SUMMARY
A novel CFD/particle dynamics computational model, previously developed by Milenkovic et al. [1,2], is employed to investigate alternate geometries of a commercial Dry Powder Inhaler. Alternate geometries were based on detailed computational investigations of the commercial device and consist of simple alterations that lead to decreased flow resistance and smoother flow patterns. The alternate geometries are evaluated in terms of generated flow, total particle deposition, and fine particle fraction are found to be improvements of the original design.

INTRODUCTION
Dry Powder Inhalers, DPIs, are one of the principle means of delivering pharmaceuticals due to their ease of use and cost-effectiveness. Dry Powder Inhalers, DPIs, have been used commercially since 1971 and are continuously being improved and updated with new models [3]. The main function of a DPI device is the dispersion of powder into particles which effectively transfer and deliver a drug to the respiratory system [4]. The optimal function of a DPI requires a sufficiently large emitted dose and fine particle fraction, FPF, in the outflow. The outflow characteristics (i.e., the velocity flow field and the spatial distribution of outflowing particles) determine particle losses due to deposition in the oral cavity [5] and thus influence the delivered dose. The emitted dose depends on the efficiency of powder dispersion and the internal losses due to deposition [6].

Several computational studies have been reported including Computational Fluid Dynamics, CFD, and the discrete element method, DEM, in order to describe DPI devices [7,8]. Coates et al. [9,10] performed systematic studies of the Aerolizer DPI including the optimization of the air-intake, mouthpiece, and internal grid. The Twincer DPI was evaluated using CFD [11] and particle deposition was reported. From the current state-of-the-art it is clear that the proper description of the powder agglomerates including the particle/agglomerate interaction with the inhaler walls are key processes that determine the dispersion and size distribution of pharmaceutical powders [12].

Recently, a detailed CFD based computational model including particle/wall interactions was employed to describe the particle motion and deposition in the Turbuhaler DPI under both steady state [1] and dynamic flow [2] conditions. The computational results were in agreement to available experimental data for total deposition as well as the Fine Particle Fraction, FPF. The results of both steady and dynamic flow simulations were found to be similar to experimental results from the literature. The dynamic simulations results were more accurate than the steady state results especially for the FPF. In this work the computational model is employed to evaluate the operation of two alternate geometries of the Turbuhaler DPI at several steady flow rates in terms of outflow characteristics, FPF, and total particle deposition.

COMPUTATIONAL METHODS
The Turbuhaler DPI geometry was constructed in a CAD/CAM environment (i.e., CATIA v5R19) and then imported into GAMBIT (v2.1) where a series of computational grids consisting of $210^6$ tetrahedral cells with a maximum skewness of 0.85 were developed (Figure 1). An extension tube was added at the mouthpiece outflow in order to facilitate convergence. The computational grids were initially refined in regions where large gradients of flow were expected and further refined based on initial near-wall solutions. The Navier-Stokes equations for airflow were solved using the commercial CFD software (i.e., FLUENT v6.3). The SIMPLEC scheme was employed to describe pressure-velocity coupling, 2nd order discretization was used for pressure and
3rd order MUSCL for momentum and turbulent variables. CFD simulations were converged when the residuals were < $10^{-4}$. Zero gauge pressure boundary conditions were employed at all the air inflows.

Different steady state airflows were simulated by imposing a wide range of pressure drops at the mouthpiece outflow ranging from 800 to 8800 Pa which corresponded to volumetric flow rates of 30 to 70 l/min. Several models for turbulent flow were employed, e.g. k-ε RNG, k-ω SST, LES to describe the airflow in the Turbuhaler DPI. Based on comparisons with a reference Large Eddy Simulation obtained at 30 l/min the SST k-ω turbulence model was found to produce the best results. Eulerian-fluid/Lagrangian-particle simulations of particle motion and deposition were conducted for particles between 0.5-20 μm in size encompassing the single particle to agglomerate size range. Particle-wall collisions resulted in deposition only when the particle velocity magnitude was less than a critical velocity which was obtained from particle cohesion models [13]. The particle cohesion models were utilized as a user-defined function (UDF) in FLUENT to determine the capture efficiency. Further details of the computational model and numerical implementations can be found in Milenkovic et al. [1,2].

