Can a cyclone spacer reduce the flow rate dependence of dry powder inhalation?

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Abstract

Dry powder inhalers are used in pulmonary disease therapies. However, lung deposition is affected by the poor inhalation flow rates achieved by patients. The ability of a cyclone spacer to reduce the flow rate dependence of aerosol emission was investigated. The aerosolization of salbutamol sulphate/lactose was studied between 30-60 Lmin⁻¹ using the Cyclohaler, with and without a manufactured-in-house Perspex cyclone device. Deposition of particles in the next generation impactor and within the devices was assessed by high performance liquid chromatography. High dose retention in the cyclone was seen: however, this decreased by increasing the flow rate. Fine particle fractions were substantially higher when the cyclone was employed (e.g. 92.2 ± 7.7 % with cyclone vs. 27.9 ± 3.5 % without cyclone at 45 Lmin⁻¹). This work has shown the potential of a cyclone-spacer to mitigate the flow rate dependency of emitted particle size and improve inhaled drug delivery.

Introduction:

Inherently breath-actuated passive dry powder inhalers (DPIs) are a growth market for the treatment of pulmonary disease such as asthma and chronic obstructive pulmonary disease (COPD). The recommended size range particles should possess an aerodynamic diameter (dₐ) of 1-6 µm for therapeutic lung deposition. Particles of this size display poor flowability due to their cohesive and adhesive properties [1] and to overcome this, they are typically formulated with a larger carrier such as lactose monohydrate which improves the liberation of the drug from the device. However, the larger particles are likely to impact in the oropharynx, causing irritation [2]. Patients with severe COPD (and asthma) do not achieve sufficient airflow [3] to aerosolize the drug particles effectively. In fact, low lung deposition (5-28%) from DPIs is reported [4] with high impaction in the throat. The concept of employing a spacer device to reduce oropharyngeal deposition from DPIs has recently been suggested [5, 6]. A DPI device (Conix™) recently licensed by 3M Drug Delivery Systems from Cambridge Consultants Ltd. [7] incorporates a reverse flow cyclone which shows potential to retain large particles such as lactose carriers. The aim of this work was to examine the suitability of a generic cyclone-spacer design to reduce the flow rate dependence of aerosol emission from carrier-based DPI formulations.

Methods:

Two miniature reverse-flow cyclones were designed from empirical models [8] to have less than 5 µm particle cut-off diameters and varying resistances under breathing conditions. The cyclones were machined from Perspex (Engineering and Design Plastics, Cambridge, UK) with 2 cm body diameters (Cyclone 1 - 4.4 mm diameter orifice inlet and Cyclone 2 - 6mm x 10mm slot inlet) and separated into 3 sections – vortex finder exit (top), inlet and cylinder (mid) and cone (bottom) for easy cleaning, assembly and geometry interchange. An inlet adapter was also manufactured to enable connectivity with commercial DPI devices.

The mixture of micronized salbutamol sulphate (SS) and lactose was removed from marketed Ventolin™ Accuhaler™ products (Allen & Hanburys, Uxbridge, Middlesex, UK). Size 4 hard gelatine capsules (Meadow Laboratories Ltd., Romford, UK) were accurately hand-filled with ~12.5 mg of the blend. Aerosolization studies were performed using a Cyclohaler™ device (AAH Hospital Supplies, Coventry, UK) with and without each cyclone at a range of flow rates between 30 – 60 Lmin⁻¹. The aerosolization performance was assessed by impaction analysis according to the British Pharmacopoeia using the next generation impactor (NGI) with a model HCP5 vacuum pump (both from Copley Scientific Ltd., Nottingham, UK). The NGI plates were coated with 10 mL 0.1 % (w/v) silicon oil (200® Fluid, Sigma-Aldrich, UK) in hexane (Fisher, UK). Drug deposition on the stages was determined by HPLC [9].

