Quo vadis dissolution testing for inhalation powders?

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ABSTRACT SUMMARY
The respiratory tract is an attractive application place for systemically active drugs. In this context, solubility is a limiting factor, especially for poorly soluble substances. Therefore dissolution testing of inhalation powders is of interest for bioavailability estimation. We studied different experimental set-ups and the important parameters impacting dissolution are evaluated. In conclusion the classic paddle apparatus and the so-called Transwell® dissolution system currently appear as the most suitable dissolution techniques.

INTRODUCTION
The respiratory tract is an interesting route of application for both local and systemic active pharmaceutical ingredients, due to the thin epithelium, the rich blood supply, the large surface area (> 100 m²) and the comparably low enzymatic activity (1;2). Even the application of macromolecules like insulin was mastered (3).

Particles with a diameter ≤ 5µm (fine particle fraction-FPF) reach the lung what is well known and controllable by aerosol physics. The pharmacopeia quality control mainly focus on the aerodynamic particle size distribution (4). In this context question about the distribution and dissolution of deposited particles are gaining interests. What is the right set-up for powder deposition (Fig.1) besides the distribution the question arises: “What happens after landing?”.

The respiratory tract has only a small volume of aqueous fluid (10-20 ml/100 m²) (1;5) and very effective defense mechanisms against foreign particulates: mucociliary clearance in the upper lungs (6;7) and macrophage clearance in the peripheral lungs (8). These mechanisms are no problem for good soluble substances (8), but this might be different for poorly soluble substances, which need longer time to dissolve.

However, so far not many efforts have been undertaken to systematically investigate the dissolution behavior of deposited aerosol particles and to interpret such data in the context of pulmonary bioavailability. For such specific purposes, the existing in-vitro set-ups need to be re-evaluated and eventually to be further developed (9-12).

Aim of this study was to compare some classical dissolution tests, like flow through cell and paddle apparatus, as well as some adaptations of the Franz Cell or Transwell® dissolution system for studying the in-vitro dissolution behavior of aerosol particles after deposition in the respiratory tract. The possible role of surfactants in the lung lining fluid was also addressed.

![Figure 1: relevant factors for dissolution testing of inhalation powders. Deposition (left: agglomeration, right: homogenous distribution), membrane type and receptor medium.](image)

EXPERIMENTAL METHODS
For dose collection a modified Andersen cascade impactor (ACI) at standard USP (4l flow, pressure drop 4 kPa) conditions was used as described before (9) As modification a stage extension (h = 5.8 cm) was inserted between the filter stage and stage 1. This modification allows the sedimentation of particles instead of impaction (13). To collect the particles, different filter materials were used such as regenerated cellulose (pore size D = 0.45 µm), polyester and po-
lycarbonate ($D = 0.4 \mu m$). For dissolution testing, a flow through cell, a Franz cell, the paddle apparatus (9) and the Transwell® dissolution system were used. The dissolution medium was phosphate buffered saline (PBS) pH 7.4 with or without adding various surfactants (e.g. DPPC, Tween 20, Tween 80 or SDS). The Solubility of substances in various dissolution media was determined. Dissolution kinetics were evaluated by Mean Dissolution Time (MDT) and f2 similarity test.

RESULTS AND DISCUSSION

For dissolution tests of inhalation powders the FPF was collected on a “dissolution-membrane”. The homogeneity of particle distribution was a crucial factor for dissolution reflected in the (MDT)$_\text{paddle}$ (Fig. 2). For normal ACI deposition (MDT) is much larger than for the modified ACI, due to the formation of more agglomerates by the use of the ACI (Fig 2).

![Figure 2: MDT for budesonide in paddle apparatus with different dose collection methods. FPF for 170 µg and 370µg, respectively](image)

Table 1: MDT for budesonide for permeability test with different membrane materials

<table>
<thead>
<tr>
<th>polymer</th>
<th>polycarbonate</th>
<th>regenerated cellulose</th>
</tr>
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<tbody>
<tr>
<td>polyester</td>
<td>56.7 ± 4.5</td>
<td>37.8 ± 5.7</td>
</tr>
<tr>
<td>polycarbonate</td>
<td>22.7 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>regenerated cellulose</td>
<td>37.8 ± 5.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: MDT of dissolution test of budesonide in paddle apparatus with PBS buffer with different surfactants

<table>
<thead>
<tr>
<th>surfactant</th>
<th>0.02% DPPC</th>
<th>0.2% SDS</th>
<th>0.2% Tween20</th>
<th>0.2% Tween80</th>
<th>without</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDT</td>
<td>35.3 ± 3.5</td>
<td>11.5 ± 5.7</td>
<td>27.6 ± 4.0</td>
<td>37.6 ± 7.9</td>
<td>37.2 ± 3.7</td>
</tr>
</tbody>
</table>

The membrane material must be carefully chosen not to hinder the permeation due to interactions. For Budesonide polymer has a retaining effect whereas polycarbonate and regenerated cellulose worked well (table 1).

The presence of surfactants showed an increased MDT for SDS and Tween 20/80 caused by increasing saturation concentration. MDT$_\text{DPPC}$ was unaffected but leads to a better reproducibility (increased wettability) (table 2).

By comparing all systems, Transwell® dissolution system and paddle apparatus showed the best discriminating power so far (data not shown). The Transwell® dissolution system is due to the small volume (2.5 - 3.85 ml) and the air liquid interface closer to the situation in the lungs. In contrast, paddle apparatus has neither an air liquid interface nor a small volume (1000 ml) but is easy to handle, reproducible, automated and very useful for a “pure” in-vitro dissolution testing.

CONCLUSION

With this study we could show that the quality of dissolution testing of inhalable particles depends on the amount and way of distributing particles on the filter membrane, the membrane material, the presence of additives and the dissolution apparatus itself. Surprisingly, the classical paddle apparatus is also for inhalation powders suitable. The most lung-like-system and hence potent test set up is the Transwell® dissolution system.

REFERENCES

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