RESEARCH ARTICLES

Dry Powder Inhaler Device Influence on Carrier Particle Performance

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ABSTRACT: Dry powder inhalers (DPIs) are distinguished from one another by their unique device geometries, reflecting their distinct drug detachment mechanisms, which can be broadly classified into either aerodynamic or mechanical-based detachment forces. Accordingly, powder particles experience different aerodynamic and mechanical forces depending on the inhaler. However, the influence of carrier particle physical properties on the performance of DPIs with different dispersion mechanisms remains largely unexplored. Carrier particle trajectories through two commercial DPIs were modeled with computational fluid dynamics (CFD) and the results were compared with in vitro aerosol studies to assess the role of carrier particle size and shape on inhaler performance. Two percent (w/w) binary blends of budesonide with anhydrous and granulated lactose carriers ranging up to 300 \( \mu \text{m} \) were dispersed from both an Aerolizer® and Handihaler® through a cascade impactor at 60 L min\(^{-1}\). For the simulations, carrier particles were modeled as spherical monodisperse populations with small (32 \( \mu \text{m} \)), medium (108 \( \mu \text{m} \)), and large (275 \( \mu \text{m} \)) particle diameters. CFD simulations revealed the average number of carrier particle–inhaler collisions increased with carrier particle size (2.3–4.0) in the Aerolizer®, reflecting the improved performance observed in vitro. Collisions within the Handihaler®, in contrast, were less frequent and generally independent of carrier particle size. The results demonstrate that the aerodynamic behavior of carrier particles varies markedly with both their physical properties and the inhalation device, significantly influencing the performance of a dry powder inhaler formulation. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association

Keywords: excipients; physical characterization; pulmonary drug delivery; formulation; morphology; particle size

INTRODUCTION

Dry powder inhaler (DPI) formulations are typically binary mixtures comprising micronized active agent blended with a coarse carrier particle population that constitutes the bulk of the formulation (>95%, w/w).\(^1\) When a patient inhales through a DPI, the energy derived from their inspiratory effort fluidizes the powdered dose, detaching a fraction of the drug from the larger carrier particles and depositing it in the deep lung where it exerts its intended therapeutic effect.\(^2\) It is well recognized that DPIs possess distinct mechanisms of powder dispersion.\(^3\) Passive DPIs rely solely on the patient’s inspiratory effort to fluidize and disperse the powdered formulation, and have evolved considerably from their inception, incorporating a diverse array of geometries, including vortex generators and cyclones, to induce turbulence and particle–inhaler collisions to maximize the detachment potential of the available flow stream.\(^4,5\) The use of computational fluid dynamics (CFD) to model the inhalation flow stream, pressure profiles, and particle trajectories within therapeutic inhalers has become increasingly prevalent, finding employment in the optimization of device parameters during development or, ex post facto, to elucidate the deagglomeration principle of a commercially available inhaler.\(^6–10\) By coupling CFD simulations with in vitro aerosol performance, information on the relative contributions of device and formulation can be obtained. A notable example of this approach is a series of studies by Coates and colleagues\(^6–10\) on the
Aerolizer® (Plastiape S.p.A., Italy) DPI, where the device geometry (e.g., air inlet area, mouthpiece length) and operating parameters (volumetric flow rate, capsule size) were varied to assess their influence on in vitro aerosol performance.

Drug detachment from carrier particles is believed to proceed through two primary mechanisms: (1) aerodynamic, or fluid-based, detachment arising from the direct interaction of the flow stream with drug particles located on the carrier surface; and (2) mechanical, or impaction-based, detachment due to collisions between carrier particles and the inhaler walls during particle transit through the device. Although the diverse internal geometries of inhalers will vary the relative contributions between aerodynamic and mechanical detachment forces, it has been reported that the magnitude of impact-based events may exceed those of flow-based events, and could potentially be the dominating factor in drug detachment from carrier particles.

Previous research in our laboratory has demonstrated that large lactose carrier particles (> 180 μm) can improve drug deposition in vitro for both anhydrous and granular lactose populations, although the improvement with carrier particle size was more pronounced in formulations with granulated carrier particles. It is speculated that the surface roughness of the granulated particles shifted the drug detachment mechanism from flow-based detachment for carrier particles with minimal surface roughness, to impaction-based detachment forces as carrier particle size and roughness increased. The aerosol performance improvement was thought to result from an increased incidence of carrier particle–inhaler collisions, given the higher inertia of larger carrier particles, which inhibit their ability to travel with the flow stream through the inhaler. However, it is recognized that the aerodynamic behavior of carrier particles can vary significantly based on the inhaler through which a formulation is dispersed, and improved performance may be observed if the carrier particle design matches the predominant mechanism(s) of detachment induced by specific inhaler types. Accordingly, the specific aim of this study was to assess the role of the DPI design on aerosol performance as the size and shape of the carrier particle population are varied. CFD simulations of carrier particle trajectories were coupled with in vitro drug deposition studies to investigate the combined influence of device and carrier on formulation performance.

