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Development and Comparison of New High Efficiency Dry Powder Inhalers for Carrier-Free Formulations

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Abstract

High efficiency dry powder inhalers (DPIs) were developed and tested for use with carrier-free formulations across a range of different inhalation flow rates. Performance of a previously reported DPI was compared with two new designs in terms of emitted dose (ED) and aerosolization characteristics using *in vitro* experiments. The two new designs oriented the capsule chamber (CC) at different angles to the main flow passage, which contained a 3D rod array for aerosol deaggregation. Computational fluid dynamics simulations of a previously developed deaggregation parameter, the NDSD, were used to explain device performance. Orienting the CC at 90° to the mouthpiece, the CC₉₀-3D inhaler provided the best performance with an ED=73.4%, fine particle fractions (FPF) less than 5μm and 1μm of 95.1% and 31.4%, respectively, and a MMAD=1.5μm. For the carrier-free formulation, deaggregation was primarily influenced by capsule aperture position and the NDSD parameter. The new CC-3D inhalers reduced the percent difference in FPF and MMAD between low and high flows by 1–2 orders of magnitude compared with current commercial devices. In conclusion, the new CC-3D inhalers produced extremely high quality aerosols with little sensitivity to flow rate and are expected to deliver approximately 95% of the ED to the lungs.

Keywords

high efficiency DPI; excipient enhanced growth (EEG) delivery; respiratory drug delivery; 3D rod array; PTFE coating; flow rate effects; multiple formulations; computational fluid dynamics (CFD); non-dimensional specific dissipation (NDSD); *in vitro* inhaler testing

INTRODUCTION

In the field of respiratory drug delivery, there is currently a need for high efficiency dry powder inhalers (DPIs).^{1–3} Current DPIs on the market have fine particle fractions (FPF) in the range of 10–70%,^{3,4} produce high mouth-throat (MT) depositional losses of approximately 30–95%,^{5–8} and have relatively low and variable lung delivery efficiencies.⁹ Considering conventional inhaled medications with wide therapeutic windows, use of these current devices is generally acceptable and provides a clinical benefit that typically outweighs the associated risks.^{1,10,11} However, systemic exposure to frequently prescribed corticosteroids has been associated with osteoporosis in the elderly, suppression of growth in children, suppression of adrenal activity, and vocal problems.^{4,12} High efficiency lung

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delivery of commonly prescribed medications to intended respiratory targets will reduce systemic exposure and decrease the associated side effects. Considering many envisioned next generation inhaled medications such as antibiotics, gene vectors, pain medications, and chemotherapy, the range of effective dosing is more narrow and side effects are more severe.^{1,11,13–15} For these medicines to be safely delivered, most current DPIs are insufficient and new high efficiency formulation and device combinations are needed.

The development of high efficiency DPIs faces a number of challenges. Most DPIs are passive devices, in which the patient's inspiratory effort is required to aerosolize the powder. Variability in inspiration characteristics commonly leads to differences in dose emission and the quality of the aerosol produced.^{2–4,16} For example, Prime et al.¹⁷ demonstrated a nearly 2-fold difference in the dose delivered from the Diskhaler (GSK, Raleigh, NC) and Turbuhaler (Astrazeneca, Sweden) between the flow rates of 30 and 90 LPM. In contrast, the Diskus (GSK, Raleigh, NC) device was less dependent on flow rate and produced a more consistent FPF;¹⁷ however, this device is reported to lose approximately 70% of the dose in the MT region.⁶ In volunteers using the Novolizer DPI (Meda, UK), Newman et al.¹⁸ demonstrated lung delivery efficiencies of approximately 20 and 32% for inhalation flow rates of 45 and 90 LPM, respectively, with MT deposition of approximately 60%. Improved emptying of the DPI device is typically achieved with higher flow rates,¹⁹ which also improves emitted dose reproducibility. However, higher flow rates are associated with increased MT deposition,²⁰ which leads to an additional source of variability in the lung delivery.⁹ It is noted that the complex relationship between device emptying, deaggregation or detachment from carriers, inhalation velocity, and MT deposition is influenced by the type of particle formulation with carrier-free powders behaving differently from powders with large carrier particles.

To maximize inhaler performance, some form of feedback to the patient is considered desirable with inhaler usage.² This can inform the patient that a correct inhalation flow rate was employed and that the dose was received. For example, capsule-based DPIs often provide a rattling sound when sufficient airflow is passed through the device. The Novolizer device has a visual cue to indicate when the dose is successfully delivered, which may have aided in the reduced intersubject variability reported in the *in vivo* study of Newman et al.¹⁸ This feedback may also improve compliance with following the prescribed regime of inhalation treatment.² A recent review of potential inhalation device innovations emphasized the need for DPI inspiratory independence, high respiratory dose efficiency, and patient friendly devices that may include feedback with correct usage.²

One potential pathway toward developing a high efficiency DPI is the use of excipient enhanced growth (EEG) technology. With this approach, the inhaler generates an aerosol from a submicrometer combination particle formulation composed of a drug and a hygroscopic excipient. The small size of the aerosol particles minimizes deposition in the device and extrathoracic airways. The particle size increases in the warm and humid lung environment due to the inclusion of a hygroscopic excipient and associated water uptake, resulting in lung deposition of the aerosol. Previous studies with spray generated aerosols and EEG delivery have demonstrated low MT deposition,²¹ the potential for significant size increase of the aerosol in the lungs,^{22–24} deposition of the droplets within airway models,²⁵ and the potential to target deposition to specific regions of the lungs.²⁵ Son et al.²⁶ previously developed an optimized EEG formulation for use with DPIs that contained albuterol sulfate (AS; model drug), mannitol (MN; model hygroscopic excipient), and L-leucine (dispersion enhancer). Use of a commercial capsule-based DPI with this formulation produced a FPF (%<5 μ m; FPF_{<5 μ m/ED}) of 95.3% and MT deposition in an established *in vitro* characteristic model of less than 5%. The study of Son et al.²⁷ implemented this optimized formulation and evaluated the effects of DPI design on the formation of

submicrometer aerosols and deposition in the MT model. The best performing device employed the capsule chamber of the HandiHaler (HH; Boehringer Ingelheim GmbH, Germany) and a novel 3D rod array to enhance deaggregation of the powder. The resulting HH-3D device produced an emitted dose (ED) of 74.2%, a mass median aerodynamic diameter (MMAD) of 1.1 μm , and less than 3% MT deposition.

Behara et al.²⁸ recently evaluated the effects of a new capsule chamber (CC) design on DPI performance for an EEG formulation. This study defined a high efficiency DPI for use with the EEG delivery approach as having an emitted dose of $\geq 75\%$, an aerosol MMAD of $\leq 1.5 \mu\text{m}$, which is expected to produce $<5\%$ MT deposition,^{26,27} and a $\text{FPF}_{<5\mu\text{m}/\text{ED}} \geq 90\%$. By introducing a new capsule chamber design along with the 3D rod array flow passage,²⁹ improved deaggregation of the EEG formulation was observed. Coating of the capsule with low surface energy PTFE was also shown to improve emitted dose. The resulting new high efficiency inhaler had an emitted dose of greater than 80% and produced an aerosol with an $\text{MMAD} = 1.3 \mu\text{m}$ and $\text{FPF}_{<5\mu\text{m}/\text{ED}} > 90\%$.

As described, the optimized EEG formulation of Son et al.²⁶ coupled with modified and new devices have produced high efficiency DPIs.^{27,28} However, further improvements are possible and additional testing is necessary. The high efficiency device developed by Behara et al.²⁸ required coating with PTFE to achieve $>80\%$ emitted dose. Previous studies have only tested high efficiency EEG DPI devices at a pressure drop of 4 kPa and flow rates of approximately 45 LPM.^{26–28} Furthermore, only one EEG formulation was previously considered for DPI administration. Ideally, a high efficiency DPI should perform well over a range of inhalation flow rates and for multiple formulations. The inclusion of visual feedback during correct usage would also be advantageous.

