Aerosolization Characteristics of Dry Powder Inhaler Formulations for the Enhanced Excipient Growth Application: Effect of DPI Design

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INTRODUCTION

The current market for DPIs has over 20 devices presently in use, and many devices under development for delivering a variety of therapeutic agents (1, 2). Conventionally, these active and passive DPIs have been designed for powder formulations containing drug particles in the 1-5 µm range, although there have been a small number of studies investigating powder formulations in the submicrometer size range. In this study, four DPIs were evaluated for their ability to effectively aerosolize a carrier-free dry powder formulation for the enhanced excipient growth (EEG) application and produce a high submicrometer particle fraction (3). Combined computational fluid dynamics (CFD) and in vitro experiments were employed to implement design modifications to one of the devices, the HandiHaler®, to improve aerosolization.

METHODS

A dry powder combination formulation, consisting of albuterol sulfate (AS), mannitol, L-leucine and poloxamer 188 in a ratio of 30:48:20:2, was prepared by spray drying using a Büchi Nano spray dryer B-90. The formulation was aerosolized using Aerolizer® (Novartis) and HandiHaler® (Boehringer Ingelheim), both passive DPIs operated at flow rates of 80 and 45 L/min, respectively. The air flow rates were selected to set a pressure drop of 4 kPa across the DPIs except Aerolizer which was tested at 80 L/min due to vacuum pump flow limitations. The Exubera® inhaler (Pfizer) and the Spiros® (Dura Pharmaceuticals) were used as active dispersion devices, each tested at
A flow rate of 30 L/min. Aerosol output was delivered to the Next Generation Impactor (NGI) for particle sizing via the pre-separator (no USP throat induction port). For each device, 2 mg of formulation was loaded into the inhaler with an aerosol generation time set to draw 4 L of air through each inhaler.

CFD studies were employed to investigate the turbulence intensity generated by the HandiHaler during aerosolization, which is expected to positively correlate to increased particle dispersion (4). Modifications to the mouthpiece were implemented to increase turbulence intensity and tested using in vitro particle sizing to evaluate the potential for increased dispersion.

RESULTS AND DISCUSSION

Table 1 shows the aerosolization characteristics of the spray dried powder formulation in the active and passive DPIs. The powder formulation was characterized by scanning electron microscopy and shown to consist largely of submicrometer particles (5). Therefore, the aerosolization characterization results indicated the relative efficiency of the DPIs to disperse the formulation to primary particles for inhalation. Emitted doses (ED) were observed to be lowest for the active DPIs, which produced mass median aerodynamic diameters (MMAD) of 2.6 and 2.0 µm for the Spiros and Exubera DPIs, respectively. For these inhalers, the FPF1µm/ED was less than 10% of the emitted dose. However, it should be noted that the conventional FPF5µm/ED was over 80% for both inhalers for this formulation. As described in a companion study (5), the passive dispersion Aerolizer operating at 80 L/min was capable of producing an aerosol with a high emitted (81.4%) and submicrometer dose fraction (28.3%) (5). In comparison, the HandiHaler operating at 45 L/min had a similar emitted dose, and MMAD compared to the Aerolizer. However, the FPF1µm/ED was only 19.5%, indicating decreased dispersion efficiency of primary submicrometer particles.

<table>
<thead>
<tr>
<th></th>
<th>ED (%)</th>
<th>FPF5µm/ED (%)</th>
<th>FPF1µm/ED (%)</th>
<th>MMAD (µm)</th>
<th>MMD (µm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spiros</strong></td>
<td>73.7 (4.1)</td>
<td>80.2 (3.1)</td>
<td>6.8 (0.6)</td>
<td>2.55 (0.06)</td>
<td>2.21</td>
</tr>
<tr>
<td><strong>Exubera</strong></td>
<td>62.8 (3.1)</td>
<td>96.3 (0.7)</td>
<td>9.6 (0.5)</td>
<td>1.95 (0.04)</td>
<td>1.69</td>
</tr>
<tr>
<td><strong>Aerolizer</strong></td>
<td>81.4 (2.0)</td>
<td>95.3 (1.1)</td>
<td>28.3 (3.1)</td>
<td>1.40 (0.05)</td>
<td>1.22</td>
</tr>
<tr>
<td><strong>HandiHaler</strong></td>
<td>78.2 (2.7)</td>
<td>87.6 (3.6)</td>
<td>19.5 (3.1)</td>
<td>1.60 (0.09)</td>
<td>1.39</td>
</tr>
<tr>
<td><strong>Modified</strong></td>
<td>74.2 (1.4)</td>
<td>97.3 (0.3)</td>
<td>38.8 (6.3)</td>
<td>1.13 (0.05)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

* MMD was derived from the MMAD and combination particle skeletal density (ρ=1.325 g/cm³), according to the following equation: \( MMAD = MMD \times \sqrt{\rho} \).
Figure 1 shows CFD predictions of turbulence intensity profiles for the original and modified HandiHaler. To increase turbulent dispersion, a three-dimensional (3D) array of tubes was included in the mouthpiece (Figure 1, right). Tube bundles such as this are known to increase transport in heat and mass transfer applications. However, the effects of this 3D structure on powder dispersion in a DPI have not previously been investigated. Volume averaged turbulence intensity through the modified HandiHaler increased by a factor of over 2, compared to the original version and significantly improved dispersion.

The emitted dose was 74.2%, suggesting no significant change (p>0.05; t-test) in device retention when it compared to that of HandiHaler. However, the aerosol fractions less than 5 µm and 1 µm were increased to 97.3% and 38.8%, respectively. Furthermore, the mass median diameter (MMD) of the aerosol was reduced below 1 µm using the modified HandiHaler.

**CONCLUSIONS**

Spray dried combination drug and excipient particles were aerosolized to produce a significant fraction of submicrometer particles suitable for the EEG application using the Aerolizer and a modified HandiHaler. Less efficient aerosolization of the formulation was observed with two active dispersion DPIs, perhaps due to their powder emptying mechanism. The capsule-based passive devices appear to provide higher sheer forces to the powder aggregates during capsule emptying.
ACKNOWLEDGMENTS

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REFERENCES


