A counter-swirl design concept for dry powder inhalers

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A B S T R A C T

A swirling airflow is incorporated in several dry powder inhalers (DPIs) for effective powder de-agglomeration. This commonly requires the use of a flow-straightening grid in the DPI to reduce drug deposition loss caused by large lateral spreading of the emerging aerosol. Here, we propose a novel grid-free DPI design concept that improves the aerosol flow characteristics and reduces the aforementioned drug loss. The basis of this design is the implementation of a secondary airflow that swirls in the opposite direction (counter-swirl) to that of a primary swirling airflow. In-vitro deposition, computational fluid dynamics simulations and particle image velocimetry measurements are used to evaluate the counter-swirl DPI aerosol performance and flow characteristics.

In comparison with a baseline-DPI that has only a primary swirling airflow, the counter-swirl DPI has 20% less deposition of the emitted drug dose in the induction port and pre-separator of a next generation impactor (NGI). This occurs as a result of the lower flow-swirl generated from the counter-swirl DPI which eliminates the axial reverse flow outside of the mouthpiece and substantially reduces lateral spreading in the exiting aerosol.

Modifications to the counter-swirl DPI design were made to prevent drug loss from the secondary airflow tangential inlets, which involved the addition of wall perforations in the tangential inlets and the separation of the primary and secondary swirling airflow by an annular channel. These modified DPI devices were successful in that aspect but had higher flow-swirl than that in the counter-swirl DPI and thus had higher drug mass retained in the device and deposited in the induction port and pre-separator of the NGI. The fine particle fraction in the aerosols generated from all the counter-swirl-based DPIs and the baseline-DPI are found to be statistically similar to each other.

1. Introduction

The performance of a dry powder inhaler (DPI) is typically assessed by its ability to generate a fine respirable dry powder aerosol upon inhalation through the device (Finlay et al., 1997). The aerodynamic particle size distribution (APSD) is one of the important factors that determine drug deposition in the lungs and is quantified in terms of the mass median aerodynamic diameter (MMAD) of the particles (Wiggins, 1991), which has an optimal range for inhalation between 1.5 and 5 μm (Usmani et al., 2005; Ziffels et al., 2015). The aerosol APSD is influenced by the patient’s inhalation effort, the formulation and properties of the drug, and the design characteristics of the inhaler (De Boer et al., 2017). All these factors have complex and strong interactions which constitute a challenge when designing a DPI with optimal aerosol performance for a specific therapeutic effect. The last of the aforementioned factors is critical because the device design regulates the DPI airflow resistance and thereby the inhalation pressure that is required for its effective operation (Clark et al., 2020). The challenge then is to modify the design of a DPI so as to control the generation of aerodynamic forces for maximum powder de-agglomeration and dispersion at a minimum inhalation pressure.

Commercially available DPIs are mostly passive and have a wide-range of design features and are traditionally categorized based on the type of dose delivered, namely: single-unit dose, multi-unit dose, and multi-dose reservoir DPIs (Newman and Busse, 2002; Islam and Gladki, 2008). For example, single-unit dose DPIs, such as the Aerolizer® (Novartis Pharma AG), Handihaler® (Boehringer I) and Turbospin®

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(PH&T S.p.A.), have a capsule that is pierced to allow the contained powder to be released as the capsule spins or shakes under the action of the inhaled airflow, in which the powder then aerosolizes. The piercing and capsule motion can occur along either axis of the capsule (Martinelli et al., 2015). On the other hand, Conix™ (3M) is a multi-unit dose DPI that uses a reverse-cyclone technology in which the inhaled airflow and drug laterally enter a cone-shaped cyclone chamber to establish a vortex that generates high angular velocities, which in turn produces de-agglomeration due to particle-wall and particle-particle collisions and by aerodynamic shear (Harrison et al., 2011). Another multi-unit dose DPI is the Ellipta® (GSK) which uses individually sealed blisters in a coiled strip within the device. A single blister is peeled when the device mouthpiece is opened and the drug is exposed for aerosolization to the inhaled airflow which enters through a grill on the device body (Grant et al., 2015). An example of a multi-dose reservoir DPI is the Spiromax® (Teva Pharmaceuticals) in which an air pump transfers the drug from the reservoir to the dosing cup, followed by de-agglomeration of the drug powder blend in a cyclone separator (Canonica et al., 2015). Finally, the Novolizer® (Viatris) is another multi-dose reservoir DPI in which the drug dose is released for aerosolization via a trigger mechanism that actuates only when the inhaled airflow rate reaches between 35 and 50 L min⁻¹.

Particle de-agglomeration then takes place in a cyclone chamber in the mouthpiece which is exposed to a sheath flow to regulate particle dispersion (Kohler, 2004).

