FACTORS TO CONSIDER IN DEVELOPING A DRY POWDER INHALER

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Inhalation Delivery Systems

- **Nebulizers (SVN)**
  - liquid or suspension
  - jet/ultrasonic
  - small mist nebulizers (Respimat®, AER₅®, Mystic®)

- **Metered Dose Inhalers (MDIs)**
  - solution or suspension (CFC vs. HFA)
  - breath-activated inhalers (Autohaler®, Easi-Breathe®)

- **Dry Powder Inhalers (DPIs)**
  - capsule
  - single or multi-dose blisters
  - reservoir
Advantages of Nebulizers

- Normal tidal breathing—little coordination
- High doses of medication
- Can use multiple drugs
- Suitable for specific age groups
- Treatment of CF patients—antibiotic
Disadvantages of Nebulizers

- Length of time to nebulize
- Equipment can be large (difficult to transport)
- Need for external power source
- Variability in performance between different nebulizers
MDI Advantages

- Mainstay of pulmonary delivery since 1950’s
- Capacity for large number of doses
- Unit dose cost is low
- Compact and portable
MDI Disadvantages

• Co-ordination of actuation with inhalation
• Knowing how many doses remain
• Drug content/dose is problematic if MDI not shaken-suspensions
• Contribution to depletion of ozone layer
• Limited to certain drugs that are stable in a propellant
• Potential for oropharyngeal drug deposition
• Mental/cognitive ability of older generation
Transition of MDIs to DPIs

- DPIs appeared on market in 1971 - Spinhaler®
- Eliminate ozone depletion concern of either CFC or HFA-based propellants
- Increased drug stability – dry powder
- Accurate pre-metering of dose
- Success of Turbuhaler® (Pulmicort®, Symbicort®) and Diskus® (Advair®)
Examples of U.S. DPIs

• Spinhaler® (capsule) 1971 cromolyn sodium NLA
• Rotahaler® (capsule) 1988 albuterol sulfate NLA
• Diskhaler® (blister cartridge) 4 doses fluticasone propionate NLA
• Diskus® (blister tape) 60 doses salmeterol xinofoate (Serevent®), salmeterol xinofoate + fluticasone propionate (Advair®)
Examples of U.S. DPIs (Con’t)

- Turbuhaler® (reservoir) 200 doses budesonide (Pulmicort®), budesonide + formoterol (Symbicort®)
- Aerolizer® (capsule) formoterol
- Handihaler® (capsule) tiotropium bromide
- Twisthaler® (reservoir) 14, 30, 60 and 120 doses mometasone furoate
DPI Disadvantages

- Requires moderate inspiratory effort (related to DPI resistance to flow)
- Few drugs available in multi-dose format
- Difficulty in operational steps
- Moisture ingress-aggregation and stability
- Number of doses available-unit cost/dose
Drug Factors

- Preparation of drug powder
  - Milling, spray drying, supercritical fluids
- Crystalline vs. amorphous
- Polymorphism—effect on solubility and hygroscopicity
- Hygroscopic drugs—more risk of instability
- Hygroscopicity may alter adhesive/cohesive properties
DPI/Formulation Factors

- Identify interactions of formulation with device
- Drug powder interparticulate forces
- Protection of drug powder from moisture (stability)
- Powder retention
- Resistance to airflow
- Number / volume of doses
- Filling / metering of powder
- Flowability of drug powder
Drug/Carrier Interaction Factors

- Surface properties of the drug and carrier (roughness)
- Ratio of drug to carrier
- Particle size of each component
- Relative humidity
- Electrostatic behavior
- Processing conditions (batch size)
- Segregation during processing, filling, and storage
Powder Deaggregation Factors

- Minimize cohesive/adhesive particle forces
- Minimize electrostatic charging of particles
- Neat drug vs. carrier/drug particle size
- Hygroscopic vs. non-hygroscopic particles
- Inspiratory flow rate
- Baffles/deaggregation channels
DPI Patient Factors

- Technique errors (correct positioning, exhaling into mouthpiece, no breath hold)
- Complication of devices (too many steps…)
- Generating sufficient inspiratory flow
- Demonstration and training of correct use (RTs, nurses, physicians)
Peak Inspiratory Flow Rate (PIFR)

- Correlation between PIFR and device resistance
- In general, dose delivery increases with air flow
- Variability in dose delivery is tolerable if working with wide therapeutic drugs
- Some resistance may be good since it opens the airways
- Most asthmatics and COPD patients have little difficulty in achieving flow rates of 45L/min
Budesonide % Emitted Dose

Testing of six Symbicort Turbuhalers at three different flow rates (formoterol component showed same trend)

Peak Inspiratory Flows

Figure 1. Peak inspiratory flows in individual inexperienced children (Pedersen et al., 1990) and groups of experienced children (Agerofter et al., 1995).