The objective of this study is to develop high efficiency DPIs that operate with combination particle EEG formulations and maintain performance at different flows and for different delivered medications. Three devices are initially considered, which are the previous CC₁-3D design of Behara et al.²⁸ and two versions of a new high efficiency DPI. This new design is intended to maximize emitted dose and increase turbulence in the 3D rod array to further improve deaggregation. Comparisons of the three devices are initially performed using computational fluid dynamics (CFD) simulations and a previously developed parameter that correlates with deaggregation of carrier-free formulations.²⁹ CFD estimates of inhaler performance are then verified with *in vitro* experiments and one of the two new devices is selected. The CC₁-3D device and new prototype are evaluated for aerosolization performance and emitted dose without and with PTFE coating. Device performance is then considered across a range of pressure drops and for two inhaled medications. Results are intended to further establish the viability of high efficiency DPI aerosol delivery using the EEG approach. Furthermore, the designs and analysis presented may also improve the performance of existing DPIs that employ conventional-sized aerosols.

MATERIALS and METHODS

Materials

Albuterol sulfate USP (AS) and terbutaline sulfate USP (TS) were purchased from Spectrum Chemical Co. (Gardena, CA). Pearlitol® PF-Mannitol (MN) was donated from Roquette Pharma (Lestrem, France). Poloxamer 188 (Leutrol F68) was donated from BASF Corporation (Florham Park, NJ). L-leucine and all other reagents were purchased from Sigma Chemical Co. (St. Louis, MO). Hydroxypropyl methylcellulose (HPMC) capsules (size 3) were donated from Capsugel (Morristown, NJ).

High Efficiency Inhaler Designs

The three DPI designs considered in this study are illustrated in Fig. 1. Each DPI employs the 3D rod array and flow passage geometry previously developed by Longest et al.²⁹ and implemented in the studies of Son et al.²⁷ and Behara et al.²⁸ This flow passage design was shown to maximize the non-dimensional specific dissipation (NDSD) parameter, which was proven to quantitatively correlate with deaggregation for a combination particle formulation across a series of eight inhalers evaluated at multiple flow rates.²⁹ Briefly, the NDSD parameter captures the relative effects of turbulent energy, inverse of the turbulent eddy length scale, and exposure time to turbulence, which each play a role in the deaggregation of carrier-free powders.²⁹

The inhalers considered in this study differ based on the capsule chamber (CC) design. The first device was developed in the study of Behara et al.²⁸ and orients the long axis of the capsule perpendicular to the incoming airflow (Fig. 1a). This DPI is referred to as CC₁-3D and includes metal rods in the 3D array, which were found to be more effective than plastic rods.²⁸ The previous study of Behara et al.²⁸ observed that perpendicular capsule alignment to incoming flow increased vibrational frequency compared with capsules aligned with the flow. Behara et al.²⁸ further showed that perpendicular alignment increased deaggregation and resulted in a smaller aerosol; however, this orientation also decreased capsule emptying. In contrast, aligning the capsule with the flow improved emptying but resulted in a small increase of MMAD. The new inhaler design employed in this study implements a capsule with the long axis aligned with the incoming airflow. The capsule chamber is positioned at an angle to the mouthpiece, and flow around this angle is intended to accelerate the airstream entering the 3D array and increase the NDSD,²⁹ thereby further improving aerosol deaggregation. This configuration has the added advantage of placing the capsule in view of the patient and raising the capsule when adequate flow is provided through the inhaler (Fig. 2). The capsule chamber is semicircular, which is intended to increase instability in the flow stream around the capsule and enhance the strength of capsule-to-wall impactions. Two versions of the new inhaler are considered that implement either a 90° (CC₉₀-3D; Fig. 1b) or a 45° (CC₄₅-3D; Fig. 1c) angle between the capsule chamber and flow passage. In both CC₉₀-3D and CC₄₅-3D, a single air inlet is located above the capsule chamber with a diameter selected to produce a flow rate of 45 LPM at a pressure drop of 4 kPa across the inhaler. This resistance is nearly equal to the CC₁-3D device with two air inlets, previously described by Behara et al.²⁸

The inhalers were created using Autodesk Inventor and exported as .STL files to be prototyped. The files were then prepared for prototyping using 3D Lightyear Software. The parts were built using a 3D Systems Viper SLA System (3D Systems Inc., Rock Hill, SC) using Accura 60 stereolithography resin (3D Systems Inc.). Once the parts were prototyped, they were cleaned using a Proclean SL Part Washer (3D Systems Inc.) and dried in a 3D Systems UV-light dryer for 90 minutes.

Preparation of Formulations

Excipient enhanced growth formulation combination particles were engineered as described by Son et al.²⁶ Briefly, a 20% ethanol in water solution containing 0.5 mg/ml of total solids concentration consisting of drug (AS or TS), MN, L-leucine and poloxamer 188 in a ratio of 30:48:20:2 (% w/w) was spray dried using a Büchi Nano spray dryer B-90 (Büchi Laboratory-Techniques, Flawil, Switzerland). The powder formulation was generated using an airflow rate of 120 LPM, 100% liquid flow rate using the 4 µm mesh nozzle diameter, and an air inlet temperature of 70°C. The resulting air outlet temperature and spray dryer pressure were 40°C and 35 mbar, respectively. Powder was collected from the electrostatic precipitator and was stored in a desiccator until it was used. The powder yield was about 50–

60%. Approximately 1 mg of powder was dissolved in 100 ml of deionized water and was analyzed for content uniformity (n=3) of AS or TS in the formulation using a validated HPLC method.

Aerosol Particle Size Characterization

To determine aerodynamic particle size distribution of the emitted aerosol, 2 mg of EEG formulation (AS formulation or TS formulation) was filled in a HPMC size 3 capsule and aerosolized into a next generation impactor (NGI; MSP Corp., Shoreview, MN) using the CC-3D inhalers at an airflow rate corresponding to a 4 kPa pressure drop across each device. In order to study the effect of flow rate, separate studies were performed using pressure drops of 2 and 6 kPa. Capsules were pierced using a custom capsule jig (Fig. 3a) with capsule aperture orientations shown in Figs. 3b–f. Optimization of capsule aperture orientation (CAO) is described in the Results. The powders were aerosolized until a total air volume of 4 L was drawn through the inhalers at ambient conditions.³⁰ All measurements were made with at least three replicates. The stages of the impactor were coated with silicone spray to minimize particle bounce and reentrainment. The powders were aerosolized with the DPI in a horizontal position; to assess the total aerosol size distribution, the USP induction port was not used. The NGI was placed in an upright position and a custom made rubber molded mouthpiece adaptor was used to connect the inhaler directly to the pre-separator. Based on images of similar powders reported in Son et al.,^{26,27} primary particle sizes of the spray dried powders were expected to be approximately 600 – 900 nm. After aerosolization, the drug retained in the capsule, CC, flow passage with 3D array, and collected on the pre-separator, impaction plates and the filter was extracted by washing with deionized water for quantitative HPLC analysis. The cut-off diameters of each stage at a specific airflow rate were calculated using the formula specified in the USP.³¹

Device Retention and Deposition

Emitted dose (ED) was calculated by subtracting the powder retained in the capsule, CC and flow passage from the loaded dose. The loaded dose was determined from the initial weight of the powder taken for aerosolization and percent of drug content in the AS or TS EEG formulations. Fine particle fraction (FPF) of the EEG formulation ($FPF_{<5\mu m/ED}$) and submicrometer FPF ($FPF_{<1\mu m/ED}$) were defined as the percent mass less than 5 μm and 1 μm , respectively, expressed as a % of the emitted dose. MMAD, $FPF_{<5\mu m/ED}$ and $FPF_{<1\mu m/ED}$ were calculated from linear regression equations resulting from cumulative percentage mass within the impactor vs. natural logarithm of the cut-off diameter for the respective NGI stages.

