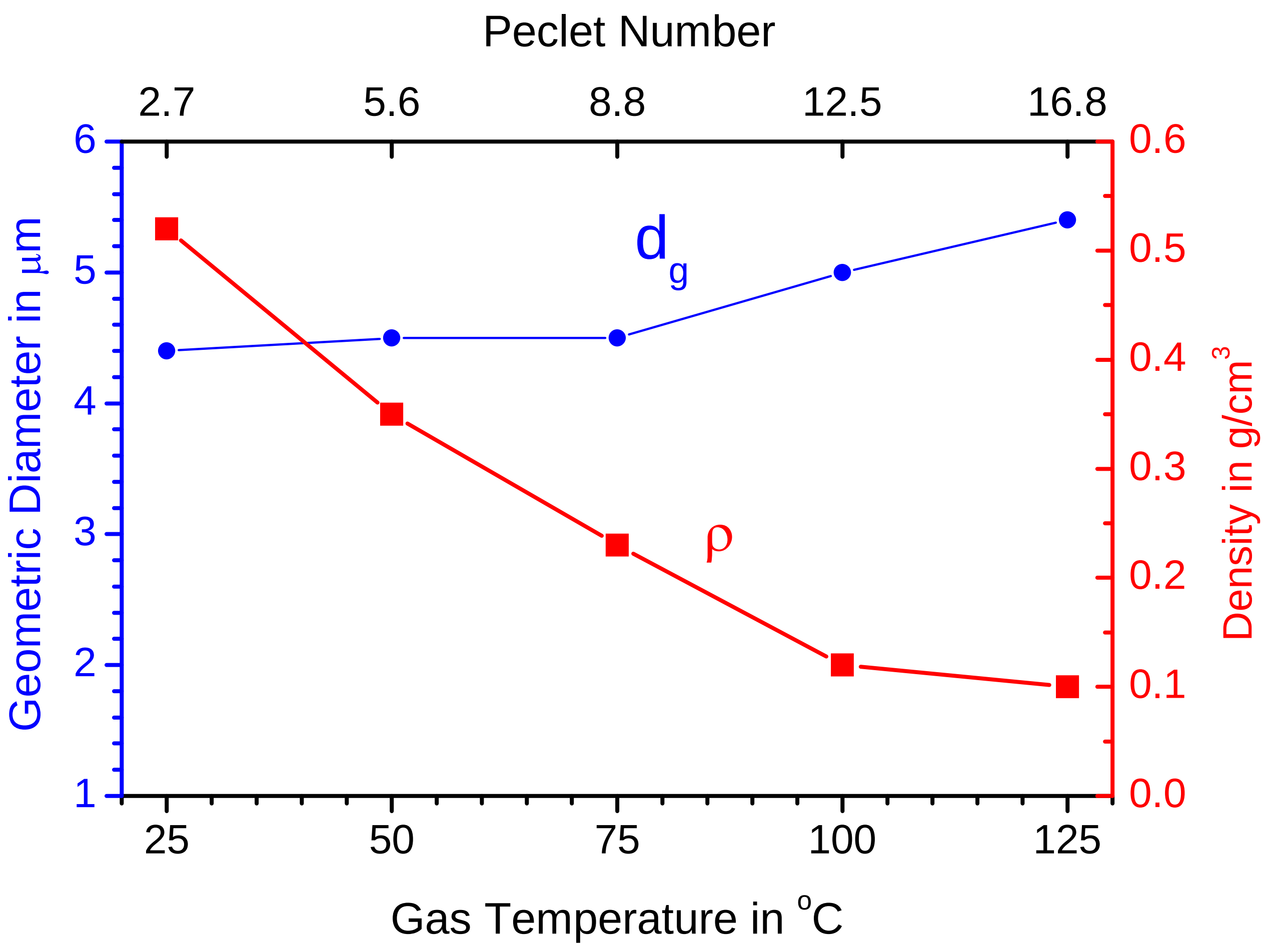
Formation Mechanism: Large Molecules



Morphology and density change with drying rate

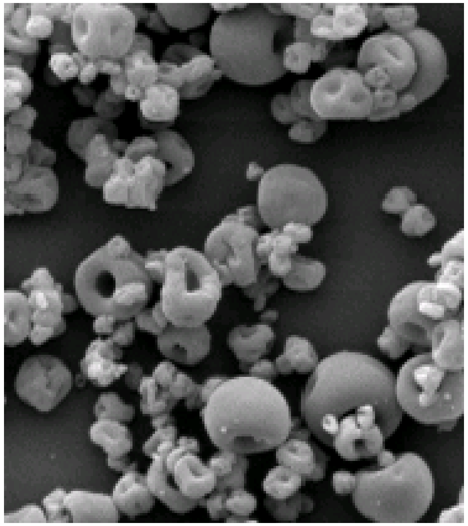
Glycoprotein, MW: 51 kDa, D: $6 \cdot 10^{-11}$ m^2/s (estimate)

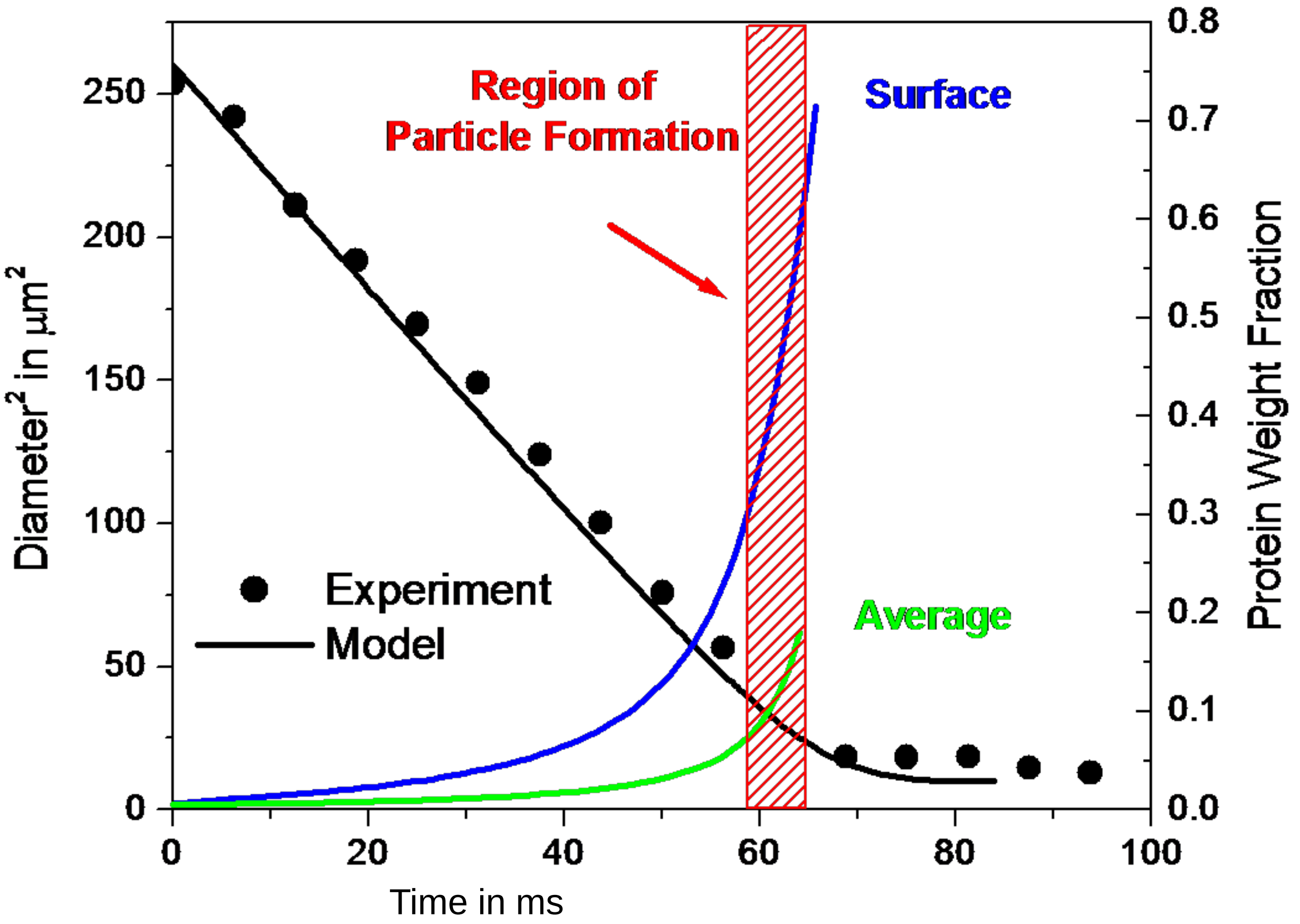
Density Decreases with Increasing Pe-Number