The aforementioned examples highlight some of the many different design features present in DPI devices. However, in order to synthesize their design characteristics, it is meaningful to consider the underlying mechanism of powder aerosolization that is responsible for the entrainment, de-agglomeration and dispersion of the drug powder into the inhaled airflow. The aerosolization of drug powder in all DPIs, irrespective of their drug loading feature, occurs through a swirling inhaled airflow produced from tangential inlets, and/or a straight channel or jet inhaled airflow produced from inline inlets. Regardless, the fundamental aspect of powder aerosolization is that the forces generated in the inhaled airflow should entrain the powder from the device loading chamber, or empty it from a capsule, and overcome the inter-particulate forces in order to de-agglomerate the powder agglomerates into fine particles.

A swirling turbulent airflow is pertinent for this application as it creates a low pressure region for powder entrainment (Kitoh, 1991) and generates fluid forces that cause large velocity gradients, and in-turn aerodynamic shear forces, that de-agglomerate the drug powder into fine respirable particles. Besides, being confined within small geometrical dimensions that are typical in a DPI, it makes the agglomerates collide with one another, and also with the device wall, which enhances de-agglomeration. Moreover, a confined swirling airflow creates a longer residence time for the particles inside the device, increasing their probability of de-agglomeration as opposed to that in a straight flow through the device (Donovan et al., 2012). Some examples of existing DPIs that incorporate a swirling turbulent airflow are the capsule-based Aerolizer® (Novartis Pharma AG), Turbospin® (PH&T S.p.A.), Podhaler® (Novartis Pharma AG) and Neohaler® (Novartis Pharma AG), and the reservoir-based Twithalmor® (Merck & Co., Inc.), Nexthaler® (Chiesi Farmaceutici S.p.A.) and Turbuhaler® (AstraZeneca PLC).

Although a swirling airflow is more effective in powder entrainment and de-agglomeration when compared with a swirl-free airflow, large lateral spreading and the formation of an axial recirculation zone, depending on the swirl level (Escudier and Keller, 1985), can occur in the emerging flow from the device mouthpiece. This reduces the delivered drug dose as the exiting particles in the airflow spread laterally and cause significant deposition losses through impaction in the mouth-throat region (dos Reis et al., 2021). A method often adopted to mitigate these losses is the use of flow-straightening grids to reduce flow-swirl (Coates et al., 2004). This however comes with drawbacks wherein the grid acts as an additional structure for particle deposition, which contributes to drug loss due to powder retention in the device (Wong et al., 2011), and it increases the device resistance, which leads to a higher inhalation effort for a patient using the device (Clark et al., 2020; dos Reis et al., 2021).

The DPI design proposed in this study provides a grid-free alternative to overcome the aforementioned drawbacks. It involves the provision of a secondary inhaled airflow that swirls in the opposite direction (counter-swirl) to that of a primary swirling inhaled airflow in a DPI. The evolution of this counter-swirl design concept is presented in the next section through an illustration of the design implementation and successive design modifications. The subsequent section includes the results of the aerosol performance and flow characteristics of the DPI devices determined using three complementary approaches, following a recently described strategy (Chaugule et al., 2022), viz. in-vitro deposition, particle image velocimetry (PIV), and computational fluid dynamics (CFD).

2. The counter-swirl DPI design

The origin of the aforesaid DPI design concept emerged from a baseline-DPI that was designed based on the geometry of traditional inhalers and studied in dos Reis et al. (2021). This device is illustrated via an isometric drawing in Fig. 1(a). The baseline-DPI has a pipe-shaped design with two diametrically-opposite tangential inlets. A hemispherical dosing cup, in which the drug powder is loaded, forms the device base, with the tangential inlets positioned just above it.
The top of the device constitutes the mouthpiece through which a patient inhales. When this happens, air flows into the DPI from the tangential inlets, generating a swirling inhaled airflow that travels axially (longitudinally) through the DPI and exits at the mouthpiece. This swirling flow is turbulent and fluidizes the drug powder in the dosing cup, resulting in the entrainment of drug agglomerates in the airflow. The device has an inner diameter of 10 mm throughout its length of 50 mm and the dimension of each inlet is 7.1 mm \( \times 2.8 \text{ mm.} \)

The flow characteristics of the baseline-DPI, which are presented in detail in dos Reis et al. (2021), show the existence of a highly swirling jet-flow in the aerosol emerging from the device mouthpiece-exit. This swirling jet-flow has an axially recirculating zone in the central region with negative mean axial velocities, and laterally spreading zones in the outer region with high mean axial and lateral velocities. These flow characteristics were found to contribute to drug loss in the form of particle deposition in the mouth-throat region. In order to reduce the flow-swirl, and thereby this drug loss, a grid with square holes was placed at the mouthpiece-exit increased the drug mass retained within the device leading to drug loss of a different form. Therefore, in order to address the aforementioned shortcomings of the baseline-DPI using a grid-free approach, a counter-swirl flow configuration was devised that involves a secondary swirling inhaled airflow with an opposite sense of rotation to the existing primary swirling inhaled airflow.