High-Speed Photography

The motion of the capsule inside of the chamber was analyzed using a Photron PCI R2 high-speed camera at 2000 frames per second. This helped to show the overall movement of the capsule as well as to determine the number of apparent chamber wall impactions per second. Rapid changes in capsule direction near the wall surface were assumed to be due to contact with the wall and counted as a capsule-wall impaction. The impactions were counted for a total of 1500 frames to determine the total number per second. Three videos were analyzed for each device and the average impactions per second were calculated from the data.

Surface PTFE Preparations

For some experiments, the capsule and device were coated with a commercial polytetrafluoroethylene (PTFE) suspension (LUTM708, SprayonTM Products, OH, USA), which is a high contact angle (or low surface energy) material.³² A suspension of PTFE was

sprayed inside the capsule, mouthpiece and CC to form a thin coating. Compressed air was blown through the coated portions until the surface appeared dry.

High-Performance Liquid Chromatography (HPLC)

Albuterol sulfate and terbutaline sulfate were analyzed using a modular HPLC system (Waters Co., Milford, MA) with a Restek Allure PFP 15×3.2 mm column (Bellefonte, PA) connected to a 2996 PDA detector. An absorption wavelength of 276 nm was used in conjugation with Empower Pro software (Waters Corporation, Milford, MA) for data acquisition and analysis. The column was maintained at 25°C. The analysis was conducted using isocratic analysis with 70:30 (%v/v) methanol-20 mM ammonium formate in water (pH adjusted to 3.4 with 90% formic acid) at a flow rate of 0.75 ml min^{-1} and an injection volume of 100 μl .

Statistical Analysis

In the current investigation, the data are expressed as the mean $\pm$ standard deviation based on a minimum three replications of each experiment. The statistical significance was carried out using one-way analysis of variance with Tukey's Post Hoc analysis and between the groups using independent sample t-test at a p-value of 0.05 using SPSS software (Version 21.0, SPSS, Inc., IL, USA).

CFD Simulations

Deaggregation of powders in the inhalers occurs as a result of both vibration of the capsule and interactions with turbulent flow structures, primarily in the 3D rod array. The capsule chamber can directly affect the vibrational frequency, strength, and wall impactions of the capsule. In addition, airflow in the capsule chamber will control inlet conditions to the 3D array and ultimately the amount of turbulence and deaggregation that occurs. The influence of upstream turbulence on particle motion, deaggregation, and deposition in inhalers was previously demonstrated in Longest and Hindle³³ and Coates et al.^{34–36} To evaluate the effects of airflow in the capsule chamber on flow through the DPIs including turbulence and predicted deaggregation, CFD simulations were conducted for each device. The inhaler geometries include the airflow inlets, capsule chambers, a size 3 capsule, and flow passage or mouthpiece with the 3D rod array. The air inlets of the inhaler were consistent with the experiments in each case. To conduct the CFD simulations in a reasonable amount of time, a fixed position of the capsule was assumed in the inhaler consistent with what appeared to be a time-averaged mean from the high speed video taken during inhaler activation. The 3D rod array consisted of a 5-6-5 pattern of 0.5 mm rods as previously described by Longest et al.²⁹ Computational grids were constructed using the mesh generator Gambit 2.4 (Ansys Inc., Canonsburg, PA). A mesh height of 0.085 mm was used on the rods in each geometry with a mesh growth ratio moving away from the rods of 1.2 and a maximum mesh dimension of 0.3 mm. Total grids for the CC₁-3D, CC₉₀-3D, and CC₄₅-3D geometries contained 2.32×10^6 , 2.28×10^6 , and 2.24×10^6 cells, respectively. Reducing the individual mesh densities by 30% had a negligible impact on key predicted parameters (maximum velocity and NDSD). As a result, grid convergence was established and results were reported for the higher resolution grids in all cases.

Flow conditions through all inhalers were assumed to be incompressible and isothermal with a steady state inlet volumetric flow rate of 45 LPM. The CFD package Fluent 12 (Ansys Inc., Canonsburg, PA) was employed to calculate the flow field and sample particle trajectories issuing from the capsule. Flow in the inhaler was turbulent and simulated with the two-equation Low Reynolds Number (LRN) $k-\omega$ model.³⁷ This approach has previously been used to establish successful correlations with inhaler performance based on turbulence metrics,³³ particle and droplet deposition,^{6,22,38,39} and powder deagglomeration.²⁹ Due to

the oscillatory nature of the flow field in the inhalers, transient simulations were required to develop converged solutions with a time step of 0.001 s and a simulation period of at least 0.5 s of flow.

Longest et al.²⁹ previously established a strong quantitative correlation between the non-dimensional specific dissipation (NDSD) parameter within an inhaler and the deaggregation of combination particle drug powders. This correlation was based on eight different inhaler types considered at multiple flow rates. Calculation of the NDSD parameter is presented in detail in Longest et al.²⁹ Briefly, this parameter captures the combined effects of turbulence energy, exposure time, and eddy size on aerosol deaggregation. It is different from previous deaggregation parameters based on the inclusion of exposure time, which enables the consistent prediction of deaggregation at multiple flow rates, and the hypothesis that small (not large) eddies are more efficient at breaking apart aggregates of small particles. In summary, volume-averaged values of NDSD strongly correlate with the deaggregation of combination particles.²⁹

In addition to flow field calculations, trajectories of 1 μm particles were also simulated in the inhaler to visualize the transport dynamics. The particles were released from a 0.5 mm aperture in the capsules and simulated through the flow field. To simulate particle trajectories, a Lagrangian model was implemented that accounted for drag, gravitational, and Brownian motion effects. To model the effect of turbulent fluctuations on droplet trajectories, or turbulent dispersion, a random walk method was implemented that included a previously described correction for near-wall anisotropic turbulence.³⁹ Deposition predictions of this model were previously shown to agree well with *in vitro* experiments for ambient aerosols, pharmaceutical sprays, and powders delivered from inhalers.^{6,38–40} A total of 1000 particles were used for flow field visualization and deposition of the particles was assumed to occur at initial wall contact.

In performing the CFD simulations, previously established best-practices were implemented to provide a high quality solution. All transport equations were discretized to be at least second order accurate. Convergence of the flow field solution was assumed when the global mass residual had been reduced from its original value by five orders of magnitude and when the residual-reduction-rates for both mass and momentum were sufficiently small. To improve accuracy and to better resolve the significant change in flow scales during deposition, all calculations were performed in double precision.

RESULTS

Effect of Capsule Aperture Orientation

The capsule aperture orientations (CAO) investigated in this study are presented in Fig. 3. Based on Fig. 1, the capsule air inlet aperture is at the top of the capsule nearest the air inlet orifice of the CC₉₀-3D inhaler. Cases 1, 2 and 3 had the capsule air inlet aperture at the same position (start of top curvature) but the air outlet aperture was in different locations (Fig. 3). The capsule was placed into the CC₉₀-3D inhaler such that the incoming air impinged directly on the head of the capsule. Case 1 CAO was previously used for the CC₁-3D inhaler from the study of Behara et al.²⁸ The drug (AS) deposition and the deaggregation efficiencies with three CAOs (Cases 1–3) are shown in Table 1 based on different air outlet apertures. Significant difference was only observed in relation to capsule ($p=0.037$; ANOVA) and CC ($p=0.009$; ANOVA) retention among the three piercings. Although significantly lower capsule retention was observed with Case 3 CAO ($p=0.043$; Tukey's Post Hoc), there was insignificant difference in ED observed between Cases 1 and 3 orientations as a result of significantly higher CC retention ($p=0.017$; Tukey's). Higher CC retention ($p=0.012$; Tukey's Post Hoc) was observed with Case 2 CAO compared to Case 1

CAO; insignificant differences in capsule and mouthpiece retentions were observed between Cases 1 and 2 resulting in similar emitted doses.