Evaporation Process for a Glycoprotein

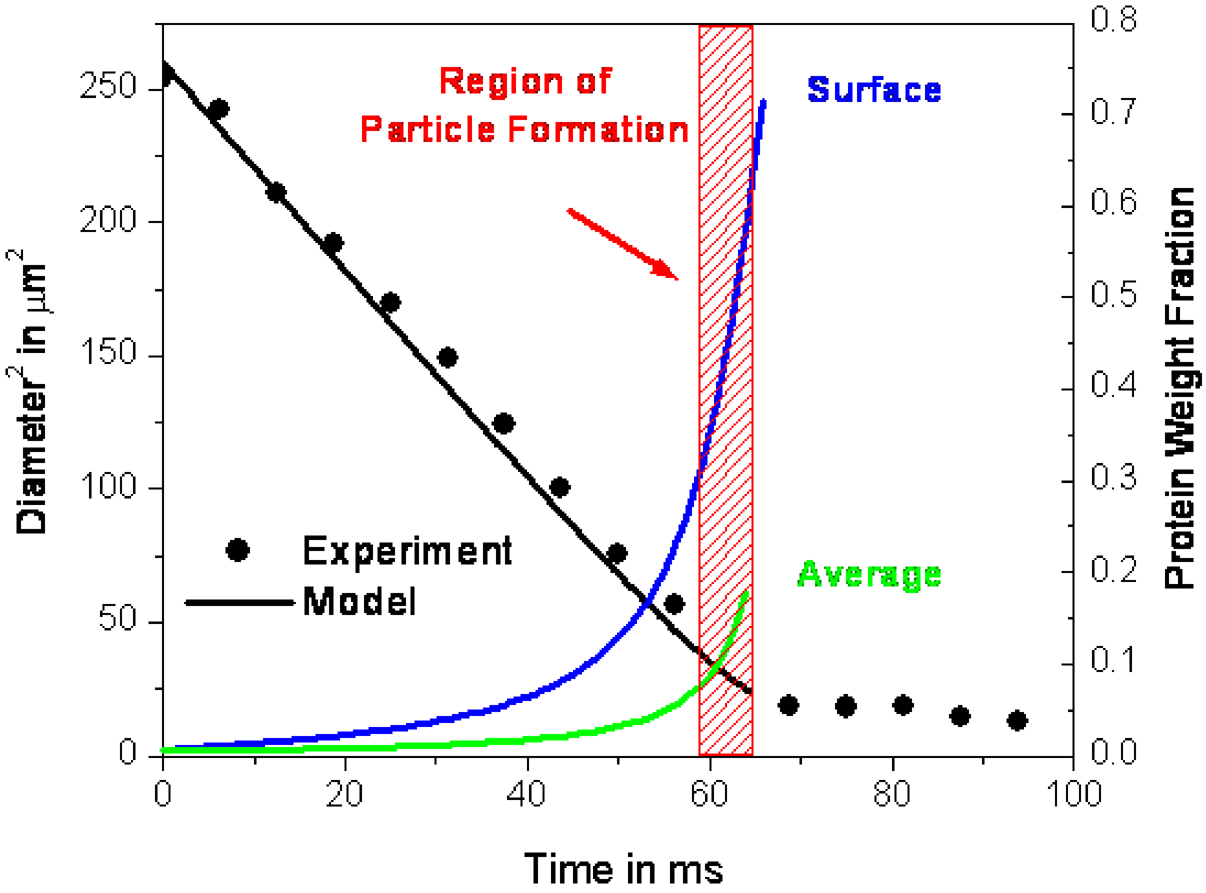
Pe = 10





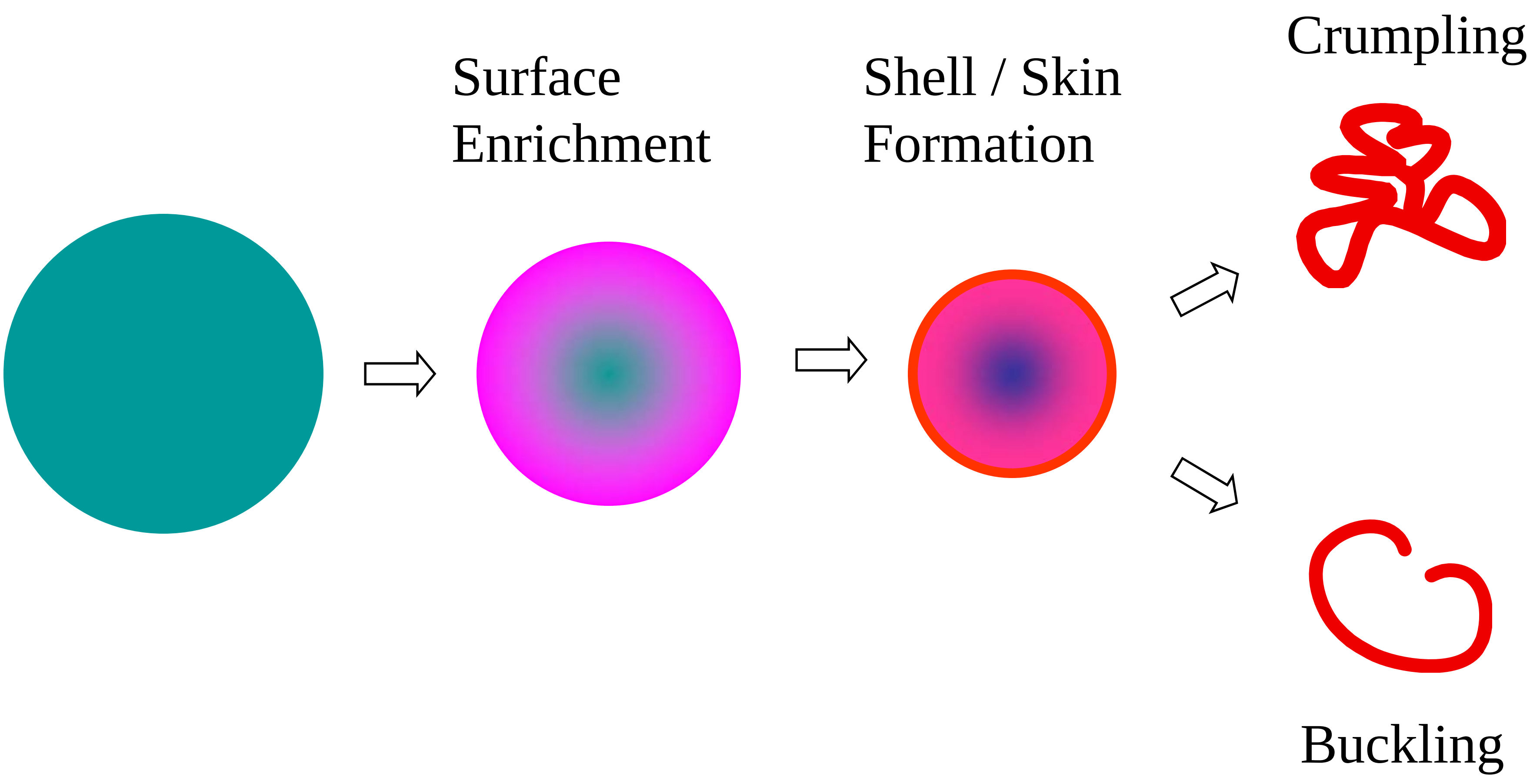
Vehring, et al., AAAR Annual Conf., Atlanta, GA, 2004

