The SimInhale International Conference
Current Challenges and Future Opportunities for Inhalation Therapies. A cross-disciplinary perspective
Athens, 30 September – 2 October 2019

WG1 Presentation
Particle engineering/processing of inhaled medicines for local/systemic action

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Aim

- address a range of fundamental knowledge gaps whose closing is a prerequisite to improving many other aspects of pulmonary delivery of medicine

Optimal deposition sites

Effects of lung disease on deposition, dissolution and absorption

Effects of airway geometry

Systemic therapies
WG1 Achievements

- White paper on effects of lung disease on the deposition-dissolution-absorption pathway
- White paper on airway geometry effects on deposition patterns
- White paper on Emerging inhaled nanomedicines and associated excipient technologies
- Library of powders classified by the excipients used
- Training of ECIs and other interested scientists in emerging particle-engineering technologies
Particle engineering

From Particles to Powders for Inhalation
Particle engineering

- Narrow particle size distribution
- Improved dispersibility
- Enhanced drug stability
- Optimized bioavailability
- Sustained release and/or specific targeting
- Specifics of inhaler design and drug delivery requirements
# Particulate properties and their effects on respiratory drug delivery

## Particle characteristics

<table>
<thead>
<tr>
<th>Temperature, pressure, solvents, pH, additives, yield, recovery, manufacturing complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallinity, polymorphism, higroscopicity, impurities, solubility, dissolution rate</td>
</tr>
<tr>
<td>Particle size distribution, shape, porosity/density</td>
</tr>
<tr>
<td>Surface morphology, energetics and electrostatic</td>
</tr>
<tr>
<td>Powder bulk density, agglomeration, cohesiveness, flow properties</td>
</tr>
<tr>
<td>Co-formulation/blending; composition/coating</td>
</tr>
<tr>
<td>Formulation, dispersion media</td>
</tr>
</tbody>
</table>

## Effects on formulation

| Process economics, development risks and costs                                         |
| Physical and chemical stability, bioavailability, toxicity                            |
| Aerosolisation behaviour, in vitro and in vivo deposition profiles, bioavailability    |
| Powder handling, inhaler filling, dose metering, storage stability, shelf-life, dose uniformity and consistency |
| Dose uniformity                                                                      |
| Modified or extended release, toxicity                                                |
| Type of inhaler                                                                      |
| Mode of administration                                                               |
Spray-dried particles

**gas temperature below boiling point**

- Rigid + Porous
- Rigid + Nonporous
- Viscoelastic

**gas temperature above boiling point**

- Rigid + Porous
- Rigid + Nonporous
- Viscoelastic + Nonporous

- Fractured
- Shriveled
- Major-
- Minor
- Fractures
- Inflated
- Collapsed
- Deformed
- Spongy

*Siminhale COST ACTION MP1407*
Solvent power and volatility influence texture and surface chemistry of spray-dried microparticles

Constant evaporation rate model
Evaporation rate constant ($\kappa$) = droplet surface area reduction in time

The Peclet number ($\text{Pe}$) can predict the particle formation process and the resulting particle properties

$$\text{Pe} = \frac{k}{8D}$$

D is the diffusion coefficient.
Tobramycin Aerosol Respirability and Particle Dissolution

Energy Dispersive Spectroscopy-Scanning Electron Microscopy

Particle formation process

Spray dried amikacin powder for inhalation in cystic fibrosis patients: A quality by design approach for product construction

Silvia Belotti a,1, Alessandra Rossi a,1, Paolo Colombo a, Ruggero Bettini a, Dimitrios Rekkas b, Stavros Politis b, Gaia Colombo c, Anna Giulia Balducci d, Francesca Buttini a,∗

<table>
<thead>
<tr>
<th>CQAs</th>
<th>Range Values</th>
<th>Negatively affected by</th>
<th>Positively affected by</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD yield (%)</td>
<td>67 - 88</td>
<td>Waxy excipient</td>
<td>High solid concentration</td>
</tr>
<tr>
<td>LOD (%)</td>
<td>7.6 - 9.7</td>
<td>Waxy excipient</td>
<td>Drying temperature</td>
</tr>
<tr>
<td>Dv(0.5) (µm)</td>
<td>1.88 - 3.52</td>
<td>-</td>
<td>High solid concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Feed rate</td>
</tr>
<tr>
<td>Bulk Density</td>
<td>Agglomeration had a positive effect</td>
<td>Waxy excipient</td>
<td>Drying Temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High solid concentration</td>
<td>Ethanol (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feed rate</td>
<td></td>
</tr>
<tr>
<td>ED (mg)</td>
<td>5.7 – 9.2</td>
<td>Waxy excipient</td>
<td>Feed rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interaction between excipient and solid conc</td>
</tr>
<tr>
<td>FPD (mg)</td>
<td>3.5 – 6.1</td>
<td>Waxy excipient</td>
<td>Interaction between excipient and ethanol</td>
</tr>
</tbody>
</table>

Half fractional factorial design \( (2^{n-1}) \)
- Factor 1: Drying temp
- Factor 2: Feed rate
- Factor 3: Ethanol %
- Factor 4: PEG_32 stearate %
- Factor 5: Solid Conc

16 experiments
Results

• Feed solution required the inclusion of 10% (v/v) ethanol
• Amikacin in the feed solution had to be kept at 1% w/v level
• Increase in drying temperature always led to an evident increase in emitted dose (ED) without affecting the fine particle dose (FPD) values.
• PEG-32 stearate did not benefit the CQAs of the spray dried powders

Spray-dried amikacin sulphate powder for inhalation in cystic fibrosis patients: The role of ethanol in particle formation

Silvia Belotti\textsuperscript{a}, Alessandra Rossi\textsuperscript{a}, Paolo Colombo\textsuperscript{a}, Ruggero Bettini\textsuperscript{a}, Dimitrios Rekkas\textsuperscript{b}, Stavros Politis\textsuperscript{b}, Gaia Colombo\textsuperscript{c}, Anna Giulia Balducci\textsuperscript{d}, Francesca Buttini\textsuperscript{a,⇑}

\textbf{Central Composite Design}

- Drying temperature: 150°C, 165°C, 180°C
- Feed rate: 2 ml/min, 3.5 ml/min, 5 ml/min
- Ethanol presence. 0%, 5%, 10%

\textbf{15 experiments}

\textbf{Emitted Dose}

\textbf{Fine Particle Dose}
Amikacin from water:ethanol
Solvent power and volatility influence texture and surface chemistry of spray-dried microparticles

The Peclet number (Pe) can predict the particle formation process and the resulting particle properties

\[ Pe = \frac{K}{8D} \]

Evaporation rate constant, \( k \) = droplet surface area reduction in time (cm\(^2\)/s)

\( D \) is the diffusion coefficient of dissolved substance in the sprayed solution

- \( Pe \leq 1 \) Dense particle
- \( Pe > 1 \) Empty shell particle

\[ \text{Water/EtOH mixtures} \]

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