In terms of deaggregation efficiency ($FPF_{<5\mu m/ED}$, $FPF_{<1\mu m/ED}$, and MMAD), each of the capsule outlet orientations aerosolized the EEG-AS spray dried formulation equally well; however, Case 2 CAO showed the best mean EEG-AS formulation deaggregation with $FPF_{<5\mu m/ED}$, $FPF_{<1\mu m/ED}$ and MMAD of 95.0%, 31.7% and 1.48 μm , respectively. Based on this performance, the investigation was further focused on the Case 2 capsule air outlet aperture with different positioning of the capsule air inlet aperture.

Two additional CAOs are shown in Fig. 3 as Cases 4 and 5. The capsule and device retentions and the deaggregation efficiencies of these cases are presented in Table 2 compared with Case 2. Case 5 capsule air inlet aperture demonstrated significantly lower capsule retention compared to Case 2; which led to lower deaggregation efficiency possibly due to less powder residence time within the capsule.⁴¹ A clear trend in decreasing $FPF_{<1\&5\mu m/ED}$ and increasing MMAD was observed as the capsule air inlet aperture was moved to the top of the capsule. Based on improved performance in terms of deaggregation with no statistical decrease in ED, the remainder of the research was conducted with the Case 2 CAO for both the CC₉₀-3D and CC₄₅-3D inhalers. The CC₁-3D inhaler implemented the Case 1 CAO, based on the study of Behara et al.²⁸

CFD Comparison of Devices

Velocity fields are illustrated in Fig. 4 as contours of magnitude on multiple planes through the inhalers. The flow field is skewed to one side as it exits the mouthpiece, which is an effect of instability, and oscillates from side to side over time. In the 3D array, flow is accelerated between rods of the same row and then impinges on the rods in the next row. This cascading mechanism generates high turbulent energy and small eddies, both of which are captured by the NDSD parameter and lead to deaggregation of carrier-free powders.²⁹ In CC₁, an unstable flow pattern occurs around the capsule, which is responsible for the rocking motion previously observed in the experimental study of Behara et al.²⁸ For the CC₉₀ and CC₄₅ designs, the high velocity through the inlet induces a low pressure based on the Bernoulli principle. This low pressure pulls the capsule up in a manner that is flow rate dependent.

Elevated NDSD values are primarily found in the 3D array of each inhaler (Fig. 5). Flow around the capsules and near the walls provides a secondary source of NDSD. Comparing the contours in Fig. 5, it appears that the elevated NDSD values and regional distributions are very similar among the three inhalers. Volume-averaged NDSD quantities were also calculated within the flow passage and reported in Fig. 5. Based on these volume-averaged NDSD values, deaggregation is also expected to be very similar among the devices. Inhalers with the highest to lowest volume-averaged NDSD are CC₉₀-3D, CC₁-3D, and CC₄₅-3D. These NDSD results are compared with the MMAD as a deaggregation metric in the next section to determine the discriminating power of this parameter. It is noted that NDSD values at a flow rate of 45 LPM are slightly different from the previous predictions of Longest et al.²⁹ due to the inclusion of the CC in the computational model of the current study.

Trajectories of 1 μm particles are illustrated in Fig. 6 based on a single 0.5 mm release position located on the capsule. In all cases, the aerosol appears to spread and pass through a majority of the 3D array volume. Less trajectory recirculation is observed in the CC₉₀ and CC₄₅ capsule chambers, compared with CC₁, which may be associated with reduced CC deposition. However, these trajectory patterns are likely a function of particle release and

capsule positions. Little deposition is observed on the 3D rod array, which is the intent of these inhalers.

In Vitro Analysis of High Efficiency DPIs

The percent emitted doses and deaggregation characteristics of the DPI designs CC₁-3D (50 LPM), CC₉₀-3D (45 LPM) and CC₄₅-3D (43 LPM) at 4 kPa are presented in Table 3. Although CC₉₀-3D and CC₄₅-3D showed emitted doses of about 75%, CC₉₀-3D did not demonstrate significantly higher ED ($p=0.051$; Tukey's Post Hoc) compared with CC₁-3D (which had a value of 65%). While the MMAD of CC₉₀-3D was similar to CC₁-3D, the $FPF_{<1\mu m/ED}$ ($p=0.003$; Tukey's) and $FPF_{<5\mu m/ED}$ ($p=0.006$; Tukey's) were significantly higher for CC₉₀-3D when compared to the previously optimized design.²⁸ Insignificant difference was observed in deaggregation of submicrometer particles with the CC₄₅-3D design compared with the control (CC₁-3D). Both the $FPF_{<5\mu m/ED}$ ($p=0.017$; Tukey's) and MMAD ($p=0.031$; Tukey's) were higher with the CC₄₅-3D design compared with CC₁-3D.

The capsule impactions ($n=3$; mean $\pm$ SD) per second with the walls of the CCs were 284 ± 14 , 296 ± 27 and 288 ± 11 for CC₁, CC₉₀ and CC₄₅, respectively, based on the high speed photography measurements. While the numbers of capsule-wall impactions were similar between the designs ($p=0.754$; ANOVA), the deaggregation efficiencies between the designs were different, which is likely due to differences in the NDSD parameter as illustrated in the previous section. The deaggregation efficiency of a DPI not only depends on the number of capsule-wall impactions, but also on the flow field within the device.

As described, the NDSD has been proposed as a key metric in the deaggregation of combination particles.²⁹ Volume-averaged NDSD values were 174, 178 and 171 for CC₁, CC₉₀ and CC₄₅-3D, respectively (Fig. 5). Although different capsule chambers were used in this study, as the NDSD increased, MMAD decreased linearly (Fig. 7) with a strong coefficient of determination ($R^2=0.88$). Considering the lowest variability in deaggregation coupled with the best deaggregation performance, the investigation was further carried out comparing CC₉₀-3D with CC₁-3D.

Analysis of Emitted Dose

The effect of coating the walls of the device (CC₁-3D and CC₉₀-3D) and capsule with PTFE on ED and deaggregation efficiency is presented in Table 4. Insignificant differences were observed between CC₁ and CC₉₀ with coating in relation to $FPF_{<1\&5\mu m/ED}$. The ED was significantly higher ($p=0.028$; t-test) and MMAD was lower ($p=0.013$; t-test) for CC₁-3D compared to CC₉₀-3D when both were PTFE coated. However, both devices achieved emitted doses in the range of 80–85% and MMADs $< 1.5\ \mu m$.

Coating the CC₁-3D device did not alter $FPF_{<5\mu m/ED}$ (Tables 3 vs. 4). However, coating significantly improved the ED of CC₁-3D from 65% to 85% ($p=0.002$; t-test), $FPF_{<1\mu m/ED}$ from 29.2% to 31.8% ($p=0.002$; t-test) and MMAD decreased from 1.52 to 1.44 μm ($p=0.001$; t-test). The $FPF_{<5\mu m/ED}$ for CC₉₀-3D decreased from 95.1% to 93.4% as a result of coating. In contrast, PTFE coating (Table 4) did not influence the performance of CC₉₀-3D in ED ($p=0.081$; t-test), $FPF_{<1\mu m/ED}$ ($p=0.228$; t-test) and MMAD ($p=1.000$; t-test) compared to the uncoated CC₉₀-3D inhaler (Table 3). From Tables 3 and 4, it was observed that at 4 kPa, PTFE coating had little effect on the performance of CC₉₀-3D, which emitted approximately 75–80% of the loaded dose, but improved the performance of CC₁-3D, as previously observed by Behara et al.²⁸

Effects of Flow Rate

It is well known that the deaggregation behavior of passive dry powder inhalers relies on the patient's inspiratory effort.^{4,17,42} The current investigation further focused on the changes of deaggregation as a result of changes in air flow rates, which arise from different pressure drops over the inhaler. The deaggregation efficiency of AS with CC₁-3D was evaluated at 35 and 61 LPM and with CC₉₀-3D at 32 and 55 LPM. These flow rates correspond to pressure drops of 2 and 6 kPa across the devices, respectively. In general, both the devices performed well across the range of airflow rates investigated in this study (Table 5). The deaggregation efficiencies (Table 5) at 35 and 32 LPM (both corresponding to a pressure drop of 2 kPa) for CC₁ and CC₉₀, respectively, served as controls in this comparison.