Theory Predicts Surface Enrichment of Protein

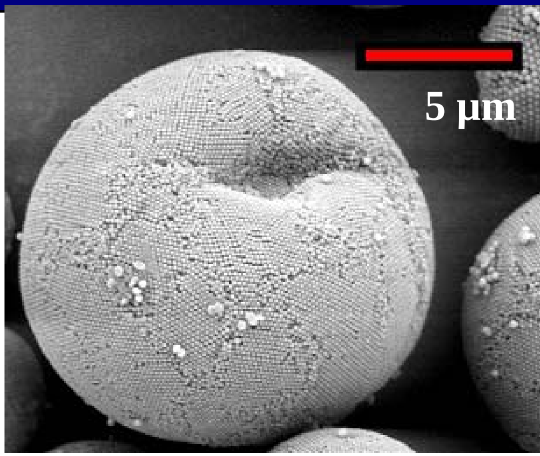


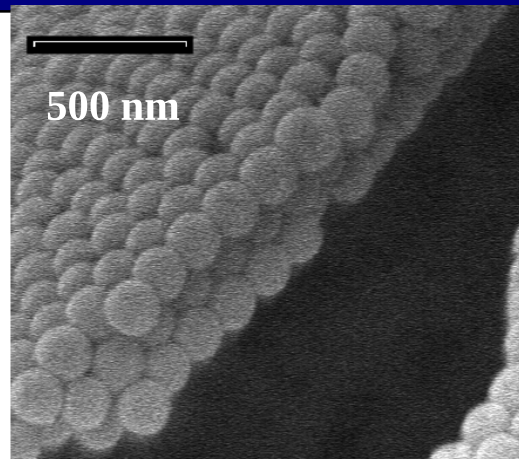
Dry particle formation coincides with predicted high surface concentration of the protein.

Diffusion Controlled Particle Formation



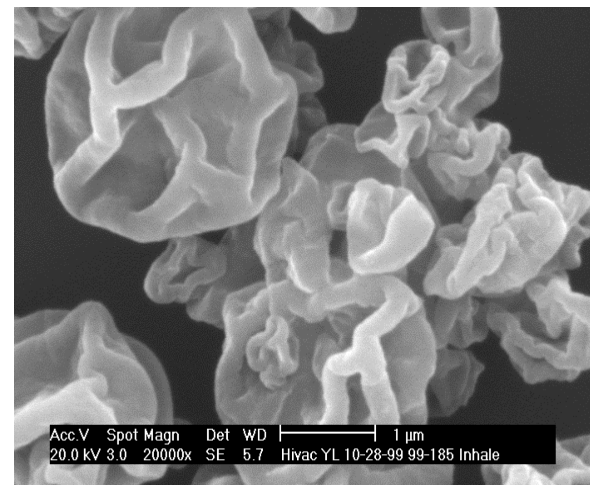
Large Peclet Number Examples

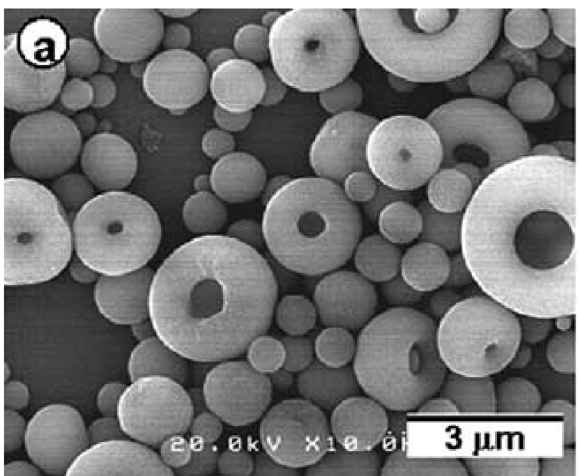




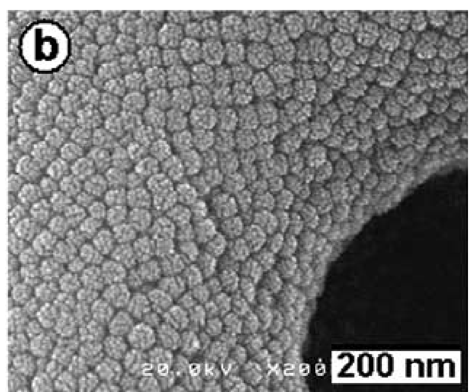
Polystyrene nanoparticle
(170 nm) suspension