**MATERIALS AND METHODS**

**Materials**

Micronized budesonide (EP) was purchased from Spectrum Chemicals (Gardena, CA) and used as received. Analytical grade ethanol was supplied by Sigma Chemical Company (St. Louis, MO). Samples of anhydrous (SuperTab® 22AN), and granulated (SuperTab® 30GR) lactose were obtained from DFE Pharma (formerly DMV-Fonterra, Princeton, NJ). Size three gelatin capsules were provided by Capsugel® (Greenwood, SC).

**Fractionation of Lactose Carrier Particles**

Samples of each lactose batch were fractionated on an Autosiever vibrating sieve shaker (Gilson Company Inc., Lewic Center, OH) with a sieve intensity, or amplitude, setting of 40 for 5 min through the following sieves: 300, 250, 212, 180, 150, 125, 90, 75, 63, 45, and 32 μm. Following the initial fractionation, the lactose carriers were again sieved to obtain narrow particle size distributions.

**Preparation of Budesonide/Lactose Binary Blends**

Budesonide and lactose were mixed in a ratio of 1:50 (w/w) via geometric dilution to obtain 500 mg of a 2% binary blend. The formulations were blended with a Turbula® orbital mixer (Glen Mills, Clifton, New Jersey) for 40 min at 46 rpm. Samples were stored in a desiccator at least 5 days prior to use. Blend uniformity was determined by randomly selecting eight 20-mg samples from each mixture, and assessing the drug content in the powder. Formulations were considered well blended and ready for use if the coefficient of variation (% CV) between the samples for a given blend was below 5%.

**Scanning Electron Microscopy**

The size and morphology of carrier particles were visually assessed by scanning electron microscopy (SEM; Supra 40VP, Zeiss, Germany). Prior to SEM, approximately 20 nm of platinum was deposited onto the particle surfaces via sputter coating.

**Surface Area Analysis**

Specific surface areas of the lactose carrier particle populations were determined via nitrogen adsorption with a single-point BET method using a Monosorb® surface area analyzer (Quantachrome, Boynton Beach, FL).

**Density of Lactose Carriers**

The true densities of the lactose carrier particles were determined with a helium multipycnometer (Quantachrome, Boynton Beach, FL).

**In Vitro Drug Deposition**

About 20 (±1) mg of powder was loaded into size 3 gelatin capsules and dispersed through an Aerolizer® (Plastiape S.p.A.) and Handihaler® (Boehringer Ingelheim Inc., Ridgefield, CT) DPI into a next generation cascade impactor (NGI; MSP Corporation, DFE Pharma (formerly DMV-Fonterra, Princeton, NJ). Size three gelatin capsules were provided by Capsugel® (Greenwood, SC).
Shoreview, MN) at a volumetric flow rate of 60 L min\(^{-1}\) actuated for 4-s intervals. To prevent particle re-entrainment, the NGI stages were precoated with a 1% (w/v) solution of silicon oil in hexane. Prior to each actuation, 15 mL of EtOH was added to the preseparator and collected following powder dispersion from each capsule. Drug depositing in the capsule, inhaler, mouthpiece adaptor, and induction port were collected by rinsing each component with 10 mL of EtOH, whereas the NGI stages were each rinsed with 5 mL. Drug content was assessed via ultraviolet-visible absorption spectroscopy at 244 nm. The emitted fraction (EF) was calculated as the ratio of the drug mass depositing in the mouthpiece, induction port, preseparator, and impactor stages over the cumulative mass of drug collected following actuation (total drug deposited in the capsule, inhaler, mouthpiece, induction port, preseparator, and stages). The fine particle fraction (FPF) of each dose was the ratio of the drug mass depositing on stages 3 through 8 (corresponding to an aerodynamic diameter less than 4.46 \(\mu\)m) of the impactor over the emitted dose. The respirable fraction (RF) was the ratio of the drug mass deposited on stages 3–8 over the entire dose recovered following each actuation.