The original DPI Turbuhaler device geometry, G-A, obtained in Milenkovic et al. [1], consists of: two powder cylinders, an inhalation channel, a circulation chamber and a helical region of the mouthpiece. The simulation results of Milenkovic et al. [1,2] revealed that particle deposition predominantly occurred in the circulation chamber and in the helical region of the mouthpiece. Consequently in this work two additional geometries (i.e., G-B and G-C) of the Turbuhaler DPI are proposed that provide smoother flow patterns and thus a reduced number of inertial particle-wall collisions. The commercial DPI geometry (i.e., G-A) and the two alternate geometries (i.e., G-B and G-C) are listed in Table 1. Geometry G-B possesses a larger circulation chamber with a spherical ceiling. Thus G-B should provide smoother flow transition from the circulation chamber to the helical region. In the G-A geometry the helical region is comprised of two circular conduits with diameter $D_c=3$ mm. In the G-C geometry the helical region is comprised of square conduits with 2.4 mm edges providing a larger cross-sectional area for flow than in G-A.

Steady flow CFD simulations were performed for $Q=30-70$ L/min for geometries G-A, G-B, and G-C described above (Table 1). Numerical convergence was achieved when all residuals (continuity, momentum, turbulence) were under $10^{-5}$.

A total of 40,000 particles were released instantaneously and uniformly from a surface situated 0.5 mm upstream from the powder loaded cylinders. The particles followed a size distribution equal to that of the free flowing budesonide (Pulmicort) powder according to the following distribution [1]:

$$ f(D) = (I / D_0) e^{-D/D_0} $$

To describe the increased aggregate breakage at higher volumetric flow rates during the powder release process the mean particle diameter was assumed to decrease linearly from $D_0 = 2.2 \mu m$ at $Q = 30$ L/min to 1.6 μm at 60 L/min according to:

$$ D_0 = 2.8 - 0.02 Q $$

where $D_0$ in μm and $Q$ in L/min [2].

RESULTS AND DISCUSSION

CFD simulations were performed with a range of different mouthpiece pressure drops, e.g., 1400-8800 Pa that correspond to steady volumetric flow rates of $Q=30-70$ L/min (Table 2). Steady state flow simulations were
Table 1. DPI geometries.

<table>
<thead>
<tr>
<th>Circulation chamber</th>
<th>G-A / circle</th>
<th>G-B / cap</th>
<th>G-C / square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conical cap</td>
<td>Conic Cap</td>
<td>Spherical Cap</td>
<td>Conic Cap</td>
</tr>
<tr>
<td>Helical section</td>
<td>Circular conduit</td>
<td>Circular conduit</td>
<td>Square conduit</td>
</tr>
</tbody>
</table>

Table 2. Steady flow rates for different applied pressure drops in the Turbuhaler DPI for three different geometries.

<table>
<thead>
<tr>
<th>Pressure Drop, Pa</th>
<th>Flow rate, L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A - circle</td>
</tr>
<tr>
<td>1800</td>
<td>26.76</td>
</tr>
<tr>
<td>2400</td>
<td>38.04</td>
</tr>
<tr>
<td>3600</td>
<td>48.00</td>
</tr>
<tr>
<td>6600</td>
<td>57.57</td>
</tr>
<tr>
<td>8000</td>
<td>70.74</td>
</tr>
</tbody>
</table>

Figure 2. Velocity magnitude, Q=60L/min. Geometries A, B and C, respectively.

previously found to provide excellent results for total deposition and fairly accurate results for the FPF. Both the G-B and G-C DPI geometries displayed slightly less flow resistance than the G-A geometry mostly at low flow rates. For example, the flow rate in G-C at ΔP=8800 Pa was increased by 8.3%.

In Figure 2 the velocity magnitudes are displayed for the three device geometries at Q=60L/min. It is clear that the flow in the inhalation channel is dominated by the two injection streams emanating from the powder loaded cylinders. The circulation chamber with the four additional flow inlets displays a more complicated flow pattern.

Strong tangential flow is developed in the helical section, leading to nonhomogeneous velocity profiles that persist through the mouthpiece extension up to the outlet surface. It should be noted that flow pattern differences are clearly observed in the circulation chamber of G-B and in the helical region of G-C.

In Figures 3 and 4 the deposited particles on the DPI surface for the three DPI geometries at volumetric flow rates of Q = 30 and 70L/min are shown. It is clear that the particle deposition patterns depend strongly on both the geometry and the volumetric flow rate. The deposition patterns in the circulation chamber are similar in geometries G-A and G-C but significantly different than geometry G-B. The larger hemispherical cap of geometry G-B affects
the flow patterns throughout the circulation chamber significantly leading to large differences in the deposition locations and patterns.