Peptide formulation



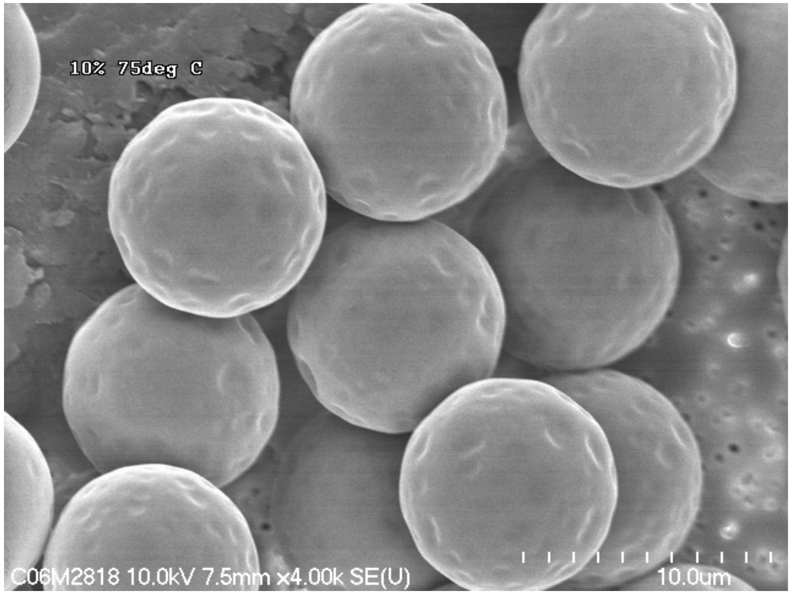


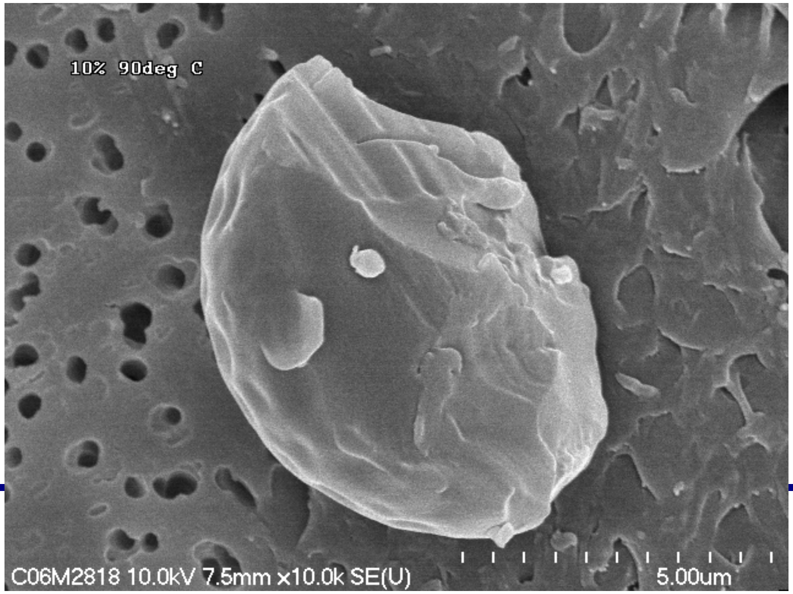
Silica nanoparticles, 25 nm

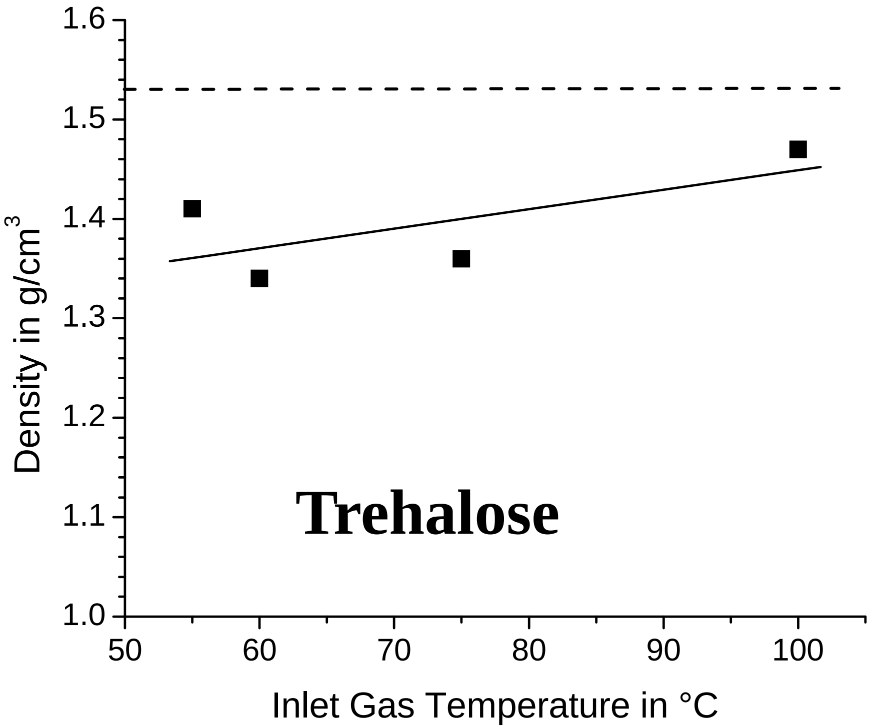


N. Tsapis et al. PNAS 99, 12001 (2002); F. Iskandar et al. Journal of Colloid and Interface Science 265, 296 (2003)

Formation Mechanism: Small Molecules

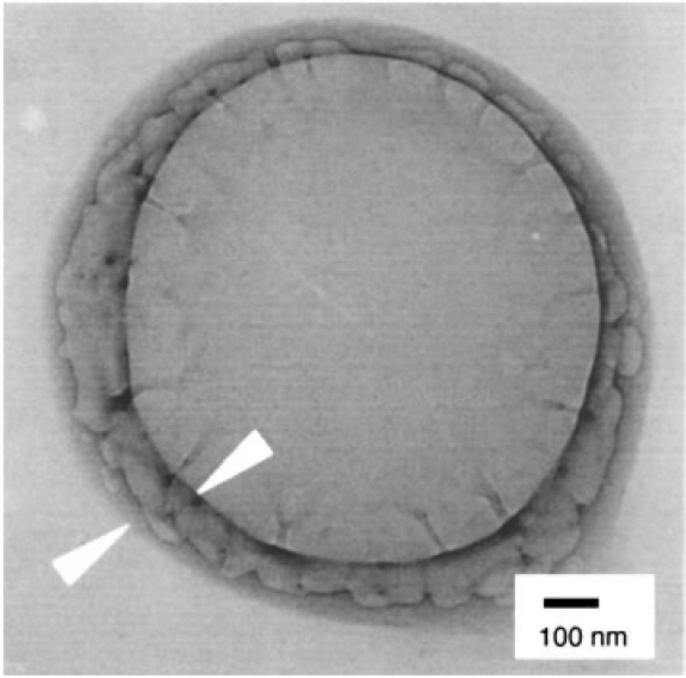


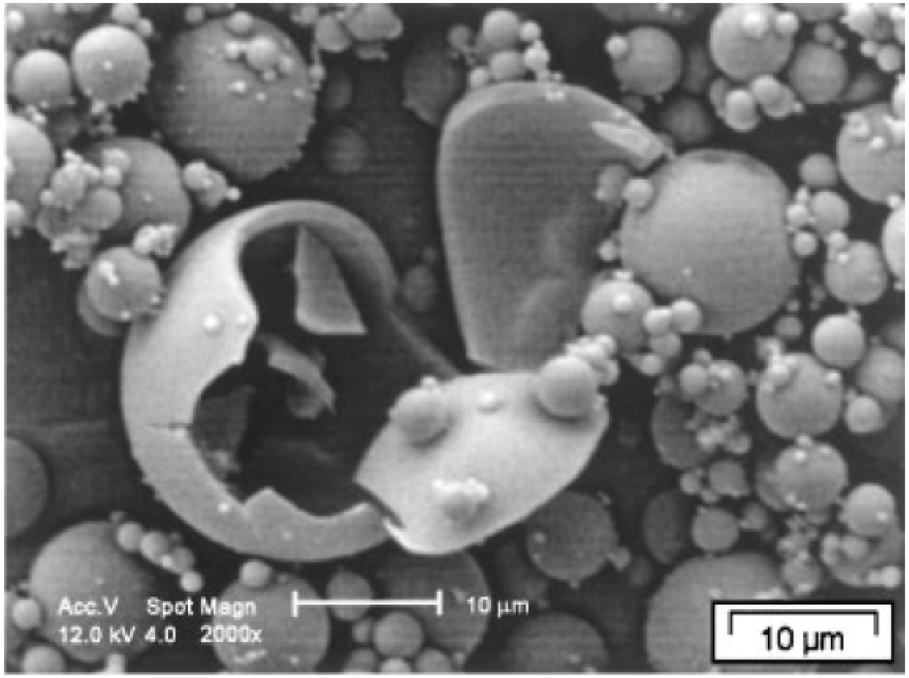




Low Peclet Number (<2) and high solubility leads to solid particles with a density close to the pycnometer density (1.53 g/cm^3)

Small Molecules at High Peclet Numbers





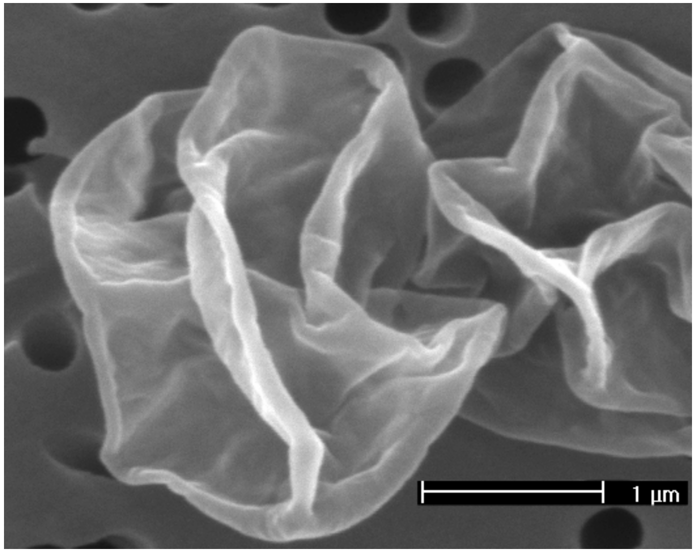
Lactose particles, dried at high drying gas temperatures (200 °C inlet)

Peclet number range: 2-5

Saccharides can form hollow particles at high Peclet numbers

Elversson, J., et al. J. Pharm Sci, 92, 900 (2003)