This counter-swirling airflow is implemented by using two sets of tangential inlets oriented opposite in direction to each other, with each set having six tangential inlets. The outcome of this implementation is illustrated via the DPI device shown in Fig. 1(b), where the bottom set of tangential inlets, placed just above the dosing cup, produce the anti-clockwise primary swirling inhaled airflow, and the set of tangential inlets positioned above and oriented in the opposite direction produce the clockwise secondary counter-swirling inhaled airflow. This device is called the counter-swirl (cs) DPI. The total inlet flow area of the counter-swirl DPI, i.e., the sum of the rectangular cross-sectional areas of all tangential inlets, is the same as that in the baseline-DPI. The inclusion of six tangential inlets in each set was to produce a more uniform swirling flow when compared to that from two tangential inlets in the baseline-DPI.

The in-vitro deposition tests on the counter-swirl DPI reveal drug loss from the top row of tangential inlets as shown in Table 1. In order to address this issue two design modifications to this DPI were carried out. The first modification involved making perforations, a uniform pattern of square holes, in the device wall where the top row of tangential inlets intersect the device. This modification is shown in Fig. 1(c) and the resulting device is called the cs-perforated DPI. The second modification involved separating the primary and secondary swirling inhaled airflows by an annular channel. This was created by radially spacing out the top row of tangential inlets around a hollow cylindrical duct through which the primary swirling inhaled airflow enters the device. The secondary swirling inhaled airflow enters the device from this annular channel in isolation from the primary swirling inhaled airflow. These flows then merge in a pipe that converges to form the mouthpiece. The resulting DPI device is shown in Fig. 1(d) and is called the cs-annulus DPI. The encircling bottom part of this device is shown enlarged on the right side to clearly depict the annular separation (0.5 mm) between the primary and secondary swirling inhaled airflows. The inner diameter of the mouthpiece exit in all the DPIs shown in Fig. 1 is the same — 10 mm.

3. Material and methods

3.1. In-vitro deposition studies

Aerosol performance of all devices was assessed using a pre-blend carrier system loaded with beclometasone dipropionate (BDP) at 1% (w/w), as previously described in dos Reis et al. (2021). Briefly, the device performance was assessed using the Next Generation Impactor (NGI, Apparatus E - British Pharmacopoeia). All stages were coated with Brij35 solution to minimize particle bouncing (USP 26-NF 21, 2005; Witham, 2010; Khalili et al., 2018). To better assess the effect of device design on deposition in the United States Pharmacopoeia (USP) induction port (IP) of the NGI, the USP IP was also coated with Brij35 solution. Each device was loaded with 10 mg of formulation (equivalent to 100 \( \mu \text{g} \) of BDP) and actuated for 4s at a flow rate \( Q_e = 60 \text{ l/min}^{-1} \) in the NGI. The formulation is loaded from the device mouthpiece into the device dosing cup, which is shown labelled as No. 3 in Fig. 1. Each stage was washed with methanol:water (80:20% v/v) solvent to recover the drug and quantified using a validated high performance liquid chromatography method (Yeung et al., 2018). The aerosol performance of the devices was analysed using Copley Inhaler Testing Data Analysis Software (CITDAS) (Version 3.10 Wibu, Copley, Nottingham, UK) and compared based on the delivered dose (DD, total mass recovered), fine particle dose (FPD, calculated as the dose in \( \mu \text{g} \) of particles below 5 \( \mu \text{m} \) in size), fine particle fraction (FPF, percentage of particles below 5 \( \mu \text{m} \) in size) and mass median aerodynamic diameters (MMAD, calculated as the 50th percentile of the distribution of particles below 5 \( \mu \text{m} \) in size). More succinctly, the MMAD is based on half of the total aerosol mass.

3.1.2. Device pressure drop and resistance

The device resistance and pressure drop are important parameters that directly affect the aerosolization of the drug formulation. Using an induction port measurement adapter (Copley, UK) between the device and the USP IP, the pressure drop (\( \Delta P \)) was measured by a critical flow controller (TPK 2100-R, Copley, UK) over 4s. Three independent measurements were performed at a flow rate of \( Q_e = 60 \text{ l/min}^{-1} \), which was set using a calibrated flow meter (Model 4040, TSI Precision Measurement Instruments, Aachen, Germany). The device resistance is calculated as \( \sqrt{\Delta P/Q_e} \) and is expressed in units of kPa\( \text{in}^{-1} \)/l/min\( ^{-1} \).

