Antibiotic DPI: particles, powders, devices and in vitro /in vivo respirability

PAOLO COLOMBO
Department of Pharmacy, University of Parma, ITA

Antibacterials & Inhalation

- Nebulizers as established products
- Cystic fibrosis infection management
- Tuberculosis
- Nontuberculous Mycobacterium
- Infection management as complement of systemic delivery
- Compliance
- Resistance

DPI: alternative to nebulizers

- Patient breath activated
- High payload and dosage (up to 400 mg)
- Prolonged high concentration at deposition site
- Drug/drug combination for resistant pathogens
- No device disinfection/cleaning (disposable)
- Reduction of treatment burden

Powders for inhalation have to be small for aerosolization and deposition, but large enough for metering during dosage form manufacturing.

Inhalation Powder: a collection of particles. A Pharmaceutical Technology Paradox

Aerodynamic Diameter

\[ d_{ae} = d_v \left( \frac{\rho}{\rho_0} \chi \right)^{1/2} \]

\( \chi \) = dynamic shape factor (1 for a sphere)
Solvent volatility and solute diffusion rate governs the structure of spray-dried microparticles.

Peclet number (Pe) predicts the particle formation structure:

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

- $k$: evaporation rate constant (droplet area reduction/time)
- $D$: components' diffusion coefficient

Drug solubility contributes to the structure and surface chemistry of microparticles as well.
However, high doses of powders can raise adverse effects during inhalation. Dry powder inhalers are able to deliver high payloads of drug in a shorter time, offering a convenient alternative to solutions for nebulization. Inhalers are able to deliver high payloads of drug in a shorter time, lower doses compared to systemic administration. Dry powder inhalers for the treatment of lung infections in Cystic Fibrosis (CF) patients caused by Pseudomonas aeruginosa are efficiently managed with antibacterial therapies. These treatments require high doses of antibiotics. However, the administration, such as cough and choking. Consequently, different approaches have been adopted to optimize size, morphology and structure of microparticles for inhalation.

The performance of a dry powder inhaler is governed by a series of critical process parameters (CPPs). In this work we focused on the role of ethanol presence on the formation of amikacin sulphate spray-dried particles, in order to maximize the respirable fraction of the drug, without compromising the powder flow properties. Ethanol has been adopted to optimize size, morphology and structure of spray-dried microparticles for inhalation. In particular, focus was given on the role of ethanol presence on the formation of these amikacin sulphate spray-dried particles.

The overall outcome of the CCD was that amikacin respirability was not substantially improved, as the optimum region coincided with areas already explored with the fractional factorial design. However, the levels of these factors were increased from two to three and their effect on amikacin respirability was evaluated. In particular, focus was given on the role of ethanol presence on the formation of the spray-dried particles. Ethanol proportion, temperature, feed rate and ethanol proportion, have been selected out of the initial five. In addition, the crucial role of this solvent on the morphology of the produced particles. Peclet number and drug solubility in the spraying solution helped to understand the formation mechanism of these amikacin sulphate spray-dried powders.

A Central Composite Design (CCD) was applied in order to identify positive combinations of the production parameters of amikacin sulphate spray-dried powders for inhalation, with the intent to expand the experimental space defined in a previous half-fractional factorial design. Three factors, namely drying temperature, feed rate and ethanol proportion, have been selected out of the initial five. In addition, these factors have been given the highest level of variation to allow for the inclusion of the central point as well as the high and low levels of variation. The overall outcome of the CCD was that amikacin respirability was not substantially improved, as the optimum region coincided with areas already explored with the fractional factorial design. However, the levels of these factors were increased from two to three and their effect on amikacin respirability was evaluated. In particular, focus was given on the role of ethanol presence on the formation of the spray-dried particles. Ethanol proportion, temperature, feed rate and ethanol proportion, have been selected out of the initial five. In addition, the crucial role of this solvent on the morphology of the produced particles. Peclet number and drug solubility in the spraying solution helped to understand the formation mechanism of these amikacin sulphate spray-dried powders.

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**Soft Pellets**

Primary microparticles held together by weak links in macro-agglomerates. Strong enough for handling, but de-agglomerated by turbulent air flow.

Particle formation process for binary mixtures of tobramycin and sodium stearate during spray drying where A low sodium stearate concentrations and B high sodium stearate concentrations.
Antibiotic DPI for Pseudomonas aeruginosa infections in Cystic Fibrosis

Two different approaches for high doses

- TOBI Podhaler: Tobramycin DPI
  Dose shared in four capsules

- Colobreath: Colistimethate DPI
  Dose cumulated in one capsule

Patient convenience, compliance and safety

1. Powder mass
   - TOBI® Podhaler
     4 cps x 50 mg
     Tobramycin 28 mg
     Excipient 22 mg
   - TOBI® Podhaler
     4 cps x 60 mg

2. Capsule strength
   - TOBI® Podhaler
     1 cps x 120 mg
   - Colobreath
     1 cps x 220 mg
**Powder Disposition or Respirability**

<table>
<thead>
<tr>
<th>Device</th>
<th>Emitters</th>
<th>mg/cps</th>
<th>Emitters Dose</th>
<th>mg</th>
<th>FPD</th>
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<tbody>
<tr>
<td>TOBI</td>
<td>28</td>
<td>∼50</td>
<td>46.0</td>
<td>92%</td>
<td>27.6</td>
</tr>
<tr>
<td>TobraPS</td>
<td>28</td>
<td>32.15</td>
<td>28.04</td>
<td>84%</td>
<td>24.0</td>
</tr>
</tbody>
</table>

**Capsule Number & Strength**

RS01 can capsize from size 3 to zero. Accumulation of intraminal powder in one or two capsize makes possible by device flexibility and high drug content.

The linear relationship between the in vitro respirability and loading validates the capsule number reduction by increasing their strength.
In Vivo Inhalation Flow Rate

Emitted Dose & Sequence of Inhalation Acts

Emitted Dose & Peak Inhalation Flux
2.1. Materials

2.2. Particle preparation

2.3. The filling of blisters

2.4. Inhalation

2.5. The physico-chemical properties of the aminoglycosides relevant to the dispersion and retention in order to decide how the Twincer™, the persible powder formulation with the aid of a relatively high content of the powder from spray drying before the dispersion (PSD) and the final water content of the powder. Powder handling speed (2.5 mL/min) were used to control the particle size distribution (PSD) and the final water content of the powder. Aspirator setting (100%), nozzle pressure (50 mm) and pump temperature was set to 130 °C.

The Cyclops disposable DPI was well tolerated in a dose of 2 mg. Because they are large crystals and become sticky or even liquefied. Powder residues in the inhaler absorb moisture from the air to good dispersion when a used DPI is stored inappropriately and needs to be modulated for spray dried aminoglycosides in this DPI remains nearly the same for the entire dose.

In studies with healthy volunteers, it has been shown that the dispersion efficiency of colistimethate sodium in this DPI remains nearly the same for the entire dose. Hence, the inhaler design has to be adjusted to suit the physico-chemical properties of the aminoglycosides relevant to the dispersion and retention in order to decide how the Twincer™, the persible powder formulation with the aid of a relatively high content of the powder from spray drying before the dispersion (PSD) and the final water content of the powder. Therefore, the aim of this study was to investigate the modulation of the product emission (no choking) in vitro/in vivo, all acts.

Disposable device:
a step forward

- Modulation of the product emission (no choking)
- Extreme ease of use
- No cleaning