Results and discussion:

Dose recovery in the impactor was within pharmacopoeial limits (range 78.4 – 92.4 %). The % emission from the DPI-Cyclone 1 increased from 14.3 ± 5.5 % to 34.5 ± 7.8 % when the flow rate was increased from 30 to
60 Lmin⁻¹, respectively. Drug retention within the cyclone decreased when the flow rate was increased (Table 1, ANOVA p < 0.05). Such high retention of the actuated dose is common in MDI spacers and does reduce oropharyngeal deposition [10]. The fine particle fractions (% FPF) of SS expressing the percentage of the emitted SS dose with \( d_{ae} < 5 \mu m \) are reported in Table 1. Although the % FPF < 5 \( \mu m \) Ex-device was flow-rate dependent, no statistically significant differences were observed for the % FPF of the aerosol emitted from the cyclone (p > 0.05).

Table 1 Aerosolization of salbutamol sulphate from a carrier based blend with and without Cyclone 1 at 30, 45 and 60 Lmin⁻¹ (mean ± SD n ≥ 4). (IP/PS= induction/pre-separator deposition, MMAD = mass median aerodynamic diameter, GSD = geometric standard deviation FPF = fine particle fraction below 5 \( \mu m \), Ex-Device is the dose which enters the impactor from either the DPI or the cyclone).

<table>
<thead>
<tr>
<th>Device</th>
<th>Flow rate (Lmin⁻¹)</th>
<th>IP/PS deposition (% ED)</th>
<th>MMAD (µm)</th>
<th>GSD (µm)</th>
<th>FPF₅µm Ex-Device (% ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI</td>
<td>30</td>
<td>72.00 ± 3.23</td>
<td>3.07 ± 0.26</td>
<td>2.12 ± 0.07</td>
<td>20.8 ± 3.0</td>
</tr>
<tr>
<td>DPI-Cyclone 1</td>
<td>30</td>
<td>14.82 ± 7.80</td>
<td>0.90 ± 0.06</td>
<td>2.46 ± 0.16</td>
<td>82.8 ± 7.8</td>
</tr>
<tr>
<td>DPI</td>
<td>45</td>
<td>66.35 ± 3.38</td>
<td>2.49 ± 0.22</td>
<td>2.10 ± 0.12</td>
<td>27.9 ± 3.5</td>
</tr>
<tr>
<td>DPI-Cyclone 1</td>
<td>45</td>
<td>6.95 ± 7.92</td>
<td>0.76 ± 0.04</td>
<td>1.91 ± 0.42</td>
<td>92.2 ± 7.7</td>
</tr>
<tr>
<td>DPI</td>
<td>60</td>
<td>61.74 ± 3.01</td>
<td>1.98 ± 0.09</td>
<td>2.17 ± 0.11</td>
<td>33.8 ± 2.9</td>
</tr>
<tr>
<td>DPI-Cyclone 1</td>
<td>60</td>
<td>22.28 ± 9.97</td>
<td>0.76 ± 0.14</td>
<td>2.08 ± 0.36</td>
<td>77.0 ± 10.1</td>
</tr>
</tbody>
</table>

Considering the aerodynamic size distribution of the aerosol emitted into the impactor, it was observed that the majority of the dose from the DPI alone deposited in the induction port/pre-separator (IP/PS) – the stages which collect non-respirable particles (Table 1). IP/PS deposition was significantly reduced by the use of the cyclone (Table 1, ANOVA + Tukey’s test, p < 0.05) and the majority of the dose emitted from the cyclone was respirable (range 82.8 ± 7.8% at 30 Lmin⁻¹ to 77.0 ± 10.1 % at 60 Lmin⁻¹ (Table 1)). The improved aerodynamic particle size distribution (PSD) when the cyclone was employed is evident in the cumulative undersize PSD (Fig. 1). It can be seen the majority of the dose which would be inhaled by a patient would be suitable for pulmonary deposition with the cyclone in place. The latter finding is also supported by the drug mass median aerodynamic diameter (MMAD) values (Table 1); where the MMADs with the cyclone in place were ~3 times smaller than for the DPI alone (ANOVA, post-hoc Tukey’s test, p < 0.05). The unaltered MMAD when the flow rate was increased was interesting due to the potential to achieve consistent lung deposition at different flow rates in patients with variable and impaired lung function.