3.1.3. Statistical analysis

The in-vitro deposition results are presented as the mean \( \pm \) standard deviation of three independent experiments (\( n = 3 \)). The means were compared using GraphPad Prism Software version 8.0 (GraphPad, San Diego, USA). The counter-swirl DPI was compared with the baseline-DPI by two-tailed unpaired t-test, whereas the cs-perforated and cs-annulus DPIs were compared with the counter-swirl DPI using two-way Anova.
followed by Tukey’s post hoc test. The differences were considered statistically different at 95% CI (‘P < 0.05, ”P < 0.01, ””P < 0.001 and ”””P < 0.0001).

3.2. Particle image velocimetry

PIV (Soria, 1996) measurements were performed to characterize the jet flows emerging from the DPI devices. These measurements were carried out on geometrically scaled-up models (three times those of the original devices shown in Fig. 1) in water-based experiments, and under flow conditions that were geometrically and dynamically similar to the DPI device operating conditions in air at $Q_{in} = 601 \text{min}^{-1}$. Each experimental DPI model was placed in a tank, specifically designed to create the aforementioned flow conditions, and a steady water flow-rate of $Q_{water} = 121 \text{min}^{-1}$ was maintained through the model to attain a Reynolds number of $Re \approx 8400$. The Reynolds number $Re$ is defined based on the average axial flow velocity $U_{mp}$ at the DPI mouthpiece exit, the mouthpiece-exit inner-diameter $D_{mp}$ (jet diameter), and the properties of the working fluid — water. This Reynolds number is equal to that for the DPI devices that use air in the in-vitro aerosolisation experiments.

The PIV measurements for each DPI model were taken within a downstream axial distance of 4 jet diameters outside of the mouthpiece exit. The coordinate system for the PIV study is shown on the right side of Fig. 1, wherein $x$ and $y$ represent the axial and lateral directions, respectively, with $u$ and $v$ being the respective velocity components. A detailed description of the experimental methodology, apparatus and associated measurement uncertainties is provided in dos Reis et al. (2021).

3.3. Computational fluid dynamics

The CFD methodology is the same as that used in our previous studies (Fletcher et al., 2021; Chaugule et al., 2023) and employs Ansys® Fluent, version 2020R1. Based on the comparison of data generated using various turbulence models with PIV data in our previous study (Fletcher et al., 2021), the Stress Blended Eddy Simulation (SBES) model was used in this work (Menter, 2018). This is a hybrid model that blends between the $k$-$
omega$ SST RANS model near the walls and a Large Eddy Simulation (LES) model in regions where the mesh is resolved sufficiently. As the name suggests, it is the eddy viscosity that is blended. The LES model used the subgrid scale closure of WALE (Nicoud and Ducros, 1999). In the $k$-$
omega$ SST model both the production limiter (that avoids excessive turbulence generation) and the curvature correction terms (that captures swirl correctly) were enabled. The maximum wall $y^+$ was less than 5 and on average around 2, so that the SST model was integrated to the wall with no wall functions used.

2000 Lagrangian particles that represent the lactose carrier particles (density $1540 \text{kgm}^{-3}$ and diameter $280 \mu m$) were tracked using the time-dependent flow-field to determine the number of particle–wall impacts and their impact energy. Particle–particle impacts were not modelled. These data are used to investigate the impact of design changes on the potential for wall-induced de-agglomerated.

A poly-hexcore mesh was used for the simulations. The flow domain inside the inhaler and downstream was filled with a uniform hexahedral mesh which was connected to an inflation mesh on the walls via a layer of polyhedra. The final meshes used comprised around 0.7 million cells for all cases. When using the SBES model care needs to be taken to ensure that the LES model operates in important areas of the flow. This was achieved by viewing the blending function and adding local refinement where necessary.

Fig. 2 shows the surface mesh on the device, together with the inlet zone and the location of particle injection region. The meshed region around the device allows the air to be drawn into the inhaler in a natural manner, which is important so that the flow is not over-constrained.

The coupled solver was used for the pressure-velocity coupling as it gave the best convergence behaviour. Gradients were calculated using the Least Squares Cell-Based method. Bound condition order differencing was used for the momentum equations, second order upwind for the turbulence variables and a bounded second order implicit time differencing scheme was selected. A timestep of $2\mu s$ was used to ensure the Courant number was less than one everywhere. Inside the device it was typically less than 0.3. Simulations were run until they reached a statistically stationary condition based on monitor point data and then transient averaging was started. These averaged data were monitored to determine when this condition was reached, which typically required 20,000 timesteps. The averaged data are shown in the subsequent plots.

