Drug-Device Combination Products for Inhalation Route

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The University of Texas at Austin

Mini Symposium: Combination Products and Innovation in Drug Delivery Systems
Inhalation Aerosols: Levels of combination

Drug

Drug + Device

Drug A + Drug B + Device

Drug A + Drug B + Device A + Device B

Inhalation Aerosols: Levels of combination
<table>
<thead>
<tr>
<th>Device Type</th>
<th>Sub Categories</th>
<th>Design Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebulizers</td>
<td>Air Jet, Ultrasonic, Vibrating Mesh</td>
<td><img src="nebulizer.png" alt="Image" /></td>
</tr>
<tr>
<td>Mechanical Aqueous Sprays</td>
<td>Silicon Wafer Based Nozzle, Laser Machined Nozzles</td>
<td><img src="spray.png" alt="Image" /></td>
</tr>
<tr>
<td>Pressurized Metered Dose Inhalers</td>
<td>HFA based</td>
<td><img src="inhaler.png" alt="Image" /></td>
</tr>
<tr>
<td>Dry Powder Inhalers</td>
<td>Multidose Reservoir, Multidose Premetered Capsule</td>
<td><img src="dry-powder.png" alt="Image" /></td>
</tr>
<tr>
<td>Evaporation Condensation</td>
<td>Single Use Disposable, User Controlled Dosing</td>
<td><img src="condensation.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Inhalation Aerosols: A large extended family
Focus of this presentation: Drug-Device Combinations
Outline

• Pulmonary drug delivery elevator pitch, (why marry?)

• Target product profiles and device selection.

• Dry powder inhaler drug device combinations
  • How formulations influence performance.
  • Device design; improving performance via knowledge of dispersion mechanisms – the marriage

• The honeymoon: happy marriages through independence
Pulmonary Route is Attractive

- Local targeting / administration
  - Onset
  - Dose
- Large surface area
- Thin epithelial barrier
- High blood flow (5 L/min)
- Metabolic advantages

Physiological/Anatomical Barriers

- Particles larger than 5 µm not deposited efficiently
- Mucociliary and cough clearance rapidly remove foreign particles
- Particles smaller than 1 µm are readily exhaled

Target product profiles and device selection

- Dose
- Drug physicochemical properties
- Stability / Compatibility
- Therapeutic window
- COGS
- Patient factors
- Barriers to entry

1. Jay Holt, Inhalation Report
Designing Inhalation Aerosols

- Aerodynamic particle size limitations: 0.5 - 5 microns

- Physics of generating aerosols in this range is challenging
  - Aqueous aerosols: significant energy required to induce droplet breakup / atomization
  - Powder aerosols: significant energy required to overcome interparticulate forces
  - Propellant aerosols: force for atomization within formulation, yields fast dynamic plumes

How formulations influence performance.

- What is formulation performance?
  - Aerosol efficiencies (fine particle fraction, emitted dose)
    - Fine particle fraction, FPF = respirable drug / emitted drug
    - Respirable fraction, RF = respirable drug / loaded drug
  - Flowability
  - Blend uniformity
Dry Powder Inhalation Systems

Fine Drug Particles
100-500 µg
Asthma, COPD

Lactose “Carrier” Particles
(60-90 µm)

Blending

Binary Blend
(<2% Drug)

Lactose Particle

Drug Particles


Carriers are multifunctional:
Dose metering
Powder flowability
Entrainment and Dispersion
Overcome cohesive forces between micronized drug
Adhesion forces dominate

<table>
<thead>
<tr>
<th>Force</th>
<th>Approx. magnitude*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Waals Electrostatic</td>
<td>$10^{-9}$ to $10^{-7}$ N</td>
</tr>
<tr>
<td>Capillary</td>
<td>$10^{-18}$ to $10^{-10}$ N</td>
</tr>
<tr>
<td>Mechanical interlocking/solid bridging</td>
<td>Material dependent</td>
</tr>
</tbody>
</table>