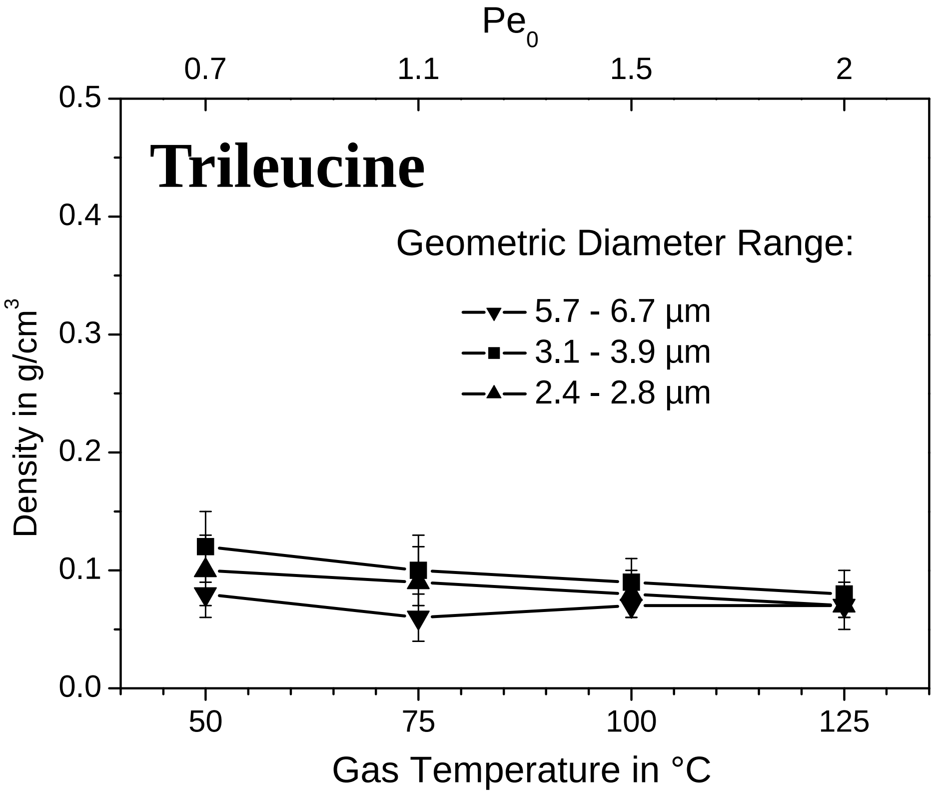
Small Molecules / Low Solubility – High Surface Activity



Solubility: 8 mg/ml (25°C, pH7)

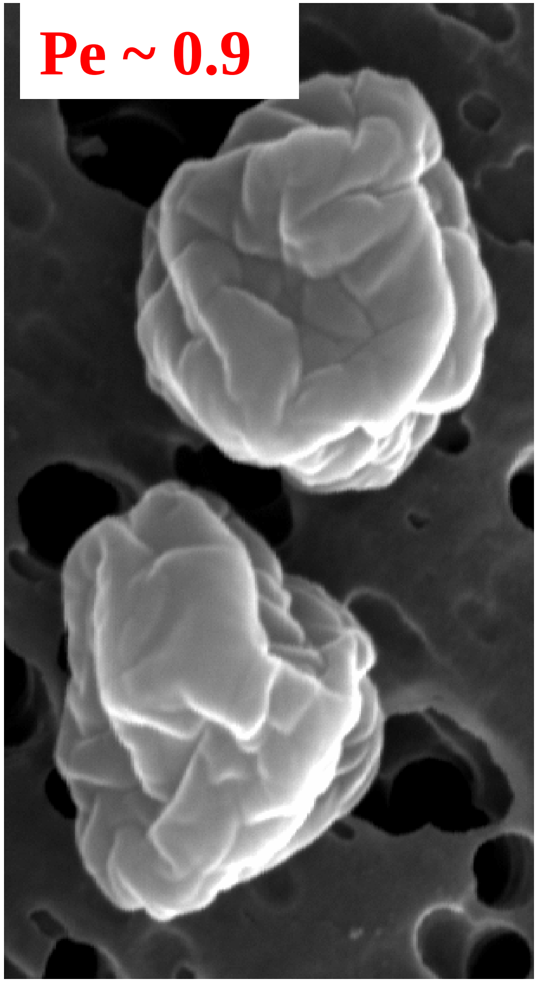
Surface Activity: 42 mN/m (sat, 25°C)

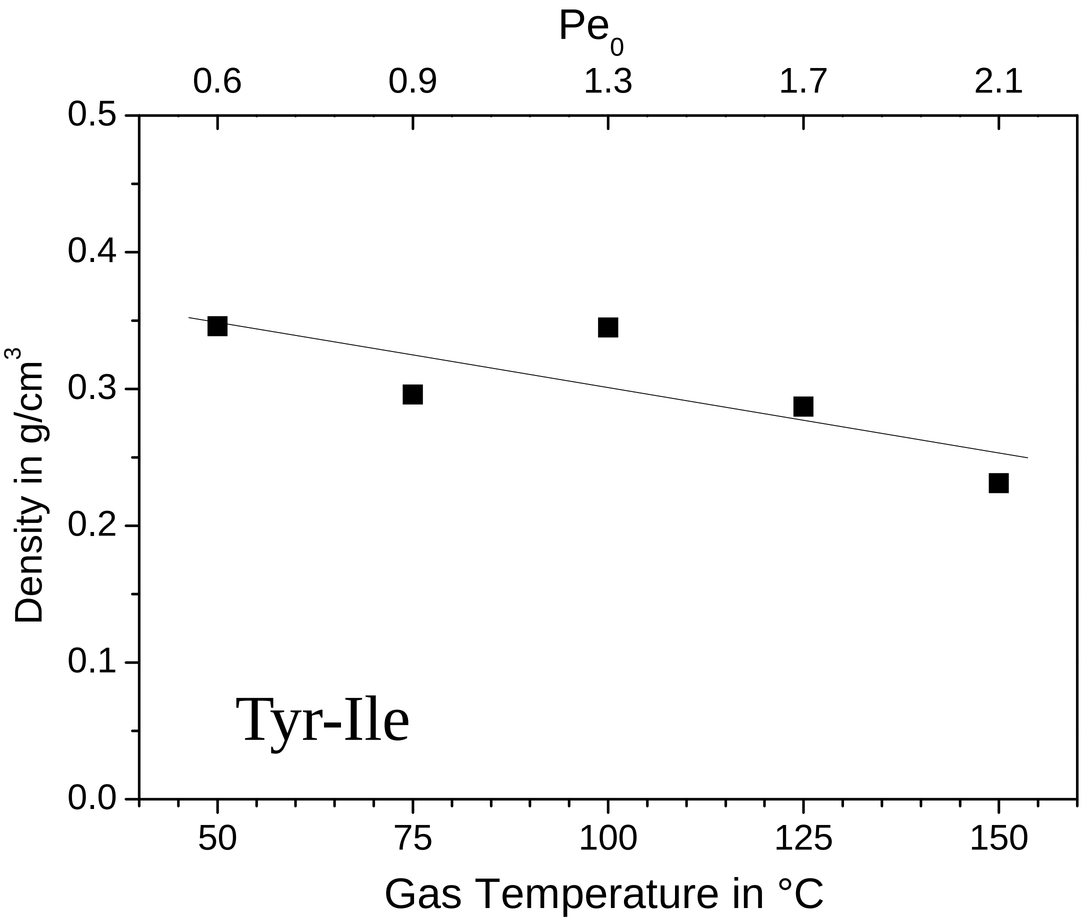
MW: 357.5 Da



Particles with very low density can be formed from small molecules

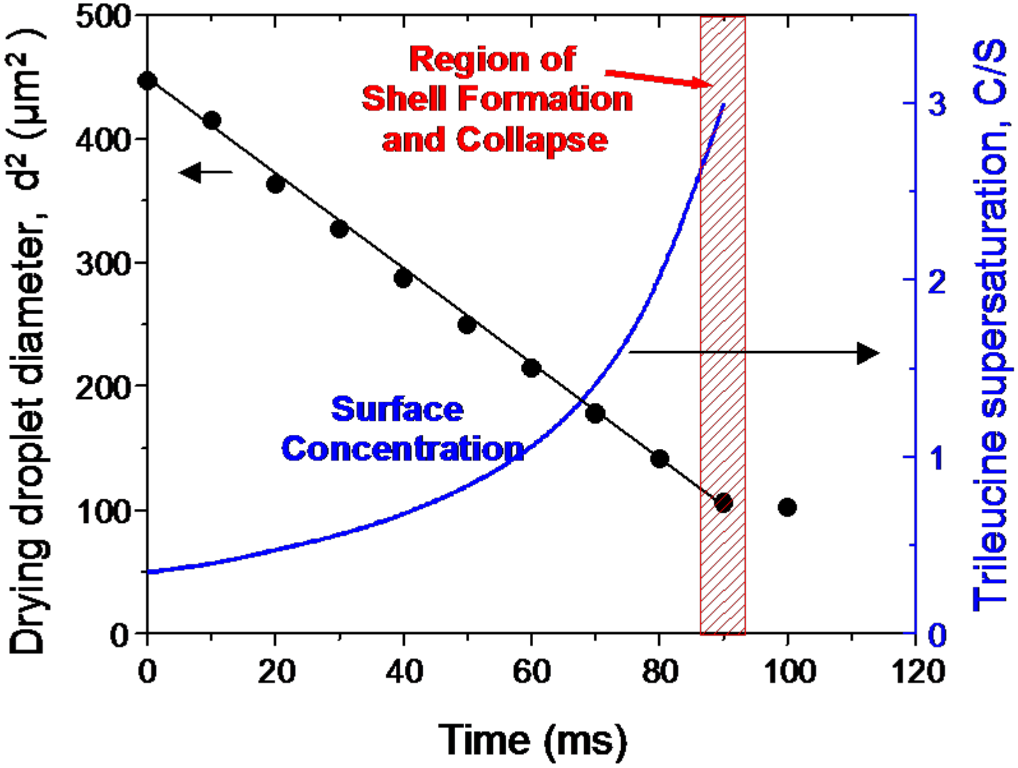
Small Molecules / Low Solubility – Low Surface Activity