**Computational Fluid Dynamics**

Computational fluid dynamics analysis was employed to study the flow field and assess carrier particle trajectories within the DPIs during actuation. The geometry of the Aerolizer\(^{\text{®}}\) was generously provided as a CAD file by the manufacturer (Plastiape S.p.A.); the computational mesh consisted of approximately 3.7 million unstructured computational volumes. By comparison, the Handihaler\(^{\text{®}}\) is composed of relatively simpler internal geometric features, which were modeled from measurements obtained with a caliper. The Handihaler\(^{\text{®}}\) geometry was modeled using 3 million unstructured computational volumes. The computational mesh, in each case, was clustered near the walls to provide better resolution of the near-wall turbulence. For instance, the \(y^+\) value, which is a normalized distance used to characterize the near-wall solution with respect to the boundary layer, was roughly 15. For both the configurations, the incoming mass flow rate was set at 60 L min\(^{-1}\). A size 3 capsule was placed in the capsule chamber. The flow inside the inhaler is turbulent, composed of a range of length and time scales. To ensure computational tractability, this turbulent flow field is modeled using the Reynolds-averaged Navier Stokes (RANS) approach.\(^{17}\) In this work, the commercial solver FLUENT\(^{\text{®}}\) (ANSYS, Inc., Canonsburg, Pennsylvania) is used to solve the RANS equations. The turbulence properties of the flow field are described using the shear-stress transport-based \(k-\omega\) model. The turbulence intensity at the inflow was assumed to be 10% for all the cases. The flow equations were discretized using a first-order numerical scheme. By using a large number of computational volumes, the dissipative errors associated with a first-order scheme were minimized. Extensive grid convergence studies demonstrated that the mesh used here provides mesh-converged results. The RANS equations were solved until a steady state solution was reached. After this step, discrete particles corresponding to the drug carrier particles were introduced in the flow. The particles were evolved using a Stokesian drag law, with nonspherical corrections imposed to account for particle shape effects (Fluent Inc. (2006) Centerra Resource Park, Lebanon, New Hampshire). The flow rate is high enough for gravitational forces to be negligible. The initial locations of the particles were different for the two configurations (as shown in Fig. 2). These locations were based on the assumption that the capsule was perforated from one side, and the particles leave the capsule with identical velocities. Because the mass loading of the particles in relation to the local fluid mass is very small, the effect of the particles on the flow field is neglected. Three different particle diameters were simulated for each inhaler. The particles were assumed to be a monodisperse population of uniform spheres with diameters of 32, 108, and 275 \(\mu\)m. In each simulation, roughly 1000 particles were initiated with zero velocity. Because the mass loading is small, collisions amongst the particles were neglected. The number of collisions that each particle experienced with different sections of the DPIs was tracked as the particles traveled through the inhaler. In order to ensure statistical convergence of the results, different particle numbers were considered. It was found that using 500 particles was sufficient to obtain converged statistics for the average number of collisions that the particles undergo with the inhaler walls.

**Statistics**

Statistical significance between performance values was determined with one-way analysis of variance with post hoc tests between groups according to the Bonferroni method (\(P < 0.05\)).

**RESULTS AND DISCUSSION**

**Physical Characterization of Carrier Particle Populations**

The double-sieving technique yielded narrow particle size distributions (Fig. 1). Although \(\alpha\)-lactose monohydrate is typically used as the carrier particle population in binary dry powder formulations, other grades including anhydrous and granulated lactose have been studied, affording the opportunity to assess the influence of carrier morphology on aerosol
The disparity in surface roughness between the anhydrous and granulated lactose particles increases with particle size, as evidenced by the diminishing specific surface areas of the anhydrous particles relative to their granulated counterparts with increasing carrier sieve fraction (Table 1). Surface areas of larger granulated lactose did not diminish appreciably as particle sizes were increased (as would be expected for perfectly smooth spherical particles). Instead, the increasing roughness (due to granulation) causes a relatively minimal decline in surface area as the size of the particles within the powder is increased. The true densities of all carrier particle size fractions in both grades of lactose ranged between 1.54 and 1.58 g/cm$^3$.

**CFD Analysis**

Internal geometries of the Handihaler® and Aerolizer® are illustrated in Figure 2. The flow stream enters the Aerolizer® via two tangential inlets found on opposite sides of the capsule chamber. The resulting turbulent flow field induces the capsule to rotate and rattle with high frequency during inhalation, assisting in ejecting and dispersing the powdered dose through the perforations in the capsule wall. It is noted that although the motion of the capsule itself is not simulated in this work, it may affect particle release and transport in the fluid flow, and it has been speculated that the emitted powder particles may collide with the capsule, though a previous investigation concluded that impactions between the powder particles and the spinning capsule do not significantly contribute to dispersion performance in the Aerolizer®. However, those studies were performed on pure spray-dried mannitol, and the inclusion of carrier particles may potentially alter this result and is a topic that merits future study.

