Wilbur de Kruijf - medspray pharma bv - the Netherlands
Development of a soft mist inhaler using simulation tools to predict lung dose and pharmacokinetics
Presentation overview

- introducing the PFSI Soft Mist Inhaler device
- in vitro test work with PFSI
- preludium predictions lung distribution
- preludium predictions pharmacokinetics
- pK clin 1 study results
- discussion
PFSI

0.5 mL Ompi Alba glass syringe

Pre Filled Syringe Inhaler
# PFSI device performance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid volume per puff</td>
<td>30 µL</td>
<td>flexible 10-50 µL</td>
</tr>
<tr>
<td>Nr of puffs in device</td>
<td>3</td>
<td>up to container volume (500 µL = e.g. 33x 15µL)</td>
</tr>
<tr>
<td>Priming</td>
<td>yes</td>
<td>1 prime shot is sufficient</td>
</tr>
<tr>
<td>MMAD</td>
<td>5.4 µm</td>
<td></td>
</tr>
<tr>
<td>GSD</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Inhalation speed</td>
<td>15 LPM (10-20)</td>
<td>Selected air flow resistance: 15 LPM at -2 kPa</td>
</tr>
<tr>
<td>Lung dose</td>
<td>&gt;50%</td>
<td>of metered dose</td>
</tr>
<tr>
<td>Alveolar dose</td>
<td>&gt;25%</td>
<td>of metered dose</td>
</tr>
</tbody>
</table>
In vitro testing

- NGI at nominal flow rate (MMAD/GSD)
- DUSA at nominal flow rate (DD, SCU)
- LD at nominal, low and high flow rate (MMAD/GSD)
- DUSA at nominal, low and high flow rate (DD, SCU)
- Robustness testing (dropping, shock/vibration, air transport, road transport)
Example design verification test programme

following ISO20072:
DFP testing then SVT testing

DFP - 15 devices

visual check  measure airflow @ -1 kPa  condition > 4h  prime 15x no air flow
DFP 1  No criteria  standard  actuation time

actuate 3x @ -1 kPa  actuate 50x No air flow  condition > 4h
actuate 3x @ -1 kPa  actuate 50x No air flow  condition > 4h
actuate 3x @ -1 kPa

DFP 2  DFP 3  DFP 2
DFP 2  DFP 3  standard  DFP 2

SVT - 6 devices

condition > 4h  prime 15x acc. IFU  actuate 3x in 1 NGI 30 L/min

standard

SVT 1

DFP - 15 devices

visual check  measure airflow @ -1 kPa  condition > 4h  prime 15x no air flow
DFP 1  No criteria  standard  actuation time

actuate 3x @ -1 kPa  actuate 50x No air flow  condition > 4h
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actuate 3x @ -1 kPa

DFP 2  DFP 3  DFP 2
DFP 2  DFP 3  standard  DFP 2

SVT - 6 devices

condition > 4h  prime 15x acc. IFU  actuate 3x in 1 NGI 30 L/min

standard

SVT 1
Realistic throat models in use at Medspray

*In Vitro* Tests for Aerosol Deposition.
VI: Realistic Testing with Different Mouth–Throat Models and *In Vitro—in Vivo* Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler
Discussion on realistic throat models

• a lot of additional work
  the standard NGI work is required anyway
  so using realistic throat models means additional lab work

• simulation based on NGI with USP throat
  has my personal preference
Mimetikos Preludium

Bo Olsson, PhD
Per Bäckman, PhD
Inhalation profile

MMAD 5.4 µm
GSD 1.88
Predicted lung deposition

- Exhaled: 1%
- Throat losses: 47%
- Total lung deposition: 52%
- Alveolar deposition: 29%

% of emitted drug mass based on in-vitro data (NGI cascade impactor)
pK predictions from Preludium compared with in vivo pK results

- accurate prediction for AUC
- slightly lower Cmax predicted vs observed: 0.8 : 1
Dose linearity

simulated and observed, divided by DD (delivered/emitted dose)

- Simulated and observed data support dose-linear response in both $C_{\text{max}}$ and $AUC_t$
Thank you