Particle dissolution and solute absorption: Key factors in the pulmonary kinetics of inhaled drugs

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Content

- Perspectives on an inhaled dose of drug particles.
- The isolated and perfused rat lung (IPL).
- Aerosol exposure of the IPL.
- Results
- Conclusions
Inhalation Exposures to Particle-associated Solutes

- A clinical exposure to dry powder aerosols — a large number of simultaneous single particle exposures of the air-blood barrier.

- Single particle kinetics are important, but cannot be directly measured under physiological conditions.

- The isolated perfused lung of rodents may help us to understand single particle kinetics by measuring organ-level kinetics.
The Overall Dissolution and Absorption of Solutes in the Lung

The Major Steps:

I. Deposition
II. Desorption / Dissolution
III. Absorption / Metabolism
IV. Perfusion

Carrier Particle of Solute
Air Interface
Epithelium
Subepithelium
Perfusion
Critical Particle Properties

- Particle size – much faster dissolution with smaller particles.

- Intrinsic properties – solubility, dissolution kinetics, crystallinity, engineering, etc.
Critical Air/blood Barrier Properties

Solute polarity a major driver for local dosimetry

Absorption Rate: Slower  Faster  Slower
Considered Today  Gerde & Scott, 2001

Anatomical region: Faster absorption in thinner alveoli than in thicker bronchi.

Patton et al.; 1996
The Lung Level Kinetics

Aerosol Exposure In

Net Solute Out

Lung Retained Fraction
The Isolated, Ventilated and Perfused Lung of the Rat

- Up to 3 h sampling period.
- Mimic clinical exposure with respirable aerosols.
- Single-pass perfusate to simulate large systemic distribution volume.
- Mass balance control

Deposited dose = Perfusate clearance + Lung retention
Dustgun Aerosol Generator

- Respirable aerosols
- Bolus exposures
- Concentrated aerosols
Measuring Pulmonary Absorption in the Isolated Perfused Lung

1. Aerosol generator
2. Isolated Perfused Lung
3. Airflow control
4. End filter
5. Fraction collector
6. Data Acquisition
7. Aerosol monitor
8. Pneumotachograph
9. Pressurized air supply
Two Mechanisms of Non-linear Behaviour

- Local saturation around dissolving particle. (how much mass/particle)
- Interference between dissolving particles. (how many particles/exposure)
Silica Particles with Benzo(a)pyrene in a Rat Lung Bronchiole

Ewing et al.; Tox Sci, 2006
Concentration of Benzo(a)pyrene in Single-Pass Perfusate

Ewing et al.; Tox Sci, 2006
Different Modes of Local Absorption

- **Subsaturation absorption:** Local tissue fluid quickly dissolves the substance before absorption to circulation. First order absorption.

- **Saturation absorption:** Local tissue fluid saturated with substance during absorption. Zero order absorption.
Interference Between Dissolving Particles

- Ten µg of 1 µm particles deposited on the tracheobronchial epithelium.

- Average distance between particles: hundreds of µm.

- Could they possibly interfere?
Focal Concentration of Benzo(a)pyrene in Canine Tracheal Epithelium
Different Modes of Lung Level Absorption

- **Non-interference absorption:** particles dissolve and absorb essentially independent of each other ⇒ normalized absorption independent of dose.

- **Interference absorption:** the dissolution plumes around the particles begin to merge and interfere ⇒ normalized absorption decrease with dose.
The Pulmonary Absorption of Some Inhalation Steroids

- From clinical to supra-clinical dose levels
- Same aerosol size, MMAD; 4.5 µM
- Different lipophilicities

<table>
<thead>
<tr>
<th>Compound</th>
<th>Log D</th>
<th>PBS Solb (µM)</th>
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<tbody>
<tr>
<td>Budesonide (BUD)</td>
<td>2.8</td>
<td>42</td>
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<tr>
<td>Fluticasone Furoate (FF)</td>
<td>4.6</td>
<td>0.12</td>
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<td>Mometasone Furoate (MF)</td>
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<td>0.075</td>
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<td>Benzo(a)pyrene (for comparison)</td>
<td>6-6.5</td>
<td>0.019</td>
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</tbody>
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- First order absorption independent of deposited dose.
- Zero order absorption independent of deposited dose.
- Zero order absorption decreasing with the deposited dose.

Ewing et al, AstraZeneca, unpublished data.
Conclusions

- The local kinetics around single deposited particles – an important driver for overall kinetics of dry powder inhalation exposures.

- The isolated perfused rat lung and well-controlled aerosol exposures – a useful tool for better understanding of pulmonary PK.

- Good opportunities to challenge and refine computer-based PK models on lung dosimetry.
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