Considering CC₁-3D, the ED and FPF_{<5μm/ED} ($p=0.015$ & $p=0.038$; ANOVA) were significantly higher while MMAD ($p=0.005$; Tukey's Post Hoc) was lower when aerosolized at 61 LPM vs. 35 LPM. The ED, FPF_{<5μm/ED} & MMAD were 61.0%, 91.3% & 1.63 μm at 35 LPM and 69.9%, 94.6% & 1.50 μm at 61 LPM respectively. Insignificant difference in FPF_{<1μm/ED} was observed between 35 and 61 LPM.

In the case of CC₉₀-3D, insignificant difference was observed in ED ($p=0.582$; ANOVA) across the airflow rates studied. Compared to aerosolization at 32 LPM, lower FPF_{<5μm/ED} and MMAD ($p=0.027$ and $p=0.007$; Tukey's Post Hoc) were observed at an aerosolization flowrate of 45 LPM; while decreased FPF_{<1μm/ED} and MMAD ($p=0.032$ and $p=0.005$; Tukey's Post Hoc) were observed when aerosolized at 55 LPM. While statistically significant, these differences were extremely small representing FPF changes of approximately 1% in value and MMAD changes of approximately 0.1 μm in value. As a result, the new inhalers, and particularly the CC₉₀-3D device appear to be insensitive to changes in flow rate for a pressure drop range of 2–6 kPa.

Comparing CC₁-3D vs. CC₉₀-3D at 2 kPa, CC₉₀-3D demonstrated higher ED ($p=0.001$; t-test). However, no difference was observed in ED at 4 and 6 kPa pressure drops between CC₁ and CC₉₀ ($p=0.067$ and 0.062 at 4 and 6 kPa, respectively; t-test). At 2 and 4 kPa pressure drop, CC₉₀-3D showed higher FPF_{<5μm/ED} ($p=0.014$ and $p=0.011$; t-test) & FPF_{<1μm/ED} ($p=0.012$ and $p=0.000$; t-test) and lower MMAD ($p=0.040$ and $p=0.008$; t-test) compared to CC₁-3D. At 6 kPa, significant ($p=0.020$; t-test) increase was observed only in the fraction of particles under 5 μm with CC₉₀-3D.

In general, the variability associated with both ED and deaggregation was lower with the CC₉₀-3D design compared to CC₁-3D. Overall, the CC₉₀-3D device demonstrated less airflow rate dependence on deaggregation and no statistical difference in ED across the airflow rates considered.

Effects of a New Formulation

From the above analysis, it is evident that although both the devices performed well, CC₉₀-3D required no PTFE coating in order to achieve approximately 75% ED. Also, CC₉₀-3D demonstrated very little airflow rate dependence and less variability in deaggregation characteristics across the airflow rates investigated. However, these results were demonstrated with only the AS EEG formulation. To expand the analysis, the comparison between CC₁-3D and CC₉₀-3D was also carried out with a TS EEG formulation at a 4 kPa pressure drop and the results are reported in Table 6. Clearly, no significant differences in ED, FPF_{<5μm/ED}, FPF_{<1μm/ED} and MMAD ($p=0.444$, $p=0.215$, $p=0.157$ and $p=0.126$; t-test) were observed between CC₁-3D and CC₉₀-3D. It was observed that the deaggregation values with TS (Table 6) were lower than with the AS formulation (Table 3); which was perhaps a result of differences in physicochemical properties between the drugs.

In comparison between AS and TS (Tables 3 vs. 6) at a 4 kPa pressure drop, although there was no significant difference in emitted doses with CC₁-3D ($p=0.056$; t-test) and CC₉₀-3D ($p=0.495$; t-test), the variability associated with CC₉₀-3D was always lower than with CC₁-3D.

DISCUSSION

A primary outcome of this study is the high aerosolization efficiency that was achieved with the CC₉₀-3D device. Based on previous studies employing EEG formulations,^{26,27,29} Behara et al.²⁸ defined high aerosolization efficiency DPI performance as producing an aerosol with MMAD $<1.5\ \mu\text{m}$, FPF_{<1 μm /ED} and FPF_{<5 μm /ED} 30% and 90%, respectively, and ED 75%. These criteria are intended to achieve $<5\%$ deposition in an adult MT geometry at standard DPI inhalation flow rates. Aerosol characteristics to achieve low extrathoracic depositional loss may be different for pediatric patients and for nose-to-lung aerosol delivery, which are also being considered for EEG DPI applications. The previous study of Behara et al.²⁸ indicated that the CC₁-3D inhaler met the high efficiency criteria when PTFE coating of the capsules and device was included. In the current study, the CC₉₀-3D inhaler achieved a MMAD $<1.5\ \mu\text{m}$, FPF_{<1 μm /ED} and FPF_{<5 μm /ED} of 95.1% and 31.4%, respectively, and ED = 73.4% without PTFE coating. In comparison with CC₁-3D, the improvement in ED provided by CC₉₀-3D (65.0 vs. 73.4%) was not statistically significant (Table 3). However from a practical perspective, increasing the ED by approximately 10% and generating a FPF near 95% represents a reasonable improvement in performance. Furthermore, the ED of the CC₉₀-3D inhaler appears to be sufficiently close to the 75% criterion. Therefore, the CC₉₀-3D device is considered to achieve high efficiency aerosolization without the need for capsule and device coatings. Additional advantages of this design include convenient loading of the capsule into the chamber and visual feedback when a sufficient inhalation flow rate is achieved. In the current CC₉₀-3D design, the capsule rises above the line shown in Fig. 2 at an inhalation flow rate of 25–30 LPM with a loaded powder mass of 2 mg. Alterations of the capsule chamber and air inlet may be required in order to tune capsule motion for lift-off at a higher flow rate or if the capsule contains a different powder weight.

While the CC₉₀-3D inhaler achieved the best overall performance without surface modification, coating the capsule and device improved performance of both CC₁-3D and CC₉₀-3D inhalers. Including PTFE coating, CC₁-3D achieved the highest ED (84.9%) and lowest MMAD (1.44 μm) of all inhalers tested in this study. Smaller improvements in performance were observed with PTFE coating of the CC₉₀-3D inhaler (Table 4). Performance improvements with PTFE coating likely arise from the low surface energy characteristics of the material.³² The PTFE coating improves capsule emptying due to reduced energy adhesion bonds between the powder and capsule walls. Similarly, powder deposition on the walls of the CC can potentially be dislodged easier from capsule-wall impactions when PTFE coating is used. Considering electrostatic forces, triboelectric charging is known to occur with pharmaceutical powders^{43,44} and is reduced when surfaces of the same material are separated compared with surfaces of different materials.⁴⁵ Therefore, coating both the capsule and CC with the same low surface energy material can reduce the buildup of electrostatic charge, which reduces an additional powder retention mechanism and allows the capsule to move more freely in the chamber.

