Introduction to Aerosol Technology for Drug Delivery

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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 $d_a > 3 \mu m$
  - Captures > 90% of particles with $d_a > 10 \mu m$
- Surface area: 150 cm$^2$
- Cilia and mucus transport particles down the nasal cavity to the pharynx. Mucociliary clearance takes 15 – 20 min.

Mouth
- Extrathoracic filter function
  - < 10% for $d_a < 3 \mu m$
  - > 65% for $d_a > 10 \mu m$
  - Depends on jaw and tongue position, and on breathing rate
- Extrathoracic volume: 50 cm$^3$
Particle Tracking with Computational Fluid Dynamics

Particle Traces Colored by particle-diameter (Time=2.0510e-01)  
Jain et al.  
FLUENT 6.3 (3d, dp, pbns, rke).

$t = 205$ ms

$100 \mu m$

$10 \mu m$

$1 \mu m$

$t = 218$ ms
CFD Particle Tracking

$t = 310 \text{ ms}$

$t = 420 \text{ ms}$
Lung Anatomy - Overview

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$^2$
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 m²) 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

- Tidal Volume: 0.5 l
- Inspiratory Capacity: 3 l
- Expiratory Reserve Volume: 1.5 l
- Vital Capacity: 4.5 l
- Residual Volume: 1.5 l
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:

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV(_1) / FVC, pd</th>
<th>FEV(_1) % pred.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>&gt; 0.7</td>
<td>&gt; 80 %</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt; 0.7</td>
<td>&gt; 80 %</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 0.7</td>
<td>50 – 80 %</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 0.7</td>
<td>30 – 50 %</td>
</tr>
<tr>
<td>Very Severe</td>
<td>&lt; 0.7</td>
<td>&lt; 30 %</td>
</tr>
</tbody>
</table>
Breathing - Mechanical Analogy

Flowrate: \[ Q = \frac{\sqrt{P_a}}{R_a} \]

- **Ra**: Airway Resistance
- **Pp**: Pleural Pressure (Drop)
- **Pa**: Alveolar Pressure (Drop)
- **IC**: Inspiratory Capacity

Chest muscle activity

Conducting Airways | Respiratory Zone
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

Device Resistance: 0.051 cm H$_2$O$^{1/2}$ / (l/min)

- PIFR: Peak Inspiratory Flow Rate
- FIR: Flow Increase Rate

- Maximum Effort
- Comfortable Breathing
Breathing Profiles and Mouth Pressure in the Diseased Lung

Outline

- Anatomy and Physiology of the Respiratory System
- **Deposition and Pharmacology**
- Delivery and Dispersion Devices
- Powder Manufacture
- Particle Engineering
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, \( \text{Re} < 1 \))

\[
F_D = \frac{3\pi \eta v_d g}{C_C}
\]

**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 \( \mu \text{m} \))

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

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

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

\[
d_a = \sqrt{\rho_p d_g}
\]

Assuming that the slip correction factors are nearly identical and using \( \rho \) in g/cm\(^3\):

Aerosol Transport – Aerodynamic Diameter
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.

\[ Stk = \frac{s}{x} = \frac{v_0 \tau}{x} \]

\[ \tau = \frac{d_a^2 C}{18 \eta} \]

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.

\[ Stk = \frac{v d_a^2 C}{9 \eta d_j} \]

\[ K = d_a^2 Q \]

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

Exhaled, Cough

Device

Package

Esophagus

Respiratory Zone

Conducting Airways

Head Deposition
Losses in Nasal Delivery

- Exhaled, Drip, Sneeze
- Device Retention
- Drip & Mucociliary Clearance
- CNS
- Lung
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

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

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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
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
- Bioavailability 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

http://www.syntnx.com/tech.php
Nose Ultrastructure

- Cilia and mucus transport particles to the pharynx.
- 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

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

http://www.nastech.com/nastech/junctions_biology
Defense Mechanisms and Ways to Beat Them

- **Mucus / Mucociliary Clearance**
  - Bioadhesives
  - Rapidly dissolving particles

- **Phagocytosis**
  - Large particles
  - Trojan Horses

- **Cellular Barrier**
  - Tight junctions modulation
  - Transporter, viral vectors
  - Molecular carriers, active transport
  - Bioactive particle surfaces
- **Lysosomal Proteases**
  - pH sensitive release

- **Filter Function**
  - Particle & Device Engineering
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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
Pulmonary Mass Inoculation Systems

