Examining the influence of carrier lactose on the performance of dry powder inhaler (DPI) formulations: A case study

Data elucidates the importance of a fundamental step in DPI formulation and device design

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Introduction
Most commercially-available dry powder inhaler (DPI) formulations utilize a carrier-based formulation concept.1 Utilizing a mixing process, micronized active pharmaceutical ingredient (API) particles are attached to the surface of larger excipient particles. Multiple studies list excipients such as mannitol, glucose monohydrate, trehalose, dextrose, maltose, sorbitol and maltitol for use in DPI formulations.1-5 However, α-lactose monohydrate remains the excipient of choice. Due to its long use in pulmonary drug delivery, it is considered safe6 and a variety of commercially-available grades of lactose have been specifically developed for use in pulmonary drug delivery. The median particle size of those commercially available inhalation grades ranges from approximately 50 µm to 200 µm.7

Although significant work has been put into understanding the influence of carrier properties, such as particle size, shape and surface characteristics8-20 on the performance of DPI formulations, there is still no standard approach or “rule of thumb” for the selection of an appropriate carrier grade for a given API and device. For this reason, carrier selection remains a crucial and challenging task in pharmaceutical development.

This study demonstrates the influence of the excipient on the performance of DPI formulations. The study was carried out with two APIs (salbutamol sulfate and budesonide), three commercially-available grades of carrier lactose and two dry powder inhaler devices (one capsule-based and one reservoir-based).

Materials and methods
Micronized budesonide and salbutamol sulfate (Figure 1) were used as lipophilic and hydrophilic model APIs, respectively. The micronized APIs (100 µg salbutamol sulfate/actuation and 200 µg budesonide/actuation) were mixed with lactose carriers of different size (InhaLac 250, 230 and 120, Meggle Excipients and Technology, Germany) (Figure 2).

The particle size distribution (n = 3) of the lactose grades (R5 lens) and the micronized APIs (R1 lens) was determined using a HELOS laser diffraction system equipped with a RODOS dry dispersion unit and a VIBRI powder feeder (dispersion pressure: 3 bar). Powder blends (batch size: 25 g) were prepared on a Turbula blender T2F (72 rpm, 60 minutes) using the double-sandwich method. During the mixing process, the blender was stopped every 15 minutes and the powders were sieved through a 250 µm sieve in order to increase mixing homogeneity. Blend homogeneity was determined by calculating the relative standard deviation (RSD) of the API content of 10 samples, which had been drawn from different spots in the mixing vessel. Only blends with a RSD < 5% were accepted for further testing.

The performance of the DPI formulations was evaluated using a reservoir-based device (Clickhaler, Vectura, UK) and a capsule-based device (Aerolizer, Novartis, Switzerland). The uniformity of the delivered dose was determined according to the monograph “Preparations for Inhalation” of the European Pharmacopoeia21 using a dose uniformity sampling apparatus (DUSA). For the capsule-based device, 10 gelatin capsules (size nr. 3) were manually filled with 25 mg and subsequently used for dose uniformity testing. Delivered doses 1-3, 49-52 and 98-100 of the reservoir-based device were used for the evaluation of uniformity.
The aerodynamic assessment of fine particles was performed using apparatus E (NGI; n = 3). The fine particle dose (FPD) was calculated as the dose from the active ingredient exhibiting an aerodynamic diameter < 5 µm. The emitted dose was the amount of the active found in the whole. The fine particle fraction (FPF) was defined as the fine particle dose divided by the emitted dose. The drug content of the mixing homogeneity, DUSA and NGI samples was determined using a high-performance liquid chromatography (HPLC) system.

Results and discussion

Two model APIs were used to study the effect of an API on DPI performance: hydrophilic salbutamol sulfate and lipophilic budesonide. The median particle size of the micronized API salbutamol sulfate ($x_{50} = 1.7 \pm 0.0 \text{ µm}$) is slightly smaller than that of the budesonide ($x_{50} = 2.1 \pm 0.0 \text{ µm}$) (Table 1). The morphology of the API materials differs distinctly (Figure 1). Salbutamol sulfate particles have a characteristic needle-like shape whereas budesonide particles are more spherical.

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**Figure 1**
Scanning electron micrograph images of the micronized APIs

<table>
<thead>
<tr>
<th>Salbutamol sulfate</th>
<th>Budesonide</th>
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<tr>
<td><img src="image1" alt="Salbutamol sulfate" /></td>
<td><img src="image2" alt="Budesonide" /></td>
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**Figure 2**
Scanning electron micrograph images of the carrier lactose grades

<table>
<thead>
<tr>
<th>InhaLac 250</th>
<th>InhaLac 230</th>
<th>InhaLac 120</th>
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<tr>
<td><img src="image3" alt="InhaLac 250" /></td>
<td><img src="image4" alt="InhaLac 230" /></td>
<td><img src="image5" alt="InhaLac 120" /></td>
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In order to study the influence of lactose carrier size on the performance of DPI formulations, three different carrier materials, InhaLac 250, 230 and 120, were used. The particle size distribution of the three materials is shown in Table 1. With a median particle size of 51.7 ± 0.7 µm, InhaLac 250 is the finest lactose grade, followed by InhaLac 230 (x50 = 87.4 ± 0.2 µm) and InhaLac 120 (x50 = 131.8 ± 1.3 µm). With decreasing particle size, the span value (which characterizes the width of the distribution) increases. This increase can be explained by the presence of intrinsic lactose fines, especially for InhaLac 250. The greater amount of fines is also visible in the SEM images of the product (Figure 2).