Smyth & Hickey, 2005
Respirable powders are cohesive

**DPI Performance**

<table>
<thead>
<tr>
<th>% of Dose</th>
<th>Aerolizer</th>
<th>Handihaler</th>
</tr>
</thead>
</table>

**Flow Rate Dependence**

<table>
<thead>
<tr>
<th>% of Dose</th>
<th>RF</th>
<th>FPF</th>
<th>Throat</th>
</tr>
</thead>
</table>

- 30 L/min
- 60 L/min
Formulation factors

- Particle/Powder surface energetics and blending (Saleem et al., 2008)
- Static characterization (Hickey et al., 2007a)
- Dynamic characterization (Hickey et al., 2007b)
- Detachment Forces (Selvam et al., 2010)
- Tuning of formulations (Donovan et al. 2009)
- Modulating drug-carrier forces (Selvam & Smyth, 2010)
- Inhaler Device Design (Selvam et al. 2010, Donovan et al. 2012)
- Carrier Particles (Donovan et al. 2010).
- Carrier particle roughness & size (Du, Du, Smyth, 2014)
Effects of Carrier Particle Size on DPI Performance

- Increasing Carrier Particle Size → Reduced Performance
Previous Lactose Carrier Particle Studies:

Dickhoff, 2005
Lahhib, 1999
Kawashima, 1998
Kassem, 1990
Steckel, 2006
Dickhoff, 2003
Zeng, 2001
Steckel, 1997
Kassem, 1989

Carrier Particle Sieve Fraction (μm)

- Lactose Monohydrate
- Spray Dried Lactose
- Anhydrous Lactose
- Granulated Lactose
Systematic Evaluation of Carrier Systems

α-Lactose Monohydrate

Anhydrous Lactose

Spray Dried Lactose

Granulated Lactose
Lactose Monohydrate Conformed With Previous Studies

α-lactose Monohydrate

Respirable Fraction (%)

Carrier Particle Sieve Fraction (um)

< 20  20 - 32  32 - 45  45 - 63  63 - 75  75 - 90  90 - 106  106 - 125  125 - 150  150 - 180  180 - 212  212 - 250  250 - 300
But, Larger Lactose Carrier Diameters Can Improve Performance

Size And Roughness Are Interrelated

Shift in the predominant detachment mechanism

Fluid Forces $\rightarrow$ Mechanical Forces

Smooth lactose

Rough lactose

Donovan & Smyth, 2010
Lead To The Hypothesis: Significant Detachment Forces Arise From Particle Collisions

- Additional Evidence
  - CFD studies on particle inhaler collisions
    - Donovan et al. 2011
  - Flow rate dependency studies
Simulations Agreed with Experiments: Inhalers With Greater Particle Collisions Perform Better With Larger Carriers

Donovan et al. 2011
Flow rate improvement of large carrier particle dispersion

- Larger carrier particles produce greater collisions forces due to their increased size, and thus, momentum

- Momentum, $p = m \cdot v$
Studies on marrying device modifications to optimize formulation performance

See following posters presented

R6042 - Evaluation of Granulated Lactose as a Carrier for High Drug Loaded DPI Formulations, (Author: Ping Du)
R6041 - Effect of Device Design on Granulated Lactose Based DPI Formulations, (Authors: Ju Du, Ping Du)

**Formulation**
- Design of granulated lactose carriers
- Increased drug loading
- Improved powder flow
- Optimization of blend uniformity vs carrier particle size

**Device**
- Capsule piercing
- Device geometry
The future: formulation independent performance?

• Very few formulations and particle engineering technologies allow optimum performance in an off-the-shelf device

• Next part of presentation:
  • Device technologies can free the inhalation system from subtleties of formulation
But, Larger Lactose Carrier Diameters Can Improve Performance

Adhesion vs Detachment Forces

- Adhesive force has a linear dependence on diameter
- Impaction force has an exponential dependence on size

Why were our findings of carrier particle size vs performance different?

\[ F_{\text{adhesion}} = \frac{A_H d_1 d_2}{12D^2(d_1 + d_2)} \]

\[ m = \frac{\rho \pi d^3}{6} \]
Single Large Carrier (SLC™) Delivery Mechanism is Traditional “Carrier” Free