4. Results

4.1. In-vitro deposition results

The aerosol performance of all the DPI devices expressed as the mass of BDP deposited and the emitted dose is presented in Fig. 3. Comparing the performance of the baseline-DPI and counter-swirl DPI first in Fig. 3(a), we see that the BDP mass deposition shows a significant decrease in the mass retained in the device ($P < 0.01$) and deposited in the USP IP and pre-separator ($P < 0.01$) for the counter-swirl DPI. This decrease is reflected as an increase in the drug mass deposited in stages 1, 2 and 3 of the NGI. The aerosol performance parameters of all the four DPI devices are listed in Table 1, which shows that the total loaded dose and the mass of BDP recovered (delivered dose) from the counter-swirl DPI were the lowest. This occurred due the loss of drug from the top row of tangential inlets in this device, as was previously mentioned in Section 2. Hence, for a consistent comparison of the aerosol performance of all the devices, whilst accounting for this difference, a more suitable parameter is the emitted dose (expressed as the percentage of the delivered dose). The emitted dose from the baseline-DPI and the counter-swirl DPI in Fig. 3(b) shows a significant decrease in deposition in the USP IP + pre-separator ($P < 0.05$) and an increase in stages 1, 2, 3 and 4 of the NGI for the latter.

A comparison of the aerosol performance of the counter-swirl, cs-perforated and cs-annulus DPIs is shown in Fig. 3(c) and (d). There is a significant increase in the BDP mass retained in the device ($P < 0.01$) and deposited in the USP IP + pre-separator ($P < 0.0005$) for the

Fig. 2. Cut away picture showing the mesh on the device, the surrounding air zone and the region where the carrier particles were released into the flow.
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Fig. 3. Aerosol performance of the devices expressed as: (a), (c) mass of BDP deposited (n = 3) and (b), (d) emitted dose across different stages of the NGI.

cs-perforated and cs-annulus DPs, as shown in Fig. 3(c). This finding should be considered in the context of the lower dose of BDP recovered in the counter-swirl DPI when compared with that in the other DPI devices. Additionally, a comparison based on %ED in Fig. 3(d) shows a significant increase in BDP deposited in the USP IP + pre-separator (P < 0.01) for the cs-perforated and cs-annulus DPs. However, similar deposition profiles in all other stages of the NGI are observed for the three counter-swirl-based DPs. Overall, the aerosol deposition results show that the cs-perforated DPI has the most BDP mass retained in the device and that both the cs-perforated and cs-annulus DPs have statistically similar BDP deposition in the USP IP, but higher than that for the counter-swirl DPI. The relatively higher variance observed in the delivered dose of the cs-perforated DPI and in the delivered dose and fine particle dose of the cs-annulus DPI is because of minor inconsistency in the 3D printing of the small perforated holes and annular gap in these respective DPI devices, which was due to the limited spatial resolution of the available 3D printing facility.

The design of a DPI device regulates the pressure drop that a patient has to generate in order to produce the required inhalation flow rate for effective aerosolization of the drug powder. This is quantified in terms of the device resistance and is listed in Table 2 for all the four

<table>
<thead>
<tr>
<th>Device</th>
<th>Pressure drop (kPa)</th>
<th>Device resistance (kPa·min/文献_version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline-DPI</td>
<td>1.79</td>
<td>0.0223</td>
</tr>
<tr>
<td>counter-swirl</td>
<td>0.87</td>
<td>0.0155</td>
</tr>
<tr>
<td>cs-perforated</td>
<td>1.67</td>
<td>0.0215</td>
</tr>
<tr>
<td>cs-annulus</td>
<td>1.22</td>
<td>0.0184</td>
</tr>
</tbody>
</table>

Table 2

Pressure drop and device resistance measured at Q_a = 601 min⁻¹.
DPI devices tested at an inhalation flow rate of $Q_a = 60\text{ l min}^{-1}$. The counter-swirl DPI has 30% lower resistance than the baseline-DPI. The addition of wall perforations in the cs-perforated DPI restricts the air inflow and produces 39% higher device resistance than the counter-swirl DPI, whereas the inclusion of the annular channel in the cs-annulus DPI increases its resistance by 19%. A comparison of the data in Tables 1 and 2 shows that the FPF of the counter-swirl-based DPIs is statistically similar to that of the baseline-DPI.