For all adhesive mixtures, a mixing homogeneity < 5% relative standard deviation (RSD) was achieved (Table 2). Mixtures prepared with budesonide showed, by trend, higher homogeneity. No dependence of the mixing homogeneity on the carrier material could be observed.

The uniformity of delivered dose was determined according to the European Pharmacopoeia, by collecting 10 doses of each adhesive mixture from the capsule-based and the reservoir-based devices. For all mixtures and all devices, the API mass in the DUSA was between 75% and 125% of the average value (Figure 3). Therefore, all products fulfilled the acceptance criteria for homogeneity of delivered dose testing.

Depending on the carrier lactose, the API and the device, an FPF between 11% and 44% was observed (Figure 4). Generally, the FFPS for the adhesive mixtures containing salbutamol sulfate were higher (17%-44%) than those with budesonide (11%-22%).

**Reservoir-based system.** The largest differences were observed for the hydrophilic API salbutamol sulfate and lactose carriers of different size (Figure 4). For the finest carrier material, InhaLac 250, which contains the highest amount of intrinsic fines, a FPF of 44% was found. A much lower FPF of 17% was determined for adhesive mixtures with the coarser InhaLac 120. Interestingly, no influence of the carrier material on the performance of the lipophilic API budesonide was observed.

**Capsule-based system.** The adhesive mixtures of salbutamol sulfate delivered via the capsule-based device showed similar behavior, however, less pronounced (Figure 4). The FPF was higher (28%) for the finest carrier material, InhaLac 250, and was lower for the coarser material InhaLac 120 (22%). A different behavior was observed for adhesive mixtures with budesonide. A higher FPF was obtained with the

<table>
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<tr>
<th>Table 1</th>
<th>Particle size distribution (x10, x50, x90 and span) of the carrier lactose grades and the micronized APIs (mean n = 3 ± SD)</th>
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<tbody>
<tr>
<td></td>
<td>x10/µm</td>
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<tr>
<td>InhaLac 250</td>
<td>19.3 ± 0.2</td>
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<tr>
<td>InhaLac 230</td>
<td>43.7 ± 0.3</td>
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<tr>
<td>InhaLac 120</td>
<td>83.9 ± 2.3</td>
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<tr>
<td>Salbutamol sulfate</td>
<td>0.5 ± 0.0</td>
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<tr>
<td>Budesonide</td>
<td>0.5 ± 0.0</td>
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<th>Table 2</th>
<th>Mixing homogeneity of the powder blends</th>
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<tr>
<td></td>
<td>InhaLac 250</td>
</tr>
<tr>
<td>Salbutamol sulfate</td>
<td>Mean/mg/g</td>
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<tr>
<td></td>
<td>RSD/%</td>
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<td>Budesonide</td>
<td>Mean/mg/g</td>
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<td>RSD/%</td>
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Figure 3
Uniformity of delivered dose of the adhesive mixtures of lactose carrier [InhaLac 250 (black), InhaLac 230 (red) and InhaLac 120 (blue)] and API (salbutamol sulfate and budesonide) delivered via a capsule-based and a reservoir-based device.

Figure 4
FPF of the adhesive mixtures of lactose carrier [InhaLac 250 (black), InhaLac 230 (red) and InhaLac 120 (blue)] and API (salbutamol sulfate and budesonide) delivered via a capsule-based and a reservoir-based device.
coarser carrier material InhaLac 120 (22%) whereas the FPF was lower for InhaLac 250 (17%) and InhaLac 230 (16%).

The results show that, for all lactose carrier qualities, an appropriate mixing homogeneity (RSD < 5%) can be achieved. All adhesive mixtures had sufficient flowability to be dosed with appropriate accuracy in the reservoir-based device, even the finest carrier material, InhaLac 250. All adhesive mixtures fulfilled the acceptance criteria of the European Pharmacopoeia for homogeneity of delivered dose. However, large differences for the FPF of the API were found. Using salbutamol sulfate, the FPF largely depended on the carrier particle size. Thus, for salbutamol sulfate, the FPF can be adjusted by choosing the appropriate carrier lactose material. A higher FPF was achieved with a carrier material of smaller size and a higher amount of intrinsic fines. The adhesive mixtures containing the API budesonide proved to be very robust with respect to the particle size of the carrier material.

Conclusion

This study shows the importance of carrier material selection in DPI development. Whereas no influence of the carrier material on the performance of budesonide-based formulations in the reservoir-based device was observed, the FPF of salbutamol sulfate-based formulations ranged from 17% to 44% (Figure 4). The difference in FPF of salbutamol sulfate for the given carrier materials was less pronounced when delivering the formulation via the capsule-based device (22% to 28%).

The study demonstrates the importance of lactose selection studies during formulation development and the need to perform such studies for every new development project. Although one carrier material may work ideally for an existing formulation, it may be wise to use a different carrier when changing the API, the concentration of the API or the device.

References


22. 2.9.18 Preparations for Inhalation: Aerodynamic assessment of fine particles for inhalation, European Pharmacopoeia.

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