**Table 1.** Specific Surface Areas (SSA) of Anhydrous and Granulated Lactose Carrier Particles by Sieve Fraction

<table>
<thead>
<tr>
<th>Carrier Sieve Fraction (μm)</th>
<th>Anhydrous (m$^2$ g$^{-1}$)</th>
<th>Granulated (m$^2$ g$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;32</td>
<td>0.94</td>
<td>1.87</td>
</tr>
<tr>
<td>32–45</td>
<td>0.48</td>
<td>1.71</td>
</tr>
<tr>
<td>45–63</td>
<td>0.38</td>
<td>1.62</td>
</tr>
<tr>
<td>63–75</td>
<td>0.43</td>
<td>1.64</td>
</tr>
<tr>
<td>75–90</td>
<td>0.37</td>
<td>1.52</td>
</tr>
<tr>
<td>90–125</td>
<td>0.41</td>
<td>1.56</td>
</tr>
<tr>
<td>125–150</td>
<td>0.38</td>
<td>1.81</td>
</tr>
<tr>
<td>150–180</td>
<td>0.38</td>
<td>1.73</td>
</tr>
<tr>
<td>180–212</td>
<td>0.40</td>
<td>1.44</td>
</tr>
<tr>
<td>212–250</td>
<td>0.42</td>
<td>1.67</td>
</tr>
<tr>
<td>250–300</td>
<td>0.36</td>
<td>1.46</td>
</tr>
</tbody>
</table>
A key feature of the internal geometry of the Aerolizer® is a grid dividing the capsule chamber and the mouthpiece to prevent capsule egress from the device during inhalation. In addition, it is noted that the grid has been demonstrated to straighten the flow and suppress turbulence downstream of its location. On the contrary, the mechanism of the Handihaler® is based on the sudden expansion of the inhalation flow stream as it passes from the inlet into the larger capsule chamber. The abrupt opening from the smaller inlet chamber to the capsule chamber causes the boundary layer of the flow stream to separate at the corner of the expansion, creating an annular region where a portion of the flow recirculates, resulting in a pressure loss in this region. The incoming flow stream pushes the capsule toward the grid while the low pressure region simultaneously attracts the capsule toward the inlet, causing the capsule to spin and vibrate in the chamber. Similar to the Aerolizer®, the Handihaler® also contains a mesh between the capsule chamber and the mouthpiece. However, this grid is made of thinner wires and its effect on the flow field is comparatively less significant than the grid located in the Aerolizer®, as the blockage represented by the wires is a very small fraction of the total surface area.

Figure 3 depicts the velocity magnitude of the flow stream in the inhalers at 60 L min⁻¹. In the Handihaler®, the maximum flow speed is found upstream of the capsule with very high shear flow around the capsule itself. In contrast, the Aerolizer® exhibits a much more complex flow pattern, as the incoming flow generates a swirling motion inside the capsule chamber. The grid between the capsule chamber and the mouthpiece constricts the flow, and consequently the velocity magnitude is very high when the fluid exits the capsule chamber through the grid spacing. The grid also regulates the swirling flow generated by the capsule chamber.

Carrier particle trajectories were simulated through the DPIs to quantify the frequency of their collisions with the internal geometry of the inhaler (Table 2). It was expected that the distinct internal geometries of the inhalers would yield distinct particle trajectories. As seen in Figure 4, the fluid flow inside the Aerolizer® actively promotes particle collisions with the inhaler wall. The tangential air inlets introduce a swirl component to the flow stream that is imparted to the powder as they exit the capsule, causing particles to swirl through the mouthpiece.

In contrast to the Aerolizer®, carrier particles within the Handihaler® experience markedly fewer collisions with the inhaler (Fig. 5). The wake region downstream of the cavity causes the particles to accelerate and travel at an angle to the vertical direction, directing the particle trajectory toward the inhaler wall. As the particles have significant inertia (increasing with carrier particle size), once they are launched on this trajectory the fluid flow is unable to significantly alter the particle trajectory. The initial acceleration around the capsule introduces the collisional movement, pushing the particles downstream toward the inhaler exit.

Table 2 shows the influence of particle diameter on the number of collisions with the mouthpiece wall experienced by the particles. It should be noted that the fluid flow corresponds to particles with zero diameter, or zero Stokes number. Increasing the particle diameter increases the Stokes number and causes a departure of the particle trajectory from the fluid trajectory. As the particles become larger, their response to changes in the fluid flow is slower. Consequently, larger particles can possess ballistic trajectories and undergo more collisions, and increasing the particle diameter increases the number of collisions. It is seen that the Aerolizer® exhibits greater sensitivity to particle size relative to the Handihaler®. This is primarily attributed to the fact that the Handihaler® does not introduce a swirling motion inside the mouthpiece, which causes the particles to have a longer residence time (or trajectory length) inside the mouthpiece.

