Clinically Relevant *In Vitro* Tests for the Assessment of Innovator and Generic Nasal Spray Products

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Nasal drug delivery

- Can be used for local or systemic delivery
- Metered dose nasal sprays are the most commonly used devices
- Drug delivery efficiency depends on:
  - Nasal geometry
  - Patient use
  - Formulation and device combination
In vitro testing: quality control vs clinically relevant methods

- Currently in vitro QC methods focus on device and formulation performance including methods to characterize spray plume and droplet size.

- The bio-relevance of these methods remains unclear.

- Nasal drug delivery efficiency and assessments of bioequivalence may be aided by the use of more clinically relevant in vitro testing using
  
  - physically realistic nasal airway models combined with
  
  - simulated patient use parameters.
Objective

To test the utility of a potential clinically relevant *in vitro* nasal deposition method and assess the effects of varying:

- Nasal geometry
- Patient use
- Formulation and device combination
Nasal geometry

<table>
<thead>
<tr>
<th>Data set</th>
<th>Guilmette data, MRI scan of an individual - VCU Model 1</th>
<th>VCU Medical Center, CT scan of an individual - VCU Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dh, nostril and nasopharynx</td>
<td>12.1 mm, 5.9 mm</td>
<td>10.6 mm, 4.5 mm</td>
</tr>
<tr>
<td>Surface area (SA)</td>
<td>8024.2 mm(^2)</td>
<td>6802.3 mm(^2)</td>
</tr>
<tr>
<td>Volume (V)</td>
<td>10832 mm(^3)</td>
<td>5118 mm(^3)</td>
</tr>
<tr>
<td>SA/V</td>
<td>0.7 mm(^{-1})</td>
<td>1.3 mm(^{-1})</td>
</tr>
<tr>
<td>SA of the nasal valve</td>
<td>1156 mm(^2)</td>
<td>1493 mm(^2)</td>
</tr>
<tr>
<td>Anterior nose volume</td>
<td>3.2 ml</td>
<td>2.2 ml</td>
</tr>
</tbody>
</table>
Experimental setup

- Two actuations of Nasonex delivered into a single nostril

- Regional drug deposition was measured on:
  
  i) Nasal spray device
  
  ii) Anterior nose region + drip
  
  iii) Middle passages + nasopharynx
  
  iv) Throat + filter
Patient use

Head angle: 30° or 50°

Position: 9 or 5 mm

Actuation force: 4.5 or 7.5 kg

Timing: D or E

Flow rate (L/min)

Actuation

DURING

END

Actuation

Timing

Actuation

DURING

END

Flow rate (L/min)
Nasonex middle passage deposition
VCU nasal model 1

- Nasal deposition varied significantly with changing patient use factors
- Coordinating inhalation with actuation increased middle passage deposition

Mean regional deposition (% recovered dose) and standard deviation (n= 4).
Nasonex middle passage deposition
VCU nasal model 2

- Low impact of patient use factors on nasal deposition in model 2

Mean regional deposition (% recovered dose) and standard deviation (n= 4).
Nasonex middle passage deposition
VCU nasal model 1 and 2

- High middle passage deposition in model 2 compared to model 1

Mean regional deposition (% recovered dose) and standard deviation (n= 4). * - p<0.05 paired t-test
Evaluation of realistic *in vitro* test method

- Formulation and device
  - Mometasone furoate: Nasonex vs “in house”
  - Fluticasone propionate: Flonase vs generic

- Nasal Geometry: VCU models 1 & 2

- Patient Use
  - Patient use conditions producing “low – level 1”, “intermediate – level 2” and “high - level 3” Nasonex middle passage deposition
Patient use factors

<table>
<thead>
<tr>
<th>Expected middle passage drug deposition</th>
<th>Angle</th>
<th>Position (mm)</th>
<th>Force (kg)</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VCU Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1 ~ 20%</td>
<td>50°</td>
<td>9</td>
<td>7.5</td>
<td>E</td>
</tr>
<tr>
<td>Level 2 ~ 40%</td>
<td>30°</td>
<td>5</td>
<td>7.5</td>
<td>D</td>
</tr>
<tr>
<td>Level 3 ~ 60%</td>
<td>50°</td>
<td>5</td>
<td>7.5</td>
<td>D</td>
</tr>
<tr>
<td><strong>VCU Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1 ~ 50%</td>
<td>30°</td>
<td>5</td>
<td>7.5</td>
<td>E</td>
</tr>
<tr>
<td>Level 2 ~ 60%</td>
<td>30°</td>
<td>5</td>
<td>4.5</td>
<td>D</td>
</tr>
<tr>
<td>Level 3 ~ 77%</td>
<td>50°</td>
<td>5</td>
<td>4.5</td>
<td>D</td>
</tr>
</tbody>
</table>
## Droplet size distributions

<table>
<thead>
<tr>
<th>Actuation force of 7.5 kg</th>
<th>Dv10 (μm)</th>
<th>Dv50 (μm)</th>
<th>Dv90 (μm)</th>
<th>Span</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasonex 50 μg (Merck &amp; Co., USA)</td>
<td>16.1 (0.6)</td>
<td>44.5 (2.7)</td>
<td>107.0 (5.4)</td>
<td>1.4</td>
</tr>
<tr>
<td>“In house” mometasone furoate 50 μg (University of Bath, UK)</td>
<td>16.1 (0.7)</td>
<td>47.2 (1.7)</td>
<td>91.2 (1.7)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Actuation force of 5.8 kg</th>
<th>Dv10 (μm)</th>
<th>Dv50 (μm)</th>
<th>Dv90 (μm)</th>
<th>Span</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flonase 50 μg (GlaxoSmithKline, USA)</td>
<td>20.9 (1.1)</td>
<td>70.8 (1.4)</td>
<td>120.3 (1.6)</td>
<td>1.4</td>
</tr>
<tr>
<td>Generic fluticasone propionate 50 μg (Roxane Laboratory, USA)</td>
<td>21.9 (0.2)</td>
<td>69.4 (2.1)</td>
<td>119.6 (0.9)</td>
<td>1.4</td>
</tr>
</tbody>
</table>
**Mometasone furoate middle passage drug deposition**

- **Model 1**
  - No statistical difference in the middle passage drug deposition for the two nasal spray products at each respective level.

- **Model 2**

Mean regional deposition (% recovered dose) and standard deviation (n= 4).
No statistical difference in the middle passage drug deposition for the two nasal spray products at each respective level.

Mean regional deposition (\% recovered dose) and standard deviation (n= 4).
Conclusions

• Realistic *in vitro* test methods could have utility as an inexpensive tool for early evaluation of regional nasal deposition

• *In vivo* validation will be needed before this method will be accepted as a technique for evaluating bioequivalence of nasal spray products

• The effects of patient use factors and geometry of the nasal cavity were found to have significant effects on middle passage drug delivery
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