Identification of crystalline forms suitable for inhalation in drug discovery

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Respiratory is a core area of R&D expertise, which has delivered significant value for the company and continues to expand to meet areas of unmet medical need in asthma, Chronic Obstructive Lung Disease (COPD) and other respiratory diseases.
Physiology of the Lung

The airways bifurcate 16-17 times in different branches before the alveoli are reached.

CONDUCTIVE ZONE
large airways, tracheo-bronchial region

RESPIRATORY ZONE
small airways, alveolar region, gas exchange area

<table>
<thead>
<tr>
<th>Surface area</th>
<th>Internal diameter</th>
<th>Cellular barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (a few m² in adults)</td>
<td>3-5 mm in bronchi</td>
<td>Monolayer of thick columnar cells (~ 60 µm)</td>
</tr>
<tr>
<td>Large (ca 100 m² in adults)</td>
<td>0.5-1 mm in terminal bronchioles, 250 µm in alveoli</td>
<td>Monolayer of thin broad cells (0.1-0.2 µm)</td>
</tr>
</tbody>
</table>
Drug Delivery to the Lung

Aerodynamic Diameter

\[ d_{ae} = d_{geo} \sqrt{\left( \frac{\rho_p}{\rho_0 \chi} \right)} \]

function of particle size, shape and density

Optimized particle deposition for \( d_{ae} \) 1-5 µm

- small enough to avoid deposition by inertial impaction on upper airways
- large enough to avoid exhalation from the lower airways

Impaction > 5 µm
Sedimentation 1–5 µm
Brownian Diffusion <1 µm
# Inhalable Drug-Delivery Systems

<table>
<thead>
<tr>
<th>pMDI</th>
<th>Nebulizers</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pressurized Metered Dose Inhaler</td>
<td>Acqueous solution/suspension</td>
<td>Dry Powder Inhaler</td>
</tr>
<tr>
<td><em>Propellant based (HFA/CFC)</em></td>
<td><em>Atomization by air jet or ultrasonic mechanism</em></td>
<td><em>Non propellant based</em></td>
</tr>
<tr>
<td><em>Solution/suspension</em></td>
<td><em>Need for power supply</em></td>
<td><em>Solid particles</em></td>
</tr>
<tr>
<td><em>Surfactant/lubricants/cosolvents</em></td>
<td><em>Active devices</em></td>
<td><em>Might contain excipient (lactose)</em></td>
</tr>
<tr>
<td><em>Generally active devices</em></td>
<td></td>
<td><em>Generally passive devices</em></td>
</tr>
</tbody>
</table>
Principle of DPI design

**ADHESION**
Rough surface of carrier particles provide high-energy active sites for the drug particles to adhere to

**DETACHMENT**
Drug particles detach from the carrier during inhalation and are released into the airways
Micronization by Jet Mill

- Well-established and well-validated technique in DPIs production
- Able to produce particles of size range required for inhalation (1–5 µm)

Particle reduction
- through high velocity particle-particle collisions
- in a flat cylindrical grinding chamber

from www.sturtevantinc.com
Micronization effects

High energy process, can alter solid state and surface properties, leading to unstable materials

- Surface amorphization:
  - thermodynamic instability, surface recrystallization, interparticle solid bridges, fused particles, strong agglomeration
  - chemical decomposition
  - water sorption

- Form interconversion

Crystal size, habit, shape and surface of micronised need to be fully controlled

Proper crystalline form selection in early phase is crucial!
Drug R&D phases vs crystallisation screening

Solid form screening must be tailored to drug development phase

…but inhalation requires even an earlier start!
Drug R&D phases vs crystallisation screening

We screen a lot of compounds!

...but with some constraints
Constraints – Molecular Characteristics of Pulmonary Drugs

- High MW (>500)
- Large PSA
- High number of HBA/HBD
- Greater number of rotatable bonds
- Challenging synthetic routes: impact on purity/material

Complex molecules!