In this study, CFD simulations provide an explanation of the observed differences in deaggregation efficiencies. The results indicate that the 3D rod array is the primary source of NDS in the flow stream. However, the strength of NDS in the 3D array, expressed as volume-averaged values, is influenced by the inlet conditions from the CC. By including a 90° bend in the flow field, higher turbulence levels enter the 3D array, which are then

further amplified resulting in efficient breakup of the combination particle aerosol. For a consistent pressure drop through the inhalers, the CC₉₀-3D model provides the highest volume-averaged NDS value and smallest MMAD. Comparisons between NDS values and MMAD for all three inhalers resulted in a linear relationship with a strong coefficient of determination ($R^2 = 0.88$). As a result, upstream conditions and inhaler design are shown to influence turbulence and deaggregation in the 3D array. Similar observations were previously made by Longest and Hindle³³ in which modifying the air inlet size at one end of a spray inhaler influenced outlet mouthpiece deposition by a factor of 1.5. Furthermore, the strong correlation between NDS and MMAD (Fig. 7) implies that turbulent eddy interaction with the powder in the flow stream is the primary source of deaggregation for a set capsule aperture orientation and the combination particle EEG formulation.

Aerosolization of powders in capsule-based devices is influenced by motion and vibration of the capsule for initial fluidization of the powder,^{28,46} airflow inside the capsule,⁴⁷ and deagglomeration of the aerosol powder in the airstream.^{29,36,48–50} Capsule impactions with the CC walls for the CC₁-3D, CC₉₀-3D, and CC₄₅-3D inhalers at a consistent pressure drop were not observed to correlate with deaggregation performance in terms of MMAD and FPF. Similarly, Behara et al.²⁸ observed that a large decrease in capsule-wall impactions, controlled by offset of the CC₁ inlets, was required to produce a statistically significant decrease in aerosolization performance. In contrast, piercing locations of the capsule were observed to significantly influence aerosolization performance in the current study (Tables 1 and 2). Therefore, it is proposed that above a lower limit, higher values of capsule-wall impactions may not improve aerosolization performance of combination particle formulations. In contrast, airflow through the capsule, controlled by location and size²⁸ of the capsule apertures, has a larger effect on deaggregation. The effects of capsule aperture orientation and capsule airflow on deaggregation is also supported by the previous study of Shur et al.,⁴⁷ where CFD simulations were conducted of inhalers and capsules including air flow inside the capsules. The degree of airflow inside a capsule and impaction velocity of carrier-based aerosols with wall surfaces were associated with differences in measured aerosol size distributions. Longest et al.²⁹ and the particle transport results presented in the current study demonstrate that particle-wall impactions are not a significant factor in the deaggregation of combination particle formulations employing submicrometer primary particles. Considering the available mechanisms for the deaggregation of the combination particles used in the CC-3D inhalers, it appears that air flow through the capsule, and, as described above, NDS generation in the 3D array control the size characteristics of the emitted aerosol. It is anticipated that this finding is true for most capsule and blister based devices used with combination particle powders.

As described, the dependence on achieving sufficient inhalation flow rate for powder delivery and dispersion is a significant limitation of most DPIs. Furthermore, the high flow rates required to deaggregate commercial DPI powders typically lead to excessive turbulence and deposition in the inhaler and MT. In contrast, the CC-3D DPIs explored in this study were found to be largely independent of flow rate. Some significant differences were observed in aerosolization performance for the CC-3D inhalers over the pressure drop range of 2–6 kPa. However, these differences appear small from a practical perspective. For example, the MMAD of CC₉₀-3D was observed to change from 1.54 to 1.48 μm across a pressure drop range of 2–6 kPa. This statistically significant difference represented a 0.06 μm change in MMAD, which will have only a minor influence on MT deposition. Overall, the CC₉₀-3D inhaler was more independent of flow rate than the CC₁-3D design. As an illustration, the ED from the CC₉₀ device did not change statistically for pressure drops ranging from 2–6 kPa.

Flow rate effects on aerosol performance are illustrated in Fig. 8 for the CC-3D devices compared with several commercial inhalers. Albuterol Diskus, Diskhaler, and Turbuhaler were previously evaluated by Prime et al.¹⁷ at set flow rates of 28 and 60 LPM. Salmeterol Diskus and Formoterol Turbuhaler were evaluated by Tarsin et al.⁴² using flow rates measured from 20 severe asthmatics. Variations in FPF and MMAD as a function of flow rate from these previous studies are compared with results of the CC-3D inhalers (Fig. 8). Considering FPF across the range of reported flow rates (Fig. 8a), values change by a percent difference of 30–70% in the Prime et al.¹⁷ data and 70–128% in the Tarsin et al.⁴² data. In contrast, FPF between flow rates of approximately 30–60 LPM changes by a percent difference of 3.5% for CC₁-3D and 0.2% for CC₉₀-3D. MMAD values at low and high flow rates change by 38–56% for the commercial products in the study of Tarsin et al.,⁴² and were not reported in the study of Prime et al.¹⁷ MMAD values for the CC₁-3D and CC₉₀-3D devices change by 8.3% and 4.0%, respectively, over a flow range of approximately 30–60 LPM. Different flow rates were used in all of the studies described above. However, these flow rates are consistent with inhaler usage and clearly indicate a trend in reduced sensitivity to flow rate with the CC-3D devices. Specifically, the percent difference in FPF and MMAD at low and high flow rates is reduced by 1–2 orders of magnitude with the CC-3D designs. It is noted that FPF was calculated differently in the three studies considered above (based on labeled vs. emitted dose). Modifying the results of Prime et al.¹⁷ and Tarsin et al.⁴² from a labeled to emitted dose basis would close the gap between the new devices and existing products in terms of FPF and MMAD values. However, it would not alter the relative changes that are reported as a function of flow rate displayed in Fig. 8.

The inhalers considered in this study provided excellent aerosolization efficiency, as a result of both formulation optimization²⁶ and device design. The reported FPFs were significantly higher than other reported devices.^{3,4} However, a critical question is whether the EEG formulation particles will increase in size by a sufficient amount to result in lung deposition and prevent exhalation of the submicrometer aerosol fraction. A number of previous EEG studies have evaluated condensational growth of combination drug and hygroscopic excipient particles to address this issue. Specifically, Longest and Hindle²⁴ developed a numerical model to predict the growth of combination drug and hygroscopic excipient particles in the lung airways with a residence time of approximately 2 s, which is consistent with a typical inhalation period. Model predictions indicated final to initial diameter growth ratios of 2.1–4.6 for a range of hygroscopic excipients with particle mass loadings of 50% and below combined with water soluble and insoluble drugs including the effects of limited available airway water vapor. Hindle and Longest²³ employed an *in vitro* coiled tube airway model to simulate aerosol exposure to respiratory thermodynamic conditions for a period of approximately 2 s. Submicrometer combination EEG particles were found to increase in size to the micrometer range with MMAD diameter growth ratios above 2 and as large as 4. The rate of droplet size increase could also be controlled by selection of the excipient and drug-excipient ratio. Longest et al.²² developed a CFD model of EEG growth in the coiled tube *in vitro* lung geometry. Prediction of aerosol growth matched the experiments to a high degree and demonstrated continuous growth of the aerosol for a majority of the 2 s exposure. Longest et al.²¹ reported concurrent *in vitro* and CFD results for an EEG aerosol formed from a RespiMat softmist spray inhaler delivering aerosol to a MT and upper tracheobronchial (TB) model designed to provide an approximate 2 s aerosol exposure time. Both the simulations and *in vitro* experiments reported <1% MT deposition and significant size increase of the aerosol with 900 nm AS:NaCl particles increasing to an MMAD greater than 3 μ m. Tian et al.²⁵ extended the CFD simulations throughout the TB airways and predicted initial submicrometer EEG particles increased in size to 5–6 μ m in the terminal bronchioles and increased the lower TB dose by 20–30 fold compared with conventional delivery devices. Son et al.²⁷ considered the growth and deposition of DPI EEG formulations in an *in vitro* MT and upper TB model simulating respiratory thermodynamic

conditions and demonstrated <3% MT deposition, MMAD increasing from approximately 1 μm to 3 μm , and a reduction of $\text{FPF}_{<1\mu\text{m}/\text{ED}}$ from 38.8% to 3%. In addition to significant particle size increase, these previous studies have also shown that maintaining MT deposition < 5% at typical inhalation flow rates can be achieved with an aerosol MMAD approximately 1.5 μm and that final aerosol droplet size is directly proportional to the initial size of the combination particles. As a result, aerosols with particles in the initial size range of approximately 900 nm - 1.5 μm can be considered optimal for delivering a high drug payload, minimizing MT deposition, and achieving a final MMAD of approximately 3 μm or greater after exposure to airway thermodynamic conditions.