One Scenario For DPI Development

• Identify the market you want to pursue
  – Disease state and patient population
• Review the patent literature covering that market
• Create concepts/designs for your DPI
• Perform preliminary FEMA
• Create SLA prototypes (quick turnaround)
• Preliminary evaluation of SLA prototype performance and conduct focus group studies
One scenario For DPI Development (con’t)

- Iterations of formulation with DPI
- Iterations of device design (prototypes)
- Retest of formulation and device
- Prepare single cavity tooling
- Laboratory testing
- Preparation of cGMP formulation
- Stability testing of formulation in device
- Clinical testing
- Prepare multi-cavity tooling
Acu-Breathe™ Product Line

Single-dose inhaler
Reusable Device

15-dose inhaler
Reusable Device
Replaceable Cartridge
Dual piercer

30-dose inhaler
Disposable Device
Dual piercer

Dual Piercing Mechanism
Acu-Breathe: I-Point Mechanism

Acu-Breathe 30-Dose

- Device Image
Acu-Breathe 30-Dose

- 30-dose cartridge exposed
Comparison of Diskhaler and Acu-Breathe – Fluticasone propionate

<table>
<thead>
<tr>
<th>Device Tested</th>
<th>Labeled/Blister Dose, µg</th>
<th>Respirable Mass, µg</th>
<th>Blister Residual, µg</th>
<th>Respirable Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diskhaler™ (no FP powder transfer)</td>
<td>250 ± 0.0</td>
<td>36.6 ± 2.2</td>
<td>29.1 ± 6.2</td>
<td>14.6 ± 0.8</td>
</tr>
<tr>
<td>Diskhaler™ (FP powder transfer)</td>
<td>248 ± 9.4</td>
<td>33.8 ± 2.6</td>
<td>23.3 ± 2.9</td>
<td>13.7 ± 1.5</td>
</tr>
<tr>
<td>Acu-Breathe™ 15-dose (FP powder transfer)</td>
<td>230 ± 8.7</td>
<td>36.2 ± 2.5</td>
<td>6.8 ± 2.1</td>
<td>15.8 ± 1.0</td>
</tr>
</tbody>
</table>

Cascade impactor experiments tested at 60L/min

## Comparison of Diskhaler™ and Acu-Breathe™ – fluticasone propionate

<table>
<thead>
<tr>
<th>Device Tested</th>
<th>Exp. #</th>
<th>FP Blister Load, µg</th>
<th>Respirable Mass, (Stages 1-filter), µg</th>
<th>Respirable Fraction, %**</th>
<th>(Pre-separator, TPS, Stages 0-filter), µg</th>
<th>Left in Blister &amp; device %</th>
<th>Emitted Dose %**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acu-Breath™ 30-dose</td>
<td>1</td>
<td>249.5*</td>
<td>42.7</td>
<td>17.1</td>
<td>221.1</td>
<td>11.4</td>
<td>88.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>250.1*</td>
<td>41.6</td>
<td>16.6</td>
<td>228.0</td>
<td>8.8</td>
<td>91.2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>250.3*</td>
<td>38.3</td>
<td>15.3</td>
<td>235.0</td>
<td>6.1</td>
<td>93.9</td>
</tr>
<tr>
<td>Diskhaler®</td>
<td>1</td>
<td>250*</td>
<td>43.0</td>
<td>17.2</td>
<td>174.5</td>
<td>30.2</td>
<td>69.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>250*</td>
<td>39.0</td>
<td>15.6</td>
<td>181.9</td>
<td>27.2</td>
<td>72.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>250*</td>
<td>43.3</td>
<td>17.3</td>
<td>196.7</td>
<td>21.3</td>
<td>78.6</td>
</tr>
</tbody>
</table>

**Cascade impactor experiments tested at 60L/min**

* Based upon six weighed amounts of the FP/lactose blend placed in each of six cartridge blisters or label claim of the Flovent® Rotadisk® product

** Based upon blister load

# Acu-Breathe™ Design Attributes

<table>
<thead>
<tr>
<th>ATTRIBUTE</th>
<th>BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Individual drug blisters</td>
<td>Improved shelf-life</td>
</tr>
<tr>
<td>• <em>i-Point™</em> breath triggered</td>
<td>Dose-to-dose consistency</td>
</tr>
<tr>
<td>• Low part count &amp; simple design</td>
<td>Ease of manufacture (cost)</td>
</tr>
<tr>
<td>• Broad drug payload capacity</td>
<td>Formulation and future product flexibility</td>
</tr>
<tr>
<td>• Compact size &amp; simple to use</td>
<td>Patient acceptance</td>
</tr>
<tr>
<td>• Dual air path and valve design</td>
<td>Dose protected from accidental exhalation</td>
</tr>
<tr>
<td>• Double-dose prevention</td>
<td><strong>Regulatory attractiveness</strong></td>
</tr>
<tr>
<td>• Dose counter</td>
<td></td>
</tr>
<tr>
<td>• Patient friendly (3-step operation)</td>
<td></td>
</tr>
</tbody>
</table>
## Acu-Breathe™ Design Attributes (Cont.)

<table>
<thead>
<tr>
<th>ATTRIBUTE</th>
<th>BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unique blister design</td>
<td>Improved blister clearance</td>
</tr>
<tr>
<td>• Dual piercing mechanism</td>
<td></td>
</tr>
<tr>
<td>• Large blister capacity (25mg)</td>
<td>Broad formulation compatibility</td>
</tr>
<tr>
<td>• Air vane audible feedback</td>
<td>Confirmation of delivered dose</td>
</tr>
<tr>
<td>• Zigzag delivery channel</td>
<td>Maximal de-agglomeration of powder</td>
</tr>
<tr>
<td>• Customizable breath trigger</td>
<td>Can fine-tune device to formulation</td>
</tr>
</tbody>
</table>
Acknowledgements

• Robert A. Casper, Ph.D. – Respirics, Inc.
• William Nadel – Respirics, Inc.