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

Fig. 1. *Diagram of equipment used to aerosolize vaccines*

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

New Nebulizer Developments

Boehringer Ingelheim, Respimat; Impinging Jet

Aerogen / Nektar, OnQ; Micropump, Vibrating mesh

Aradigm AERx; Microorifice / Disintegrating jet

Stand-Alone, Hand-Held Nebulizer (Pari)

eFlow Anatomy:

- Battery Compartment Door
- Medication Reservoir Cap
- LED and Sound Indicators including “End of Treatment”
- Aerosol Chamber
- Valved Mouthpiece Minimizes Wastage
- Vibrating Stainless Steel Aerosol Head
- Internal Circuit Board—The Brain of the eFlow

Uses 4 AA Batteries, Disposable or Rechargeable
Pressurized Metered Dose Inhalers

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

Canister
Drug suspension or solution with propellant
Metering Valve
Mouthpiece
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
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
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

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

Ergonomic Tip-Seal Nasal Actuator
(spring loaded tip sealing mechanism)

New Pump Generation
(cartridge pump as an inner part of the closure)
Provides sealed dead volume

Interchangeable Finger Flange

Mechanical Removal Prevention

Approved Filter System
(micro filtration of the incoming air)

Metering Spray Pump working as a closed system: (Aerodiol® from Servier, Nezeril® from Astra Zeneca, and Otrivin® from Novartis)
Nasal Delivery Devices – Metered Sprays

Technical Data

- 3 Plastic Parts
- 3 External Components


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

Nozzle

Valve

Cap

Barrel

Plunger

Dose Divider

Spray.
Bi-dose.
Metered.

MedImmune, Inc., FluMist
Nasal Delivery Devices – Bidirectional

**OptiNose**

- Breath actuated drug release into airflow
- Side view showing closed soft palate

**DirectHaler**

- Soft palate closes automatically
- Blow into the device

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
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- 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

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
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- **Particle Engineering by Spray Drying**
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.
Problem:
The two phase flow in an actual spray dryer is difficult to model. Heat and mass transfer processes are difficult to study \textit{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

- \textit{Single droplets} (acoustic, electrodynamic, optical levitation, concave hot plate, filament technique)
- \textit{Droplet chains} (vibrating orifice, droplet-on-demand)
- \textit{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
The flow field in the spray dryer is inhomogeneous.
Idealized Environment: Droplet Chain Technique

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

Monodisperse, Monomorph Particles

Production Lot

Model 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

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

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

Wet bulb temperature: \( T_{wb} = 137 \left( \frac{T_b}{373.15} \right)^{0.68} \log(T_G) - 45 \)

A = 10.113
B = 1685.6
C = -43.154
T in K, P in Pa
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, \( R = r/r_s \),

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

\( D: \) Diffusion coefficient, \( c: \) concentration, \( r_s: \) droplet radius, \( d: \) droplet diameter, \( \kappa: \) evaporation rate.

Solution

\[
c = c_m \frac{\exp\left( -0.5\text{Pe}R^2 \right)}{3 \int_0^1 R^2 \exp\left( -0.5\text{Pe}R^2 \right) dR}
\]

\[
\text{Pe} = \frac{r_s \partial r_s}{D \partial t} = \frac{\kappa}{8D}
\]

where the concentration is expressed as a function of the average concentration in the droplet, \( c_m \). \( \text{Pe} \) is the Peclet number.

Peclet Number and Surface Enrichment

Definition: \[ Pe_i = \frac{K}{8D_i} \]

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

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

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: \[ \tau_D = \frac{d_0^2}{\kappa} \]

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 \( \tau_{sat} \) or \( \tau_t \). 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

![Graph showing the relationship between Peclet Number and geometric diameter and density.](image-url)
Evaporation Process for a Glycoprotein

$Pe = 10$

Vehring, et al., AAAR Annual Conf., Atlanta, GA, 2004
Dry particle formation coincides with predicted high surface concentration of the protein.
Diffusion Controlled Particle Formation

Surface Enrichment → Shell / Skin Formation

Crumpling → Buckling
Large Peclet Number Examples

Polystyrene nanoparticle (170 nm) suspension

Peptide formulation

Silica nanoparticles, 25 nm

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

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
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

- Bulk Precipitation
- Supersaturation
- Surface Precipitation
- Shell Formation
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

- \( D_p = 5-30 \ \mu m \)
- \( D_a = 1-5 \ \mu m \)

Example 2: Lipid Based Particles (Nektar Therapeutics)

- 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

Small Molecule Formulation

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

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

Crystalline Amino Acid Shell

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

Netilmicin Sulfate

0 % Leu₃

15 % Leu₃

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.