**In Vitro Aerosol Performance**

*In vitro* drug dispersion profiles for all experimental formulations are presented in Tables 3 and 4. The percentage of the nominal dose emitted from the Handihaler® exceeded that emitted from the...
Table 2. Average Number of Collisions Between a Carrier Particle and the Inhaler As It Exits the Device During Actuation from the Aerolizer® and Handihaler® at 60 L min⁻¹

<table>
<thead>
<tr>
<th>Carrier Particle Sieve Fraction (μm)</th>
<th>Aerolizer®</th>
<th>Handihaler®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaler–carrier collisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32 (μm)</td>
<td>107.5 (μm)</td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.7</td>
</tr>
</tbody>
</table>

Figure 4. Carrier particle trajectory inside the Aerolizer® at 60 L min⁻¹ (From left, \(d_{\text{particle}} = 32, 108, \text{and} 275 \, \mu\text{m}\)).

Aerolizer®, yielding over 75% EF for all carrier particle sizes between both lactose grades. For anhydrous lactose formulations dispersed from the Handihaler®, the enhanced EF did not correspond to improved drug deposition compared with the Aerolizer®, as RF values were generally comparable between devices across most carrier particle size fractions. The disparity between EF and RF is reconciled by the higher FPF values obtained from the Aerolizer®, indicating that although for anhydrous formulations the Handihaler® is more effective at emitting drug from the device, the Aerolizer® demonstrates a greater tendency for detaching drug from the carrier particles. In contrast, granulated carrier particle formulations dispersed from the Handihaler® outperformed those from the Aerolizer® for all but the largest carrier particle size fractions.

From the drug dispersion profiles, it is observed that the increased number of collisions between the carrier particles and inhaler does not directly translate into improved aerosol performance, as measured by RF. For a given dry powder formulation, RF values reflect the combined EF and FPF, revealing an inhaler’s potential to both emit the drug from the device and detach it from the carrier, such that it can travel to the deep lung.¹⁸ By itself, EF is a metric describing the inhaler’s ability to emit the drug from the device and deliver it to the patient, but reveals nothing as to whether the drug is detached from the carrier, and drug that remains adhered to the coarse carrier particles will deposit in the mouth, throat and upper airways. Accordingly, FPF is a better measure of an inhaler’s drug detachment potential, providing the fraction of detached drug exiting the device relative to the total amount that leaves the inhaler. A high EF coupled with a high FPF will generate excellent RF values, but opposing EF and FPF performance (e.g., high EF and low FPF) will only yield moderate respirable fractions.

Although significant differences in emitted dose were observed between the devices, this did not yield a consistent disparity in overall performance, as the relatively high EF from Handihaler® was offset by the Aerolizer®’s enhanced tendency to emit drug particles detached from the carriers. To provide an approximate measure of the relative drug detachment potential of the DPIs, the ratio of FPF values from the Aerolizer® over the Handihaler® (\(\text{FPF}_{\text{Aerolizer}}/\text{FPF}_{\text{Handihaler}}\)) against the carrier particle size fraction were plotted (Fig. 6). Values >1 indicate the Aerolizer® may be more effective at drug detachment while a ratio less than unity gives the advantage to the Handihaler®. It must be noted that detached drug particles may be agglomerates of primary drug particles, which due to their large size will deposit in the throat and conducting airways. This is especially relevant for the corticosteroid budesonide, which has been demonstrated to be a
relatively cohesive drug. However, as the same formulation was used for each size fraction within a lactose grade, the extent of drug agglomeration was presumed constant between samples, with the inhaler as the variable. For the anhydrous carrier formulations, all but a single size fraction (90–125 μm) exceeded 1 (Fig. 6), indicating the ability of the Aerolizer® to emit drug particles detached from the carrier outperforms the Handihaler®. Conversely, most granulated carriers yielded better drug detachment from the Handihaler® (ratios were less than 1). However, at carrier particle sizes greater than 75–90 and 90–125 μm fractions for the granulated and anhydrous carriers, respectively, the FPF ratio began to increase, indicating an improvement in drug detachment potential of the Aerolizer® relative to the Handihaler® for large carrier particle formulations. It is speculated that the higher frequency of carrier–inhaler collisions within the Aerolizer® as carrier size is increased may account for the observed improvement in drug detachment. In these larger carrier formulations, impaction-based forces may be a significant mechanism of drug detachment as discussed below.