With traditional fixed-particle-size inhalers, increasing the flow rate is expected to both reduce particle size and increase upper airway deposition due to impaction.⁶ However, these expected trends are based on particles that do not change size during transport through the respiratory tract. In contrast, results of this study indicate that the initial EEG particle size is largely independent of inhalation flow rate. Corresponding lung simulation results for EEG aerosols presented by Tian et al.²⁵ report that slower inhalation allows more time for the aerosol droplets to grow in the upper airways and promotes deposition in higher TB regions. In contrast, faster inhalation of EEG aerosols slows droplet growth and promotes penetration of the droplets to lower TB and alveolar spaces. Based on these observations, it can be concluded that EEG technology provides a new mechanism for targeting the deposition of inhaled medications that may not follow previously established assumptions associated with fixed particle sizes.²⁵

Limitations of the *in vitro* experiments employed in this study include the use of square-wave actuation profiles, evaluation of a single loaded dose weight (2 mg), and a relatively large size of the TS aerosol. The inhalers were actuated with a square inhalation waveform equal to the reported mean inhalation flow rates. For the relatively high resistance devices considered, a square waveform is a reasonable approximation. However, implementing measured inhalation waveforms may alter the aerosolization characteristics. Increasing the loaded dose may increase the ED considering that a certain amount of the formulation will likely adhere to the capsule walls. However, large increases in loaded dose may decrease capsule emptying. Finally, the CC-3D inhalers demonstrated high ED with the TS powder; however, the overall MMAD of the aerosol was around 2 μm . It may be necessary to optimize the spray drying conditions for TS as performed by Son et al.²⁶ with AS, to achieve a smaller MMAD.

Considering the CFD simulations, assumptions include a stationary capsule location without internal flow through the capsule, steady state inlet flow, and use of a two-equation turbulence model. The intent of the current CFD simulations was to evaluate the flow fields and NDS parameters in the inhalers for making relative comparisons. However, based on the findings of Shur et al.,⁴⁷ future simulations may include flow in the capsule as a second metric of deaggregation. It is expected that capsule motion does not strongly influence the overall turbulence characteristics of the device, but may influence airflow through the capsule. NDS values were evaluated for a constant steady state inlet flow. However, transient inhalation waveforms may affect these predictions and the MMAD of the aerosol. Finally, a two equation turbulence model was implemented to resolve the complex time-averaged turbulence characteristics of the flow field and particle dispersion. While these assumptions may have affected the calculated NDS values, it is expected that the relative predictions for each inhaler will remain largely unchanged with different model conditions and illustrate a similar association between NDS and MMAD.

Practical considerations for the use of the developed inhalers as commercial products include storage of the powder in HPMC capsules and coating of the devices with PTFE.

Considering the capsules, moisture ingress was not observed to be an issue over the course of the study. However, for long-term storage of the EEG powders, removable foil coverings of the capsules may be needed to seal out ambient humidity. PTFE coating was not observed to delaminate from the devices with the simple spray application method employed in this study. However, more advanced PTFE application methods or PTFE manufactured components could be used to prevent delamination if necessary. Furthermore, the CC₉₀-3D inhalers did not require PTFE coating for high efficiency performance.

CONCLUSIONS

The new DPIs considered in this study achieved high aerosolization efficiency performance with a previously optimized combination particle EEG formulation. The new CC₉₀-3D design met the criteria of producing a high efficiency aerosol without the need for surface modifications; however, coating the inhaler and capsule surfaces with PTFE improved the performance of both the CC₁ and CC₉₀ inhalers. Primary factors controlling aerosolization performance were determined to be airflow in the capsule, as controlled by the capsule aperture orientation, and particle interactions with turbulent flow, based on the NDSD parameter. CFD results revealed that the upstream CC could influence NDSD in the 3D array and the resulting MMAD of the aerosol. A strong linear correlation was identified between experimental measurements of MMAD and CFD prediction of NDSD. Aerosols produced by the new CC-3D devices were found to be largely independent of flow rate in the range of 2–6 kPa pressure drops. Specifically, the new devices reduced the percent difference in FPF and MMAD between low and high flows by 1–2 orders of magnitude compared with current commercial devices. Based on previous studies, the MT depositional losses of aerosols from the CC-3D inhalers are expected to be <5%^{26,27} with significant size increase of the particles within the lungs.^{23–25} Future studies are needed to evaluate the performance of the CC-3D inhalers in terms of loaded dose effects, realistic inhalation waveforms, intersubject variability in lung delivery, and *in vivo* performance.

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ABBREVIATIONS

3D	three-dimensional or three-dimensional rod array
AS	albuterol sulfate
CAO	capsule aperture orientation
CC	capsule chamber
CFD	computational fluid dynamics
DPI	dry powder inhaler
ED	emitted dose
EEG	excipient enhanced growth
FPF	fine particle fraction
HH	HandiHaler
HPLC	high-performance liquid chromatography

HPMC	hydroxypropyl methylcellulose
LPM	liters per minute
LRN	low Reynolds number
MMAD	mass median aerodynamic diameter
MN	mannitol
MT	mouth-throat
NDSD	non-dimensional specific dissipation
NGI	next generation impactor
PDA	photo diode array
PTFE	polytetrafluoroethylene
R²	coefficient of determination
SD	standard deviation
TB	tracheobronchial
TS	terbutaline sulfate

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Figure 1.

Dry powder inhalers (DPI) considered consisting of different capsule chambers (CC) coupled with the 3D rod array flow passage: (a) CC₁-3D with two air inlets and the capsule oriented perpendicular to the inlet airflow; (b) CC₉₀-3D with the capsule oriented parallel to the inlet airflow and a 90° angle between the CC and flow passage; and (c) CC₄₅-3D with a 45° angle between the CC and flow passage.

Figure 2.

The CC₉₀-3D inhaler with the capsule in the (a) loaded (no flow), and (b) in-use (45 LPM) position. A minimum flow rate of 25-30 LPM is required to elevate a capsule containing 2 mg of powder above the red line marked in the capsule viewing window.

Figure 3.

Capsule piercing jig (Fig. 3a) and capsule aperture orientations (CAO; Fig. 3b–f) for optimizing performance in the CC₉₀-3D inhaler. The head (H) and base (B) of the capsule are marked in Panel a. To pierce the capsule, it was placed in the jig and 0.5 mm pins were inserted through small open holes to provide the correct CAO.

Figure 4. CFD predictions of velocity fields at a flow rate of 45 LPM for the (a) CC₁-3D, (b) CC₉₀-3D, and (c) CC₄₅-3D inhalers. Panels (b) and (c) include midplane views of the flow passage as observed from the top of the inhaler.

Figure 5. CFD predictions of non-dimensional specific dissipation (NDSD) contours at a flow rate of 45 LPM for the (a) CC₁-3D, (b) CC₉₀-3D, and (c) CC₄₅-3D inhalers. Panels (b) and (c) include midplane views of the flow passage as observed from the top of the inhaler. NDSD values reported are volume averages taken over the flow passage.