4.2. PIV results

The mean velocities and turbulence intensities in the jet flows arising from the three counter-swirl-based devices, and obtained using PIV, are presented in this section. All velocities are presented in a non-dimensional form upon division by the average axial flow velocity at the DPI mouthpiece exit $U_w$, while the spatial coordinates appear in this form upon division by the mouthpiece-exit inner-diameter $D_w$. The corresponding results for the baseline-DPI device can be found in dos Reis et al. (2021) and Fletcher et al. (2021) and are not presented in this paper.

The mean axial velocity $U/U_w$ distributions over the lateral coordinate $y/D_w$ and at axial locations up to $x/D_w = 3$ are shown in Fig. 4. The profiles for the counter-swirl device in Fig. 4(a) show a trough in the jet-central region (core) and peaks in the jet-edge regions (shear layer). The peak velocities decay with increasing downstream distance from the mouthpiece exit, whereas the trough velocities first decrease, to become marginally negative at $x/D_w = 1$, and then increase. The profiles for the cs-perforated device in Fig. 4(b) show negative values in the jet core throughout the measured downstream distance, exemplifying a jet flow with a very low swirl level.

The mean lateral velocity $V/U_w$ distributions along the lateral direction are shown in Fig. 5. The profile for the counter-swirl device at its mouthpiece exit $x/D_w = 0$ in Fig. 5(a) shows maximum positive and negative values of the mean lateral velocity occur close to $y/D_w = 0.5$ and $-0.5$, respectively. These profiles are not symmetric about the jet centre-line $y/D_w = 0$ and decay with increasing downstream distance. The cs-perforated device has similar profiles, as shown in Fig. 5(b), but the maximum positive and negative values at $x/D_w = 0$ are higher than those for the counter-swirl device. The profiles for the cs-annulus device in Fig. 5(c) show that mean lateral velocities in the jet flow are lower than those for the other two devices, signifying a reduced lateral spreading in the flow exiting this device mouthpiece.

The mean axial and lateral velocity profiles for the three devices show that the design of the cs-annulus device is the most effective for reducing the swirl level in the jet flow. The least effective on the other hand is the design of the cs-perforated device, wherein the square-holes perforations restrict the counter-swirling inflow into the device.

The turbulence intensities are represented in the form of root-mean-square (rms) axial and lateral velocity fluctuations in Figs. 6.
Fig. 5. PIV: mean lateral velocities for: (a) counter-swirl; (b) cs-perforated; (c) cs-annulus; at $x/D_w = 0$, $x/D_w = 1$, $x/D_w = 2$ and $x/D_w = 3$.

and 7, respectively. The rms axial velocity fluctuation $u_{rms}/U_w$ for the counter-swirl device at $x/D_w = 0$ in Fig. 6(a) shows four peaks along the lateral direction, two in the jet core and two at jet edge. These peaks occur in the inner and outer jet shear layers, respectively, where there are large velocity gradients when the swirling jet exits the mouthpiece and mixes with the quiescent surrounding fluid. The peak velocity fluctuations decrease and spread out laterally as the jet decays downstream due to further mixing. The fluctuating velocity profiles for the cs-perforated device in Fig. 6(b) are similar to those for the counter-swirl device, but have higher fluctuations. However, in comparison with both these devices, the rms axial velocity fluctuations in the jet-flow arising from the cs-annulus device are the lowest, as shown in Fig. 6(c). The fluctuating velocity profiles for this device do not show two distinct peaks in the jet-core and the decay and spread of the velocity fluctuations with downstream distance is also slower. Furthermore, the peak axial velocity fluctuations at the jet-edge remain largely unchanged with increasing downstream distance. Similar observations for the rms lateral velocity fluctuations can be found in Fig. 7. The remarkable difference is the peak lateral velocity fluctuation at the jet centre-line which occurs where the mean lateral velocity is zero. Overall, the rms axial and lateral fluctuations for the cs-annulus device are small when compared with the other devices at all axial distances reported, which is due to the reduction of flow-swirl that in turn reduces the amount of jet mixing with the ambient fluid.

4.3. CFD results

Results from the CFD simulations are presented in the next three subsections for the flow-field, pressure drop and particle behaviour. The corresponding results for the baseline-DPI device can be found in Fletcher et al. (2021) and Chaugule et al. (2023) and are not presented in this paper.