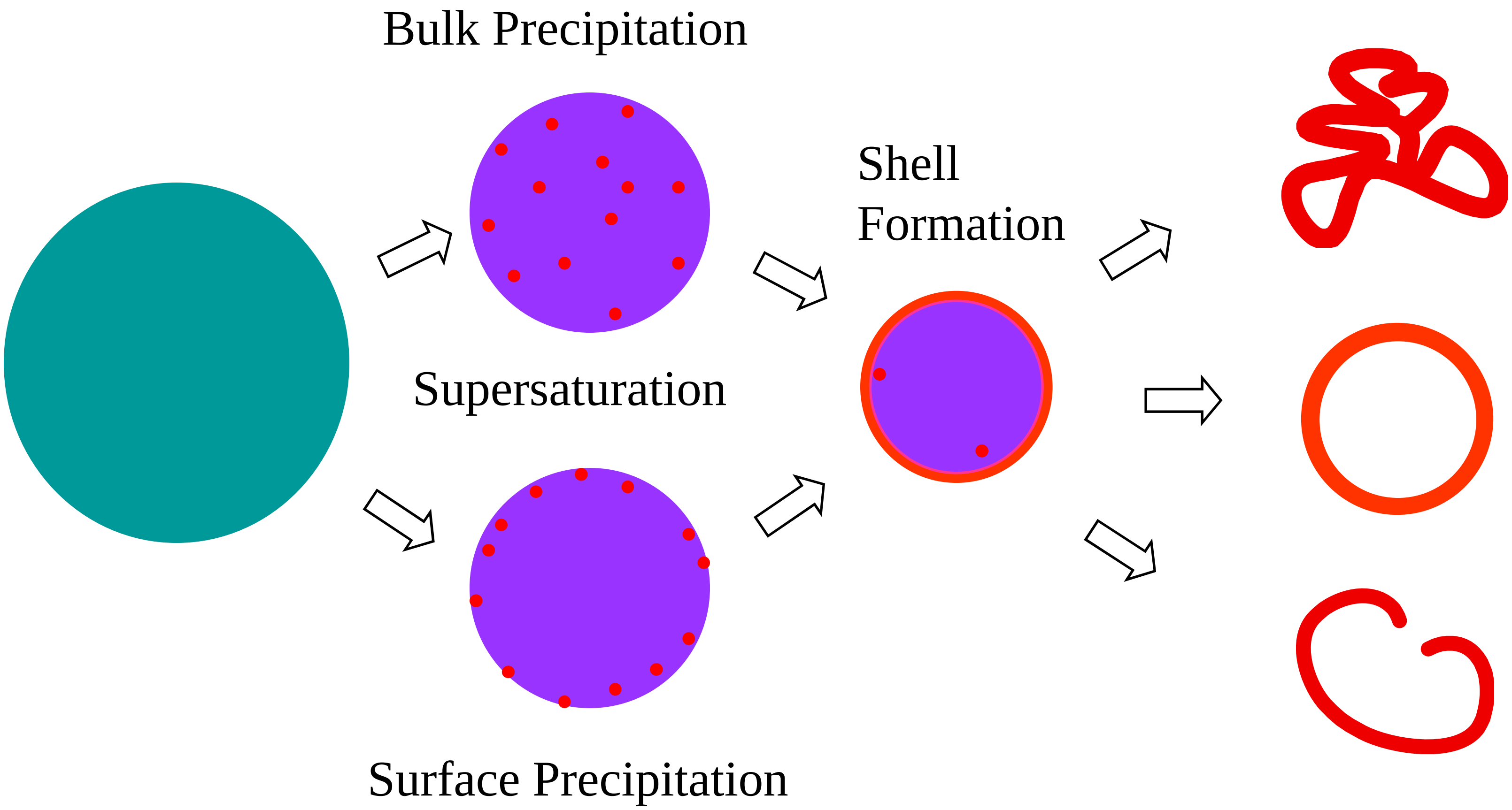
Surface activity is not necessary for low particle density