Figure 6.

CFD predictions of particle trajectories emitted from a single 0.5 mm capsule aperture and passing through the (a) CC_1 -3D, (b) CC_{90} -3D, and (c) CC_{45} -3D inhalers operated at a steady flow rate of 45 LPM. Trajectories are colored based on local velocity.

Figure 7.

Comparison of experimentally determined MMAD vs. CFD predicted NDSD. The dashed line represents a linear best fit to the data, which produced a correlation coefficient of $R^2 = 0.88$. The error bars represent $\pm$ one standard deviation in the experimental results of MMAD. The NDSD parameter provides a good prediction of emitted aerosol size for the carrier-free formulation even though the devices employ different capsule chambers and the capsules have different vibrational frequencies and patterns of motion.

Figure 8.

Comparison of flow rate effects for the CC-3D inhalers and previously reported commercial products in terms of (a) FPF_{<5μm} and (b) MMAD. Salbutamol Diskus, Diskhaler, and Turbuhaler were considered in the study of Prime et al.¹⁷ at flow rates of 28-60 LPM. Salmeterol Diskus and Formoterol Turbuhaler were considered by Tarsin et al.,⁴² and the illustrated line represents the reported linear best fit of the data.

Table 1

The effect of capsule air outlet aperture orientation on the mean AS deposition and aerosolization performance for three different cases as presented in Fig. 3 (Cases 1–3) when dispersed using CC₉₀-3D tested at a 4 kPa pressure drop. Standard deviation is shown in parenthesis [n=3].

Description	Case 1	Case 2	Case 3
Emitted dose (%)	72.3 (3.3)	72.5 (3.1)	72.3 (1.7)
Capsule retention (%) *	9.4 (0.4)	7.9 (0.5)	7.6 (1.0) **
Capsule chamber retention (%) *	9.1 (1.6)	13.0 (0.4) **	12.7 (0.9) **
Mouthpiece retention (%)	9.2 (1.9)	6.7 (3.9)	7.4 (2.3)
FPF _{<5µm/ED} (%)	91.0 (3.3)	95.0 (0.1)	94.5 (0.2)
FPF _{<1µm/ED} (%)	28.1 (3.5)	31.7 (1.3)	30.4 (0.4)
MMAD (µm)	1.57 (0.09)	1.48 (0.04)	1.52 (0.01)

* $P < 0.05$ significant effect of capsule aperture orientation on % capsule & capsule chamber retentions (one-way ANOVA).

** $P < 0.05$ significant difference compared to Case 1 orientation as shown in Fig. 3 (post hoc Tukey).

Table 2

The effect of capsule air inlet aperture orientation on the mean AS deposition and aerosolization performance for three different cases as presented in Fig. 3 (Cases 2, 4 and 5) when dispersed using CC₉₀-3D tested at a 4 kPa pressure drop. Standard deviation is shown in parenthesis [n=3].

Description	Case 2	Case 4	Case 5
Emitted dose (%)	72.5 (3.1)	68.4 (2.7)	71.0 (1.0)
Capsule retention (%) *	7.9 (0.5)	7.9 (0.6)	6.2 (0.7) **
Capsule chamber retention (%)	13.0 (0.4)	14.5 (2.2)	15.8 (0.7)
Mouthpiece retention (%)	6.7 (3.9)	9.2 (4.6)	7.1 (1.1)
FPF _{<5μm/ED} (%) *	95.0 (0.1)	94.2 (1.9)	90.8 (0.7) **
FPF _{<1μm/ED} (%) *	31.7 (1.3)	28.2 (2.4)	20.9 (1.2) **
MMAD (μm) *	1.48 (0.04)	1.57 (0.05)	1.75 (0.03) **

* $P < 0.05$ significant effect of capsule aperture orientation on % capsule retention, FPF_{<5μm/ED}, FPF_{<1μm/ED} and MMAD (one-way ANOVA).

** $P < 0.05$ significant difference compared to Case 2 orientation as shown in Fig. 3 (post hoc Tukey).

Table 3

The effect of powder inhaler design on the mean AS deaggregation performance when aerosolized at a 4 kPa pressure drop. Standard deviation is shown in parenthesis [n=3].

Description	CC ₁ -3D	CC ₉₀ -3D	CC ₄₅ -3D
Emitted dose (%) [*]	65.0 (4.1)	73.4 (4.1)	75.7 (0.4) ^{**}
FPF _{<5μm/ED} (%) [*]	91.4 (1.4)	95.1 (0.2) ^{**}	94.3 (0.6) ^{**}
FPF _{<1μm/ED} (%) [*]	29.2 (0.2)	31.4 (0.1) ^{**}	28.3 (0.8)
MMAD (μm) [*]	1.52 (0.01)	1.49 (0.00)	1.57 (0.02) ^{**}

^{*} $P < 0.05$ significant effect of inhaler design on % emitted, FPF_{<5μm/ED}, FPF_{<1μm/ED} and MMAD (one-way ANOVA).

^{**} $P < 0.05$ significant difference compared to CC₁-3D (post hoc Tukey).

Table 4

The effect of PTFE coating on emitted dose and deaggregation efficiencies of AS when aerosolized at a 4 kPa pressure drop. Standard deviation is shown in parenthesis [n=3].

Description	CC ₁ -3D	CC ₉₀ -3D
Emitted dose (%)	84.9 (2.0)	79.5 (2.1) *
FPF _{<5μm/ED} (%)	93.4 (0.6)	93.4 (0.1)
FPF _{<1μm/ED} (%)	31.8 (0.6)	31.9 (0.7)
MMAD (μm)	1.44 (0.01)	1.49 (0.02) *

* $P < 0.05$ significant difference in % emitted and MMAD (independent samples t-test).

Table 5

The effect of airflow rate on aerosolization of AS using CC₁-3D and CC₉₀-3D designs. Standard deviation is shown in parenthesis [n=3].

Description	CC ₁ -3D		CC ₉₀ -3D	
Air flow rate (LPM)	35	50	61	55
Pressure drop (kPa)	2	4	6	6
Emitted dose (%) [*]	61.0 (1.4)	65.0 (4.1)	69.9 (1.2) ^{**}	73.2 (1.9)
FPF _{<5μm/ED} (%) ^{^A}	91.3 (1.7)	91.4 (1.4)	94.6 (0.3) ^{**}	95.1 (0.2) ^{**}
FPF _{<1μm/ED} (%) ^{^A}	27.1 (1.7)	29.2 (0.2)	28.6 (1.2)	30.0 (0.7) ^{**}
MMAD (μm) ^{^A}	1.63 (0.04)	1.52 (0.01) ^{**}	1.50 (0.03) ^{**}	1.48 (0.02) ^{**}

^{*} $P < 0.05$ significant effect for CC₁-3D of air flow rate on % emitted, FPF_{<5μm/ED}, FPF_{<1μm/ED} and MMAD (one-way ANOVA).

[^] $P < 0.05$ significant effect for CC₉₀-3D of air flow rate on FPF_{<5μm/ED}, FPF_{<1μm/ED} and MMAD (one-way ANOVA).

^{**} $P < 0.05$ significant difference compared to 35 LPM with CC₁-3D and 32 LPM with CC₉₀-3D, respectively (post hoc Tukey).

Table 6

The aerosolization efficiency of CC₁ and CC₉₀ designs with TS at a 4 kPa pressure drop. Standard deviation is shown in parenthesis [n=3].

Description	CC ₁ -3D	CC ₉₀ -3D
Emitted dose (%)	73.4 (3.6)	75.2 (0.6)
FPF _{<5μm/ED} (%)	88.6 (0.8)	89.4 (0.5)
FPF _{<1μm/ED} (%)	14.6 (1.2)	12.0 (2.3)
MMAD (μm)	1.93 (0.04)	2.01 (0.06)