<table>
<thead>
<tr>
<th>Class</th>
<th>Average MW</th>
<th>Average PSA</th>
<th>Average rotatable bond count</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA</td>
<td>498</td>
<td>116.63</td>
<td>13</td>
</tr>
<tr>
<td>LAMA</td>
<td>385</td>
<td>43.15</td>
<td>6</td>
</tr>
<tr>
<td>MABA</td>
<td>717</td>
<td>148.55</td>
<td>16.73</td>
</tr>
<tr>
<td>PDE4 muscarinic duals</td>
<td>691</td>
<td>122.5</td>
<td>12.25</td>
</tr>
<tr>
<td>Phosphate prodrugs</td>
<td>969</td>
<td>173</td>
<td>26.2</td>
</tr>
<tr>
<td>Oral (from market)</td>
<td>305</td>
<td>60.37</td>
<td>4.7</td>
</tr>
<tr>
<td>Inhaled (from market)</td>
<td>370</td>
<td>89.2</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Selby, Future Med. Chem. 2011
Constraints – Counter-ions

Sensitivity of bronchial mucosa requires lack of any irritative potential

**limited number of counter-ions for inhalation**

- Pharmaceutically acceptable counterions sources
  - GRAS substances database
    (Generally Recognised As Safe)
  - Handbook of Pharmaceutical Salts:
    Properties, Selection, and Use

- First select precedentend counterions for marketed inhaled drugs, and consider “class preferences”

Best if known to be safe in the lung

Selby, Future Med. Chem. 2011
Constraints – Excipients

Sensitivity of bronchial mucosa requires lack of any irritative potential

limited number of excipients for inhalation

<table>
<thead>
<tr>
<th>Accepted or interesting additives for DPI</th>
<th>Description</th>
<th>Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Description</td>
<td>Excipients</td>
</tr>
<tr>
<td>Sugars</td>
<td>Coarse/fine carrier</td>
<td>Lactose, Glucose, Mannitol, Trehalose</td>
</tr>
<tr>
<td>Hydrophobic additives</td>
<td>Protection for drug moisture</td>
<td>Mg stearate</td>
</tr>
<tr>
<td>Lipids</td>
<td>Used in liposomes, matrix, coating</td>
<td>DPPC, DSPC, DMPC, cholesterol</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Improved aerosol efficiency</td>
<td>Leucine, treleucine</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Production of light and porous particles</td>
<td>Poloxamer, Bile salts</td>
</tr>
<tr>
<td>Absorption enhancers</td>
<td>Absorption for proteins &amp; peptides</td>
<td>HP-β-CD, natural γ-CD, Bile salts, Chitosan, trimethylchitosan</td>
</tr>
<tr>
<td>Biodegradable polymers</td>
<td>Used in sustained release formulations</td>
<td>PLGA</td>
</tr>
</tbody>
</table>

Coarse α-lactose monohydrate (30-250 µm)
approved and most commonly used as carrier
to improve flowability and dispersibility of fine API

Compatibility recommended, assess it early!

Grasmeijer et al., PloS one 2013

Pilcer & Amighi, Int. J. of Pharm. 2010
Opportunities – What about Cocrystals?

- Advantages
  - Improvement of candidate drugability
    - Stability
    - Solubility
    - Bioavailability/PK
  - Patentability
  - Combo application
    - Synergistic effect
    - Fixed combination
  - Chance to identify crystalline hits

- Particle engineering for inhalation to be properly addressed
  - Need for alternative to jet mill?

1:1 co-crystal of tramadol hydrochloride–celecoxib
Opportunities – What about Computational Prediction?

Advantages

- prediction of most stable polymorphic form
- prediction of crystal habit: high impact in inhalation (aerodynamics)
- aid for selection of promising counterions/coformers
- pka
- solvent solubility

Our experience

- not so spread among CROs
- some specialized groups
- some useful indication, even if inhalation compounds very challenging
Crystallisation screening

- Screening conditions
  - Medium Throughput
  - Quick solvent screening
  - 1-5 crystallisation techniques
  - If possible recycle material
  - 5-20 mg/experiment
  - 3-24 solvent systems

- Analytical approach
  - XRPD
  - Polarized Light Microscopy

<table>
<thead>
<tr>
<th>Approach</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST/PRELIMINARY</td>
<td>200mg - 2g</td>
</tr>
<tr>
<td>EXTENDED/ABBREVIATED</td>
<td>5-20g</td>
</tr>
<tr>
<td>FULL/COMPREHENSIVE</td>
<td>20-100g</td>
</tr>
</tbody>
</table>

Case studies
Conclusions

Start early, learn & fine tune screening…

…and lower expectations!
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