**Figure 3.** Deposited particles, $Q=30$L/min. Geometries A, B and C, respectively.

![Deposit](image1.png)

**Figure 4.** Deposited particles, $Q=70$L/min. Geometries A, B and C, respectively.

![Deposit](image2.png)

In Figures 5 and 6 the emitted particles from the mouthpiece outflow surface for the three DPI geometries at volumetric flow rates of $Q=30$ and 70L/min are shown. The positions of emitted particles for all geometries are strongly non-uniform, segregated in terms of particle size and weakly dependent on the volumetric flow rate. The outflow patterns of geometries G-A and G-B are fairly similar to each other but significantly different than the outflow pattern from geometry G-C. It is important to note that the outflow pattern from G-C is more spatially uniform and this may be a desirable feature for DPIs as the outflow patterns strongly affect the deposition patterns in the oropharyngeal region [5].

The total particle depositions in the DPI devices are shown in Figure 7. It is clear that both alternate geometries have decreased particle losses due to deposition in the device, and therefore increased emitted dose, for all flow rates but especially for the smaller flow rates. This is an important improvement as individuals how
are most in need of an adequate drug dose often possess impaired respiratory function and cannot apply sufficient pressure drop to generate large flow rates (e.g., 70L/min) where the DPIs function best. Geometry G-B (i.e., spherical capped circulation chamber) clearly has the least deposition.

**Figure 5.** Emitted particles, Q=30L/min. Geometries A, B and C, respectively

**Figure 6.** Emitted particles, Q=70L/min. Geometries A, B and C, respectively

**Figure 7.** Total particle deposition in the DPI device for three geometries.

**Figure 8.** Fine Particle Fraction in the DPI device for three geometries.
Table 3. Total deposition (DEP) and FPF for three different geometries of the Turbuhaler DPI.

<table>
<thead>
<tr>
<th>Geom</th>
<th>30 L/min</th>
<th>50 L/min</th>
<th>70 L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEP</td>
<td>FPF</td>
<td>DEP</td>
</tr>
<tr>
<td>A</td>
<td>48.30</td>
<td>18.73</td>
<td>29.66</td>
</tr>
<tr>
<td>B</td>
<td>15.21</td>
<td>29.20</td>
<td>7.96</td>
</tr>
<tr>
<td>C</td>
<td>35.90</td>
<td>21.95</td>
<td>23.89</td>
</tr>
</tbody>
</table>

In Figure 8 the emitted FPFs are shown for the three DPI geometries. The G-C geometry (i.e., square helical conduit) provided a small increase in emitted FPF compared to geometry G-A (except for Q = 40L/min). Geometry G-B (i.e., spherical capped circulation chamber) displayed a significant improvement in emitted FPF compared to the other two geometries. These increased emitted FPF values are important as the fine particles (i.e., Dp < 4 μm) penetrate easier to the upper respiratory region.

The results of deposition and FPF results of Figures 4 and 5 are summarized in Table 3. It is clear that both alternate geometries (i.e., B and C) display decreased total deposition and increased FPF with geometry B providing the largest improvements in terms of particle deposition and FPF.

CONCLUSIONS

A multi-scale CFD-based computational model developed in Milenkovic et al. [1,2] was employed to describe the particle deposition, FPF, and outflow in three different geometries of a DPI. The simulations for the commercial DPI (i.e., geometry G-A) were previously investigated in detail and validated against literature experimental data for particle deposition and FPF [1,2]. Based on the previous work it is expected that the simulations for the modified geometries (i.e., G-B and G-C) to be very accurate for particle deposition (e.g., Figure 7). The calculated FPFs, assuming steady state flow, were previously found to moderately underpredict the experimental results from ~20% at Q=30L/min to ~40% at Q=70L/min. Consequently, the FPF results of this work (e.g., Figure 8) should be considered qualitatively, i.e., with respect to the corresponding values of the geometry G-A.

Overall the simulations reveal that simple changes in one of the inhaler’s components can lead to improvements in the generated flow (e.g., up to 8%), significant improvements in the deposition (e.g., less than half the deposition) and very likely significant increases in the FPF (e.g., between 30-40%). It should be noted that the performance of the DPI (e.g., >30% FPF and <10% deposition) with the suggested simple modifications in component geometry (i.e., circular cap in the circulation chamber and/or square conduit cross-section in the helical section) would be a significant improvement over the currently available commercial devices and in fact competitive with the next-generation DPIs coming into market today.

REFERENCES