Particle Formation Coincides with Supersaturation

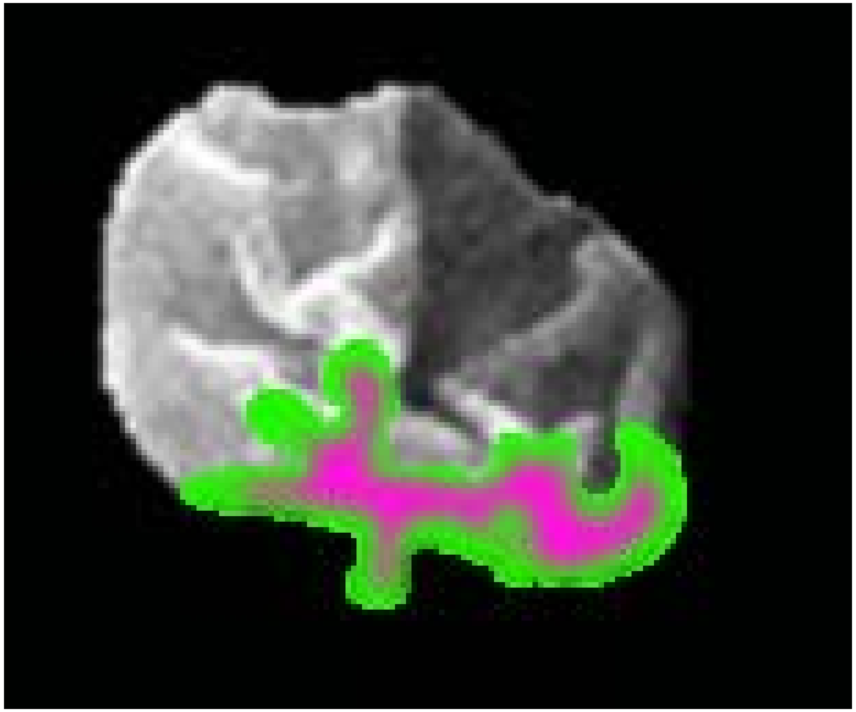


Precipitation leads to sharp increase in Pe - number

Particle Formation with Early Phase Separation



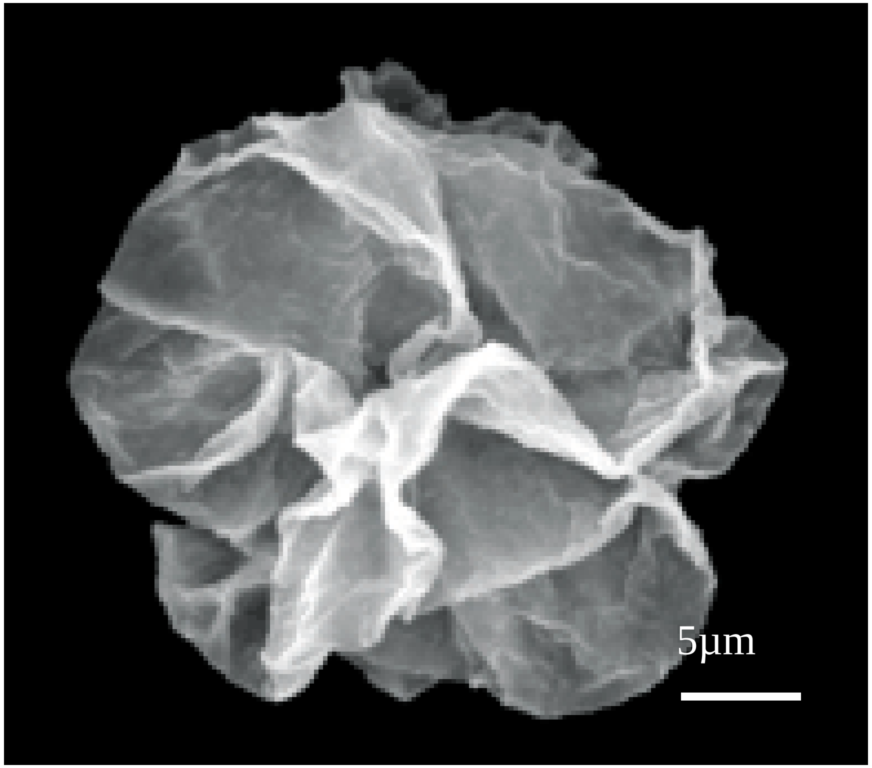
Designing Structured Particles - Applications



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

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

Example 1: Large Porous Particles (Alkermes / AIR)



- Large particles with small aerodynamic diameter

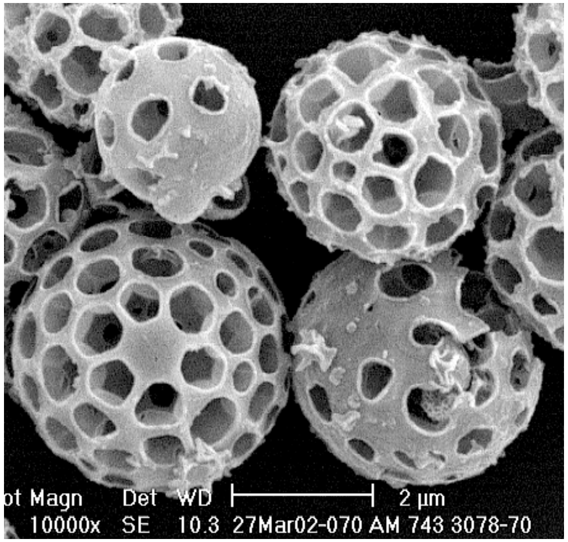
$$D_a = D_p \sqrt{\rho_e}$$

  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.

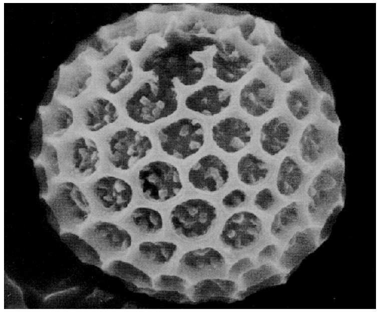
Example 2: Lipid Based Particles (Nektar Therapeutics)



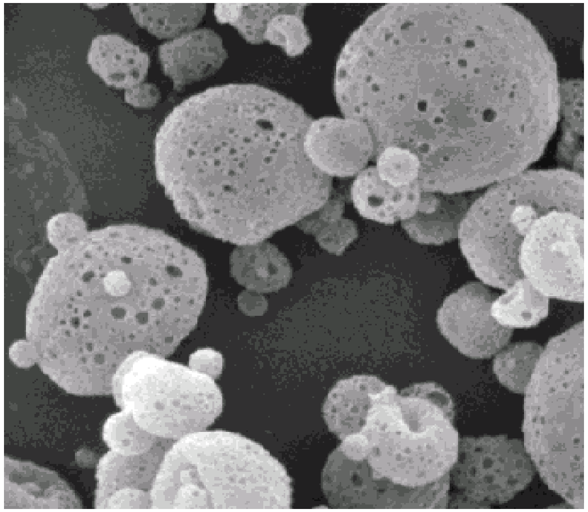
Small
Molecule
Formulation

PulmoSphere®

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



Mushroom Spore

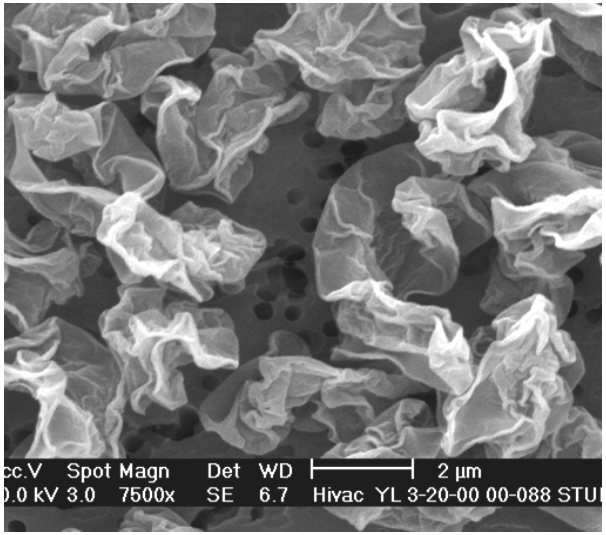


Calcitonin

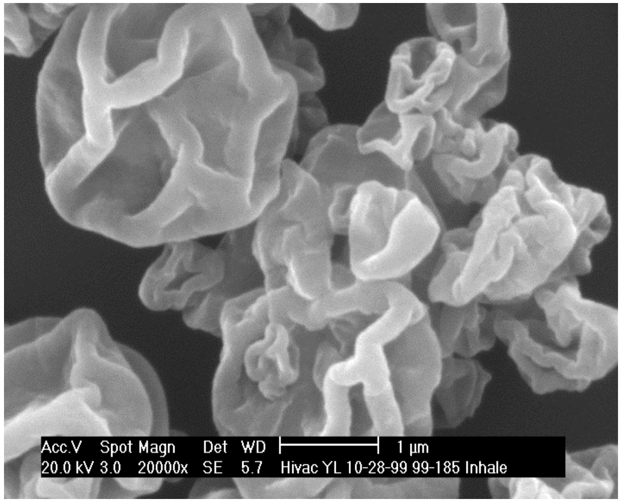
Vehring, R. IBC 4th Annual Conference, Delivery Strategies for Proteins and Peptides, Boston, MA, 2004