4.3.1. Flow field

The axial flow on the centre-plane for the DPI devices is shown in Fig. 9. The central region inside the counter-swirl and cs-perforated DPIs consists of negative axial velocities near the tangential inlets and low axial velocities downstream, whereas the peripheral region along the wall consists of high axial velocities. These transform into an axial reverse flow region with lateral spreading outside the mouthpiece-exit, which is stronger for the cs-perforated DPI. The axial reverse flow in the inlet region inside the device also occurs in the cs-annulus DPI and is comparatively larger in magnitude and spatial extent. However, it disappears downstream and transforms into a uniform high axial velocity region across the top half of the device, which then emerges as a jet from the mouthpiece-exit with significantly lower lateral spread and no axial reverse flow.
The axial reverse flow region outside the mouthpiece-exit of counter-swirl and cs-perforated DPIs indicates vortex breakdown and is a result of the strong flow-swirl within these devices, as can be seen in Fig. 10. In contrast, the flow-swirl within the cs-annulus DPI is massively reduced and there is no vortex breakdown and consequently much less lateral spreading of the jet outside the mouthpiece-exit. The above observations accord perfectly with the streamlines, displayed in the PIV results of Fig. 8, which shows very similar reverse flow and spreading behaviour and the prominent vortex breakdown for the cs-perforated DPI. The CFD results show the internal flow in the DPI device and how the exit flow is a result of the particular geometry, with the swirl reduction being key.

Fig. 11 presents the turbulence kinetic energy for the DPI devices plotted on the same plane. The turbulence in the jet outside the mouthpiece is highest for the cs-perforated DPI and lowest for the cs-annulus DPI, where the latter again shows the reduced spreading of the jet. There is an opposite occurrence inside the device wherein the turbulence kinetic energies for the counter-swirl and cs-annulus DPIs are significantly higher in the region where the secondary and primary swirling inhaled airflows vigorously mix with each other.

4.3.2. Pressure drop

The measured and CFD predicted pressure drops for the DPI devices are shown in Fig. 12. The predicted pressure drop is higher than the measured for all DPI devices except for cs-perforated DPI. This difference could arise from a number of sources, for example, the spatial resolution in the 3D printed DPI model used for the in-vitro experiments, some residual mesh dependence or measurement uncertainties. However, despite the complexity of the flow, the agreement between the experimental data and CFD is good with the trend captured correctly.

4.3.3. Particle behaviour

This section presents the results obtained by releasing the lactose carrier particles in the hemispherical cup at the bottom of the DPI device and tracking their behaviour. Two different statistics were collected: (i) total number of wall impacts per particle, and (ii) the total impact-energy per particle, with the results shown in Figs. 13 and 14, respectively.

Fig. 13 shows that the median number of impacts per particle (50th percentile) varies from 22 for the counter-swirl DPI, 29 for the cs-perforated DPI and to 33 for the cs-annulus DPI. At the 85th percentile, the counter-swirl and cs-perforated DPIs have 42 impacts per particle, whereas the cs-annulus DPI has 56. It is observed that a small number of particles (> 90th percentile) undergo a large number of wall impacts, with the highest number of such particle–wall impacts occurring in the cs-annulus DPI. Overall, the mean number of particle–wall impacts is the highest for the cs-annulus DPI. A similar trend also applies to the total impact-energy per particle in Fig. 14, with the cs-annulus DPI having the highest mean impact-energy per particle.

5. Discussion

The in-vitro deposition results showed that the counter-swirl DPI produces significantly less drug deposition in the USP IP + pre-separator and more in the initial stages of the NGI when compared with the baseline-DPI (Fig. 3(a) & (b)). These deposition patterns are a result of
the lower flow-swirl generated from the counter-swirl DPI which substantially reduces the axial reverse flow and lateral spreading in the exiting aerosol, as shown by the flow characteristics presented in the PIV results (Figs. 4(a) & 5(a)) and the CFD results (Fig. 9(a) & Fig. 10(a)), as well as those of the baseline-DPI reported in Fletcher et al. (2021). This clearly demonstrates the effectiveness of the grid-free design of the counter-swirl DPI in reducing USP IP deposition drug losses.

The subsequent design modifications made to the counter-swirl DPI however turn out to be not as effective because the cs-perforated and cs-annulus DPIs are found to produce higher USP IP deposition than the counter-swirl DPI, wherein the former also has the highest drug mass retained in the device (Fig. 3(c)). The wall perforations to prevent drug loss in the cs-perforated DPI reduce the counter-swirling inhaled airflow into the device when compared with that in the counter-swirl DPI. This flow blockage in the secondary tangential inlets forms a stronger axial reverse flow region within the device, induced by the swirling inhaled airflow from the primary tangential inlets, just downstream to the inlets (Fig. 9(b)). Although this reverse flow region does not persist downstream, the ensuing low mean axial velocities in the central region and the high swirl velocity along the wall (Fig. 10(b)) form a stronger reverse flow region outside the mouthpiece-exit, accompanied by higher lateral spreading (Fig. 5(b)). These undesirable flow characteristics lead to the aforementioned drug losses in the cs-perforated DPI.