Influence of Device on Performance

Because of the marked variation in the internal geometries of the two inhalers, differences in aerosol performance were expected between the Aerolizer® and Handihaler®. Regarding device resistance, the Aerolizer® and Handihaler® reside on opposing ends of the spectrum, as the Aerolizer® has less than half the resistance [0.072 (cm H2O)0.5/(L min−1)] of the Handihaler® [0.158 (cm H2O)0.5/(L min−1)]9,24 This increased resistance of the Handihaler® arises from the narrow inlet tube at the base of the capsule chamber (Fig. 2).11 It is noted that the flow rate selected for this study (60 L min−1) is much higher than that typically generated through the Handihaler®, but is readily attainable by > 90% of adult patients through an Aerolizer®.24–26 The relationship between inhaler resistance (R), volumetric flow rate (Q), and pressure drop (ΔP) across a device is (ΔP)0.5 = QR27 For a fixed flow rate, a higher resistance device will produce a greater pressure drop, which has been found to correlate with improved aerosol performance.28–30 In addition, the overall energy passing through an inhaler can be approximated from the product of the

Table 3. Emitted Fraction (EF), Fine Particle Fraction (FPF), and Respirable Fraction (RF) for 2% (w/w) Budesonide Formulations with Anhydrous Lactose Carrier Particles Characterized In Vitro from the Aerolizer® and Handihaler® Dry Powder Inhalers at 60 L min−1

<table>
<thead>
<tr>
<th>Carrier Particle Sieve Fraction (μm)</th>
<th>Aerolizer®</th>
<th>Handihaler®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EF</td>
<td>FPF</td>
</tr>
<tr>
<td>&lt;32</td>
<td>63.5 (1.6)</td>
<td>29.1 (1.4)</td>
</tr>
<tr>
<td>32–45</td>
<td>64.5 (1.8)</td>
<td>21.3 (0.8)</td>
</tr>
<tr>
<td>45–63</td>
<td>63.1 (2.2)</td>
<td>21.3 (1.8)</td>
</tr>
<tr>
<td>63–75</td>
<td>68.9 (1.8)</td>
<td>15.1 (0.4)</td>
</tr>
<tr>
<td>75–90</td>
<td>71.8 (2.4)</td>
<td>15.2 (0.3)</td>
</tr>
<tr>
<td>90–125</td>
<td>62.3 (1.9)</td>
<td>13.7 (0.6)</td>
</tr>
<tr>
<td>125–150</td>
<td>62.7 (2.1)</td>
<td>15.6 (1.4)</td>
</tr>
<tr>
<td>150–180</td>
<td>62.3 (2.0)</td>
<td>12.1 (0.8)</td>
</tr>
<tr>
<td>180–212</td>
<td>61.8 (1.9)</td>
<td>14.1 (1.1)</td>
</tr>
<tr>
<td>212–250</td>
<td>63.4 (2.3)</td>
<td>15.5 (0.8)</td>
</tr>
<tr>
<td>250–300</td>
<td>61.6 (1.7)</td>
<td>15.0 (1.1)</td>
</tr>
</tbody>
</table>

Values are given as the mean of N = 3 replicates, and values within parentheses represent the standard deviation for N = 3 replicates.

Table 4. Emitted Fraction (EF), Fine Particle Fraction (FPF), and Respirable Fraction (RF) for 2% (w/w) Budesonide Formulations with Granulated Lactose Carrier Particles Characterized In Vitro from the Aerolizer® and Handihaler® Dry Powder Inhalers at 60 L min−1

<table>
<thead>
<tr>
<th>Carrier Particle Sieve Fraction (μm)</th>
<th>Aerolizer®</th>
<th>Handihaler®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EF</td>
<td>FPF</td>
</tr>
<tr>
<td>&lt;32</td>
<td>57.0 (1.4)</td>
<td>18.5 (1.2)</td>
</tr>
<tr>
<td>32–45</td>
<td>69.1 (3.7)</td>
<td>11.1 (0.6)</td>
</tr>
<tr>
<td>45–63</td>
<td>74.4 (4.1)</td>
<td>8.9 (1.2)</td>
</tr>
<tr>
<td>63–75</td>
<td>73.8 (3.7)</td>
<td>12.6 (1.4)</td>
</tr>
<tr>
<td>75–90</td>
<td>73.9 (6.6)</td>
<td>9.7 (2.1)</td>
</tr>
<tr>
<td>90–125</td>
<td>77.8 (1.8)</td>
<td>11.6 (0.9)</td>
</tr>
<tr>
<td>125–150</td>
<td>71.3 (4.2)</td>
<td>18.9 (1.5)</td>
</tr>
<tr>
<td>150–180</td>
<td>73.8 (2.5)</td>
<td>14.2 (1.3)</td>
</tr>
<tr>
<td>180–212</td>
<td>72.6 (3.2)</td>
<td>20.8 (1.1)</td>
</tr>
<tr>
<td>212–250</td>
<td>68.7 (5.4)</td>
<td>20.2 (1.5)</td>
</tr>
<tr>
<td>250–300</td>
<td>68.5 (4.5)</td>
<td>20.1 (1.5)</td>
</tr>
</tbody>
</table>