SLC™ Coated Sphere

Design Paradigm: “Bigger is Better”

- Sudden flow-stream expansion develops low pressure zone near inlet = bead oscillation
- Drug released by oscillating momentum transfer
- No barrier contact needed to detach drug
SLC-DPI™ Prototype - Superior Single Drug Delivery Efficiency vs. Existing DPI

Fluticasone Propionate
SLC DPI Efficiency - Independent of Patient Inhalation Effort vs. commercial DPI

Fixed Dose Combination DPI Product

- Drug A
- Drug B

Pressure Drop ($\Delta P$)

Delivery Efficiency (%)

1 kPa 2 kPa

Respira SLC DPI Prototype

* Data shown are means ± 1 Std Dev, n=3 tests
Delivery Efficiency Maintained Across Multiple APIs / Classes

- SLC DPI Prototype Test Results

<table>
<thead>
<tr>
<th>API</th>
<th>Dose / Bead</th>
<th>FPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>215 mcg</td>
<td>83% (2%)</td>
</tr>
<tr>
<td>Mometasone Furoate</td>
<td>140 mcg</td>
<td>81% (1%)</td>
</tr>
<tr>
<td>Fluticasone Propionate</td>
<td>112 mcg</td>
<td>81% (2%)</td>
</tr>
<tr>
<td>Albuterol Sulphate</td>
<td>81 mcg</td>
<td>91% (2%)</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>36 mcg</td>
<td>89% (3%)</td>
</tr>
<tr>
<td>Tiotropium Bromide</td>
<td>20 mcg</td>
<td>85% (2%)</td>
</tr>
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*In vitro* cascade impactor testing - Flow Rate = 90 L/min (2kPa)  
Mean (± std. deviation) for N = 3
Scintigraphy studies confirm high lung deposition

Handihaler

Handihaler Lactose 23% Lung Deposition

Stomach

Bead 53% Lung Deposition

SLC DPI

Same Patient Cross-Over Study Result – Tc99m Albuterol
Axial Oscillating Sphere (AOS™) Drug Powder Deaggregation Technology

**PURE DRUG POWDERS**

(1 – 5 µm)

Or, Lactose Blends

Drug Particles

(1 – 5 µm)

Lactose “Carrier” Particles

(60 – 90 µm)

**HIGH-EFFICIENCY DRUG DE-AGGREGATION**

**Bead Remains in the Inhaler**

**AOS Powder Deaggregator**

- Enables delivery of high payloads
- Pure drug or existing blend formulations
- 70+% of drug leaving inhaler is delivered to lung
- <30% of drug delivered to oropharynx
AOS Enhances Performance in Capsule System

- **Handihaler® vs. Handihaler capsule system + AOS-DPI**

- 20 mg capsule fill of 20% API/lactose blend

- **AOS enhances % FPF by 2.9X**

- **Emitted dose not impacted**

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<tr>
<th>Device</th>
<th>Emitted Dose (mcg)</th>
<th>%FPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handihaler</td>
<td>256.6 (7.4)</td>
<td>22.8</td>
</tr>
<tr>
<td>Handihaler capsule system + AOS</td>
<td>251.9 (7.0)</td>
<td>67.1</td>
</tr>
</tbody>
</table>

20mg - 20% API blend, 4KPa
AOS Enhances Performance in Blister System

- **Flovent Diskus® + AOS**
  - 1.5X increase in % FPF
  - ED not impacted

- **AOS-DPI enhances performance of existing formulations in blister system**

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<th>Device</th>
<th>Emitted Dose (mcg)</th>
<th>%FPF 4kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flovent Diskus</td>
<td>256.6 (7.4)</td>
<td>26.4±1.0</td>
</tr>
<tr>
<td>Flovent Diskus + AOS</td>
<td>251.9 (7.0)</td>
<td>40.0±1.4</td>
</tr>
</tbody>
</table>

AOS Enhances Performance in Blister System
Ready to tie the knot?

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  • Ju Du, MS
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