The flow characteristics of the cs-annulus DPI on the other hand show a much larger and stronger axial reverse flow region downstream of the inlets within the device (Fig. 9(c)), but this region disappears further downstream where the secondary and primary swirling inhaled airflows merge to significantly reduce flow-swirl (Fig. 10(c)). The aerosol then emerges outside the mouthpiece with higher axial velocity (Figs. 4(c) & 9(c)) and considerably lower lateral spreading (Fig. 5(c)) when compared with the other DPIs. It is the higher axial jet velocity that causes the de-agglomerated drug particles to impact in the USP IP and increase drug deposition in this region. The significantly reduced flow-swirl and lateral spreading in the emerging aerosol from this device shows that the cs-annulus DPI design can be the basis of future counter-swirl-based DPIs which produce low axial velocity at the mouthpiece-exit through suitable modification of the geometry of the tangential inlets, annular separation and/or connecting mouthpiece.

An important result of the in-vitro deposition study is that the FPF of all examined DPI devices is similar. The FPF is controlled by de-agglomeration which means that de-agglomeration of a similar level occurs in all of devices. De-agglomeration is caused by (1) the action of aerodynamic shear due to lift and drag forces and that of turbulent eddies, which impart a relative motion to the particles in the powder agglomerates, and (2) the collisions of powder agglomerates with a surface (wall or grid) or with other agglomerates, which induce rapid accelerations that cause particles to separate (Voss and Finlay, 2002). These mechanisms are flow driven and do not occur in isolation from each other as agglomerates subjected to aerodynamic forces and turbulence can also undergo collisions in the small confined geometries in DPIs. Moreover, de-agglomeration can also occur during powder entrainment from the dosing cup where large pressure and viscous forces are exerted on the surface of the agglomerates (Finlay, 2001). Therefore, the role that these mechanisms play in de-agglomeration will vary depending on the flow characteristics and geometry of the inhaler.

All the counter-swirl-based DPIs have significant negative axial velocities in the centre of the device inlet region, which combined with...
high positive axial velocities along the wall in the same region produce large axial velocity gradients (Fig. 9). There are also large swirl velocity gradients in the inlet region, particularly where the primary and secondary swirling airflows mix with each other (Fig. 10). These combined flow patterns produce high aerodynamic shear and turbulence (Fig. 11) which indicate that these mechanisms play an important role in particle de-agglomeration in these DPI devices. However, a small number of particles in the DPI devices get trapped in the axial reverse flow in the inlet region and undergo a large number of wall impacts due to the action of the local flow-swirl. This axial-reverse-flow induced particle–wall impacts become amplified in the case of the cs-annulus DPI due to the presence of the axial duct through which the primary swirling inhaled airflow enters (Fig. 1(d)), thereby producing a more broader distribution of particle–wall impacts (Fig. 13). To conclude,
Fig. 10. CFD predictions of the time-averaged swirl velocity component for the DPI devices. (The range of the variable has been clipped to improve contrast.)

Fig. 11. CFD predictions of the turbulence kinetic energy for the DPI devices. (The range of the variable has been clipped to improve contrast.)

Fig. 12. Comparison of the experimentally measured and CFD predicted pressure drop across the DPI devices.

Fig. 13. Distribution of cumulative number of wall impacts per particle for the DPI devices.
both particle–wall collisions and aerodynamic shear and turbulence appear to cause de-agglomeration in the counter-swirl-based DPIs.

6. Conclusions

The counter-swirl DPI conceptualized and demonstrated in this study presents a novel grid-free design that utilizes a counter-swirling inhaled airflow to reduce drug deposition loss in the USP IP of a NGI. The in-vitro deposition study shows that the counter-swirl DPI has significantly lowered drug deposition loss in the USP IP and higher drug deposition in the initial stages of a NGI when compared with a baseline-DPI which has no counter-swirling inhaled airflow. The CFD and PIV results for the axial, lateral and swirl velocity characteristics in the flow within and emerging from the counter-swirl DPI show the reduced flow-swirl and lateral spread in the exiting aerosol and corroborate the in-vitro deposition findings.

Design modifications made to the counter-swirl DPI in order to reduce drug loss from the counter-swirling tangential inlet involved the inclusion wall perforations and an annular channel for isolating the swirling inhaled airflow. These DPI designs were successful in that aspect but produced greater drug loss in the form of higher mass deposition in the USP IP and mass retained in the device. The FPF of all the counter-swirl-based DPIs is found to be statistically similar and the CFD, PIV and carrier particle behaviour results together indicate that aerodynamic shear, turbulence and particle–wall impacts all contribute to de-agglomeration in these DPIs.

CRediT authorship contribution statement

Vishal Chaugule: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. Larissa Gomes dos Reis: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. David F. Fletcher: Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing. Paul M. Young: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. Daniela Traini: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. Julio Soria: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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