![Fig 1 Cumulative aerodynamic undersize (%) of salbutamol sulphate of emitted dose from DPI at 30 Lmin⁻¹ (●), 45 Lmin⁻¹ (▼) and 60 Lmin⁻¹ (◆), and of the emitted dose from Cyclone 1 at 30 Lmin⁻¹ (○), 45 Lmin⁻¹ (▽) and 60 Lmin⁻¹ (□) (mean ± SD; n ≥ 4).](image-url)
The prototype cyclone was intended as a generic spacer for use with a variety of marketed DPIs. However, the original prototype (Cyclone 1) offered high resistance to inhalation (0.06 kPa\(^{1/2}\) min L\(^{-1}\)); therefore a second cyclone (Cyclone 2) was designed to offer lower inhalation resistance (0.04 kPa\(^{1/2}\) min L\(^{-1}\)) than Cyclone 1 such that a reasonable flow rate could be achieved through the cyclone by patients with lung disease. In fact, other marketed DPIs, such as Turbuhaler (0.03 kPa\(^{1/2}\) min L\(^{-1}\)) and Handihaler (0.05 kPa\(^{1/2}\) min L\(^{-1}\)) are still used successfully by patients with obstructive lung disease [11, 12]. Aerosolization studies were performed with a total pressure drop across the DPI and Cyclone 2 in series of 2 kPa (= 37 L min\(^{-1}\)) and 4 kPa (= 51 L min\(^{-1}\)), to represent values achievable by patients. The IP-PS deposition dramatically decreased compared to the DPI alone when the cyclone was employed (Table 2). The fraction deposited in the IP-PS increased when a higher flow rate was studied with the cyclone in place (11.82 ± 2.80 and 18.44 ± 2.79 % at 2 and 4 kPa, respectively, p value < 0.05). The fine particle delivery (%FPF < 5 µm) of the dose emitted from the Cyclone was similar at both low and high flow rates (p value > 0.05). Significantly, using a system suitable for use at flow rates achievable by patients with obstructive lung disease, the fine particle delivery was higher than from a DPI alone (Table 2). The MMAD was lower for particles emitted from the cyclone than from the DPI, and crucially, the MMAD was not affected by changes in the flow rate when the cyclone was employed.

Table 2 Aerosolization of salbutamol sulphate from a carrier based blend with and without Cyclone 2 at 2 and 4 kPa (mean ± SD \(n \geq 3\)).

<table>
<thead>
<tr>
<th>Device</th>
<th>Flow rate (L/min)</th>
<th>Pressure drop (kPa)</th>
<th>IP/PS deposition (% ED)</th>
<th>MMAD (µm)</th>
<th>GSD</th>
<th>FPF&lt;sub&gt;5μm&lt;/sub&gt; Ex-Device (% ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI</td>
<td>80</td>
<td>2</td>
<td>67.24 ± 2.09</td>
<td>3.00 ± 0.12</td>
<td>2.06 ± 0.01</td>
<td>24.9 ± 1.6</td>
</tr>
<tr>
<td>DPI-Cyclone 2</td>
<td>37</td>
<td>2</td>
<td>11.82 ± 2.80</td>
<td>1.29 ± 0.06</td>
<td>2.19 ± 0.06</td>
<td>84.4 ± 2.9</td>
</tr>
<tr>
<td>DPI</td>
<td>100</td>
<td>4</td>
<td>64.44 ± 2.49</td>
<td>2.65 ± 0.13</td>
<td>2.04 ± 0.01</td>
<td>29.0 ± 2.6</td>
</tr>
<tr>
<td>DPI-Cyclone 2</td>
<td>51</td>
<td>4</td>
<td>18.44 ± 2.79</td>
<td>1.08 ± 0.05</td>
<td>2.16 ± 0.07</td>
<td>79.7 ± 2.8</td>
</tr>
</tbody>
</table>

Conclusions

This work has shown the potential of a prototype cyclone to be used as a spacer device to improve the in vitro drug delivery from a commercial DPI. Although dose deposition in the cyclone was high, it retained large drug and carrier particles leading to high respirable fractions. The aerodynamic size distribution of the aerosol was also smaller when the cyclone was employed and did not change with increasing the flow rate. Thus, the flow-rate independence of the aerodynamic diameter was a promising finding. Future work will investigate the functioning of the cyclone with alternative marketed DPI products, as well as a computational fluid dynamics investigation into the particle separation and break-up mechanisms within the cyclone.

References