Values are given as the mean of N = 3 replicates, and values within parentheses represent the standard deviation for N = 3 replicates.
Figure 6. Ratio of the FPF values obtained from the Aerolizer® over the Handihaler® for both anhydrous and granulated lactose formulations.

pressure drop across the device, volumetric flow rate, and actuation time.\textsuperscript{31} Thus, although the volumetric flow rate is the same through both inhalers (60 L min\textsuperscript{−1}), a greater pressure drop, and hence a higher energy value is calculated for the Handihaler®, which is predicted to improve performance from this DPI. However, despite the device differences, RF values exhibited minimal dependence on the inhaler for the anhydrous carrier particles, varying instead as a function of carrier particle size, with larger carrier particle diameters diminishing overall performance (Fig. 7). By comparison, granulated lactose formulations showed some device dependency, notably in the smaller carrier particle size fractions, with both inhalers demonstrating comparable performance as carrier size increased.

For anhydrous lactose formulations, the relatively flat surfaces of the carriers permit direct interaction between the drug particles and inhalation flow stream. The overall dispersion performance between the devices is similar across all anhydrous carrier size fractions, indicating the comparable ability of the DPIs to detach drug readily accessible to the air flow. However, in granulated lactose formulations, where direct interaction between the drug and flow stream is inhibited by the surface roughness of the carriers, the Handihaler® exhibited higher RF values up to the largest size fractions, when it is speculated that increasingly larger mechanical forces allowed the Aerolizer® to improve its detachment potential (as indicated by the increasing FPF ratio), and attain comparable RF values. The improved performance at smaller carrier sizes of granulated lactose in the Handihaler® may be attributed to the greater energy input through this device (as mentioned above), which has been found to correlate positively with dispersion performance.\textsuperscript{31} Furthermore, a previous study on the Handihaler® revealed that a pressure gradi-
number of carrier particles relative to the smallest carrier size ranges. Previous studies have reported that lactose fluidizes from capsules via two distinct mechanisms dependent upon the flowability, and hence the cohesiveness, of the powder.32–34 Powders with good flowability are entrained by way of an “erosion” mechanism, where the powder is fluidized by layers and exits the inhaler gradually as a continuous stream.33,34 By contrast, for poorly flowing powders fluidization occurs by the “fracture” mechanism whereby the powder fluidizes as multiple agglomerates, and in extreme cases may fluidize as a single aggregated powder plug.

It has been proposed that smaller carrier particle size fractions, particularly those with a significant concentration of lactose fines, improve aerosol performance by coupling the fracture entrainment mechanism with an extensive number of carrier particles, thereby generating a high density aerosol cloud that promotes collisions between lactose carriers.33,34 In the present study, only anhydrous formulations exhibited performance consistent with this mechanism, but performance from granulated carriers was incompatible with this theory, as the $<32\mu m$ carrier populations did not yield RF values significantly higher than the larger carriers. However, variables apart from carrier particle size can affect the extent to which interparticle collisions may occur. For instance, the DPI employed may influence interparticle collisions, as devices with more complex internal geometries may enhance the frequency and/or magnitude of interparticle collisions relative to inhalers with simpler internal geometries. In addition, the cross-sectional area of the capsule perforation may likewise affect interparticle collisions, as smaller openings can prevent the powder from exiting the capsule as agglomerated plugs, thus limiting the density of the aerosol cloud. Thus, it is noted that the inhalers employed in these studies may not be ideal for promoting interparticle interactions, as the swirling particle trajectories in the capsule chamber of the Aerolizer® may be offset by the small cross-sectional area of the capsule perforations, whereas the larger diameter capsule openings from the Handihaler® are coupled with an internal geometry that may not induce extensive interparticle collisions relative to the Aerolizer®. Accordingly, although interparticle collisions may influence aerosol performance under certain conditions, this detachment mechanism was not supported by the data for both lactose grades, and thus CFD simulations capturing carrier–carrier interactions were deemed beyond the scope of the present study.