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

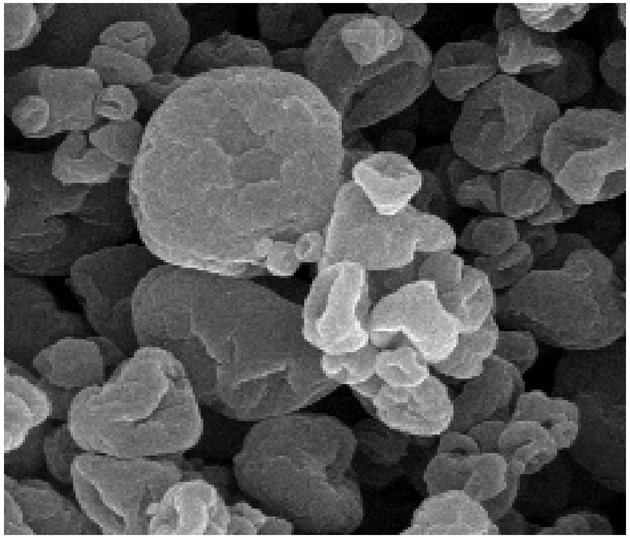
Trileucine Shell



Protein Formulation



Crystalline Amino Acid Shell



Typical Excipients

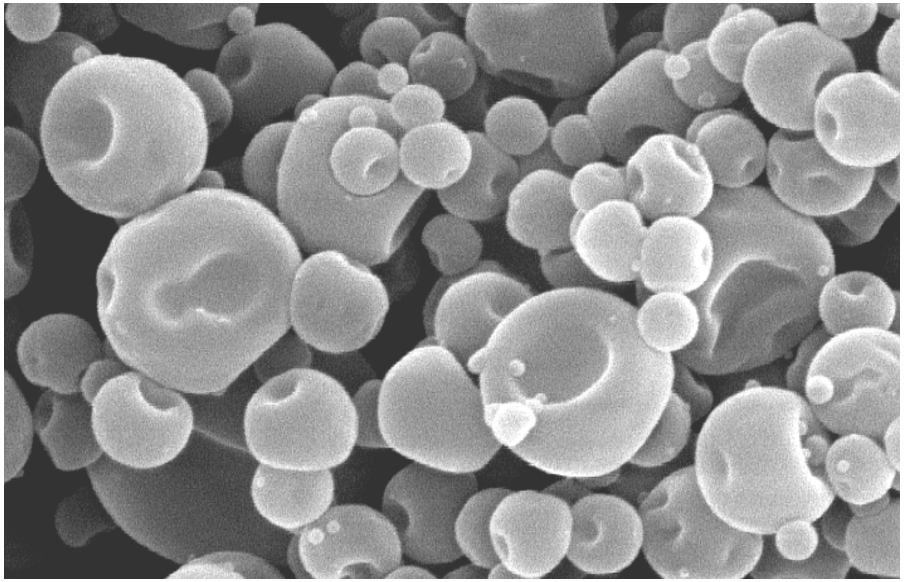
- Amino acids, di-, tripeptides
- Sugars
- Organic Salts

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

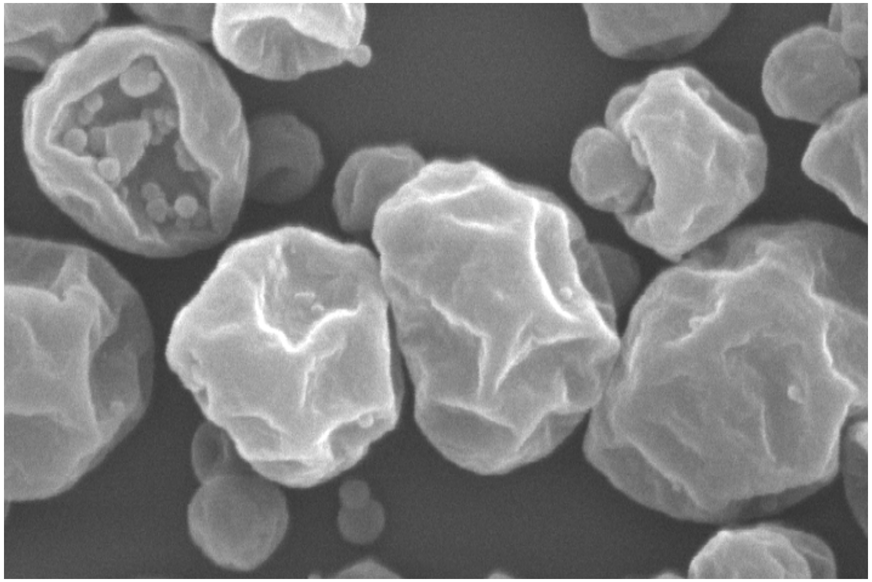
Successful Encapsulation of a Model Molecule

Spray-dried from a co-solvent system:

100 % PVP K17

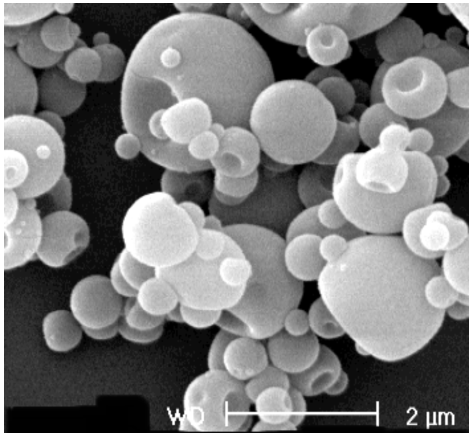


90 % PVP, 10 % Amino Acid

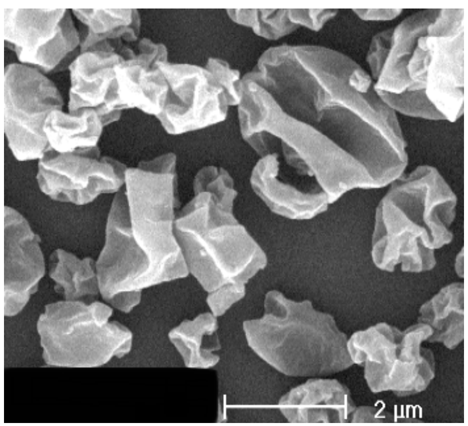


Vehring, et al., AAPS 1st Annual Pharmaceutics and Drug Delivery Conference, Arlington, VA, 2002

Designing for Dispersibility

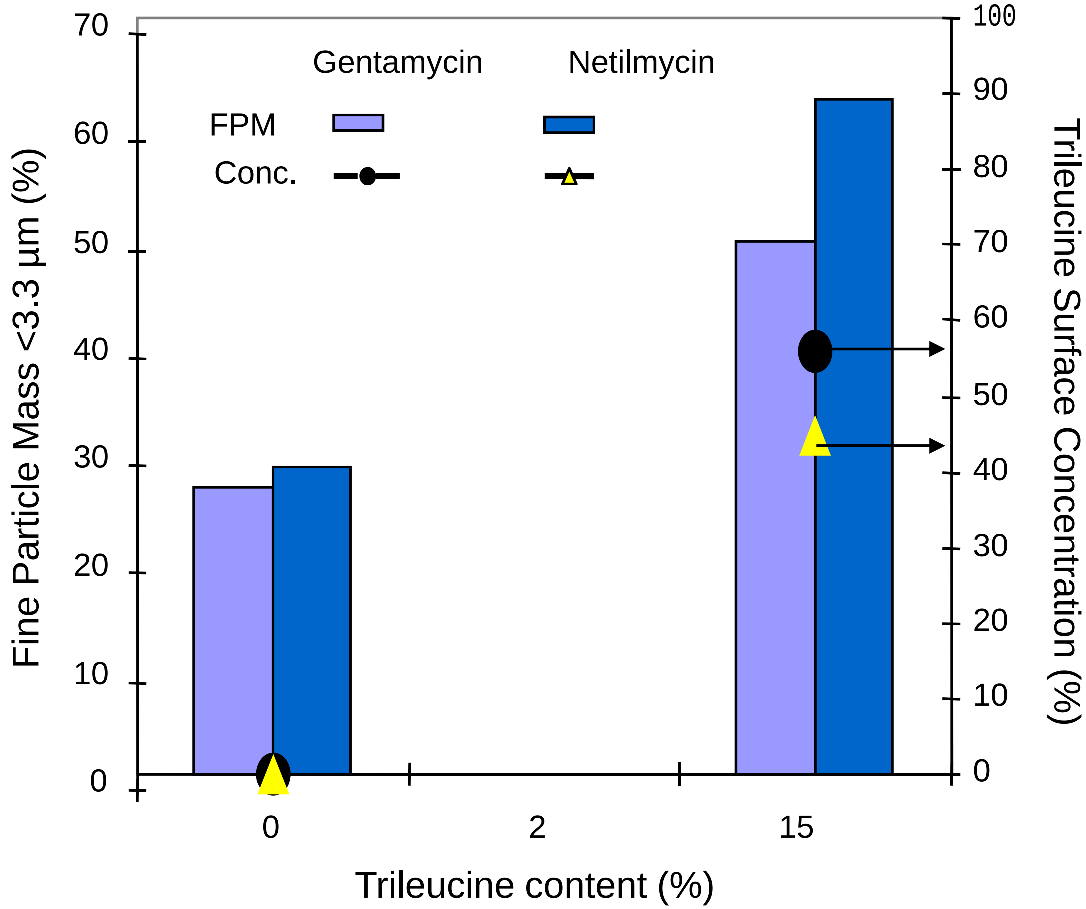


0 % Leu_3



15 % Leu_3

Netilmicin Sulfate



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

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