**Mass Median Aerodynamic Diameter**

In contrast to the respirable fraction, the mass median aerodynamic diameter (MMAD) of drug depositing on the stages of the cascade impactor varies significantly between inhalers for both anhydrous and granulated lactose formulations (Fig. 8). Furthermore, although the MMAD from the Aerolizer® displayed an overall decreasing trend with increasing carrier particle size for both lactose populations, MMAD values obtained from the Handihaler® were generally independent of the formulation. The disparity between the MMAD values for formulations dispersed through the inhalers were greatest at the smaller carrier particle formulations, and eventually converged on a mutual value for the largest carrier size fractions. In our previous study, it was postulated that the reduction in MMAD obtained from larger carrier particles dispersed through the Aerolizer® may be attributed to the increased detachment of smaller drug particles from the carrier surface.16 As the collision force between a particle and inhaler is dependent on the mass, and thus the volume, of the carrier particle, the momentum generated from a collision increases with the cube of the carrier particle diameter, assuming a relatively constant particle velocity (as volume $\propto$ diameter$^3$).2 Thus, larger carrier particles

Figure 8. Mass median aerodynamic of budesonide particles following dispersion of 2% (w/w) formulations with (a) anhydrous lactose, and (b) granulated lactose carrier particles at 60 L min$^{-1}$ from both the Aerolizer® and Handihaler® DPIs. Values are given as the mean of $N = 3$ replicates, with error bars representing the standard deviation for $N = 3$ replicates.
can generate strong mechanical detachment forces, which can potentially exceed fluid-based forces.\textsuperscript{3,13,14}

These strong mechanical forces may dislodge drug particles resistant to fluid-based detachment, including small aggregates and primary drug particles located within carrier particle surface asperities, inhibiting their interaction with the flow stream. Accordingly, the size of drug particles depositing in the impactor would be expected to decrease with larger carrier particle populations, as observed in both the anhydrous and granulated formulations dispersed from the Aerolizer\textsuperscript{®}. Comparing MMAD values obtained from the Aerolizer\textsuperscript{®} with the corresponding RF values, the carrier particle size fraction when the MMAD markedly declined matched the carrier size when aerosol performance exhibited a local improvement; this corresponded to the 180–212 μm size fraction for anhydrous carriers, and 90–125 μm for granulated lactose ($p < 0.05$). Conversely, MMAD values in the Handihaler\textsuperscript{®} were relatively consistent between carriers for both lactose grades, displaying no general trend with performance, although the MMAD from formulations dispersed through the Handihaler\textsuperscript{®} was consistently lower than that dispersed from the Aerolizer\textsuperscript{®}, with the exception of the largest carrier sizes (>180 μm).

In combination with the particle trajectory simulations, the aerosol performance data suggest the presence of an impaction-based mechanism of drug detachment in the Aerolizer\textsuperscript{®} whereby the relatively numerous and high energy collisions between large carriers and the inhaler wall generate a force sufficient in both magnitude and direction to detach smaller drug particles immune to detachment by the flow stream. As discussed in detail elsewhere, this favors large carrier particles with extensive surface roughness, and accordingly the improvement in aerosol performance with larger carrier populations is more pronounced in granulated lactose formulations.\textsuperscript{16} However, it is noted that while the present studies were performed at a fixed flow rate, the velocity, and hence momentum, of the carrier particles may significantly affect performance, particularly for larger carrier populations. Accordingly, studies exploring the effectiveness of mechanical detachment forces at variable flow rates are presently under investigation in our lab.

**CONCLUSION**

Coupling the CFD particle trajectory simulations with the in vitro results, it is concluded that impaction-based forces are not a significant mechanism of detachment in the Handihaler\textsuperscript{®}, as reflected by both the absence of improved performance at the large carrier fractions and the minimal increase in simulated carrier particle–inhaler collisions with carrier diameter. In contrast, the internal geometry of the Aerolizer\textsuperscript{®} is capable of generating a higher number of particle–inhaler collisions, with the frequency of the collisions markedly increasing with carrier diameter. Accordingly, aerosol performance from this DPI exhibited a dependence on the carrier particle size fraction, which was not observed in the Handihaler\textsuperscript{®} to a similar extent. In addition, performance was also significantly influenced by carrier particle morphology, and although granulated lactose is not commonly employed in DPI formulations, the use of this lactose grade afforded greater insight into distinctions in DPI performance than relatively smooth surfaced anhydrous lactose. In conclusion, the results of this study suggest that matching the physical properties of the carrier population to the predominant detachment mechanism of the DPI may significantly influence aerosol performance.

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