Development of an Inline Dry Powder Inhaler That Requires Low Air Volume

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Abstract

Background: Inline dry powder inhalers (DPIs) are actuated by an external air source and have distinct advantages for delivering aerosols to infants and children, and to individuals with compromised lung function or who require ventilator support. However, current inline DPIs either perform poorly, are difficult to operate, and/or require large volumes (~ 1 L) of air. The objective of this study was to develop and characterize a new inline DPI for aerosolizing spray-dried formulations with powder masses of 10 mg and higher using a dispersion air volume of 10 mL per actuation that is easy to load (capsule-based) and operate.

Methods: Primary features of the new low air volume (LV) DPIs are fixed hollow capillaries that both pierce the capsule and provide a continuous flow path for air and aerosol passing through the device. Two different configurations were evaluated, which were a straight-through (ST) device, with the inlet and outlet capillaries on opposite ends of the capsule, and a single-sided (SS) device, with both the inlet and outlet capillaries on the same side of the capsule. The devices were operated with five actuations of a 10 mL air syringe using an albuterol sulfate (AS) excipient-enhanced growth (EEG) formulation. Device emptying and aerosol characteristics were evaluated for multiple device outlet configurations.

Results: Each device had specific advantages. The best case ST device produced the smallest aerosol [mean mass median aerodynamic diameter (MMAD) = $1.57\ \mu\text{m}$; fine particle fraction $<5\ \mu\text{m}$ (FPF $_{<5\ \mu\text{m}}$) = 95.2%] but the mean emitted dose (ED) was 61.9%. The best case SS device improved ED (84.8%), but produced a larger aerosol (MMAD = $2.13\ \mu\text{m}$; FPF $_{<5\ \mu\text{m}}$ = 89.3%) that was marginally higher than the initial deaggregation target.

Conclusions: The new LV-DPIs produced an acceptable high-quality aerosol with only 10 mL of dispersion air per actuation and were easy to load and operate. This performance should enable application in high and low flow mechanical ventilation systems and high efficiency lung delivery to both infants and children.

Keywords: active DPI, high efficiency DPI, inline DPI, nose-to-lung aerosol delivery, pediatric aerosol delivery

Introduction

INLINE DRY POWDER INHALERS (DPIs) are actuated by a stream of gas that is passed through the device from an external positive pressure source.^(1–4) These devices are useful for generating and delivering an aerosol to patients that may not be able to use a DPI such as children younger than approximately 5 or 6 years.^(5–7) The positive pressure gas source can be used to assist with deep inspiration and help maintain a breath hold in individuals with compromised lung function. This deep positive pressure inspiration may enable the aerosol to penetrate further into the lungs compared with negative pressure inhalation through a high resistance device. Inline DPIs can be connected directly into both noninvasive and in-

vasive mechanical ventilation systems allowing for the simultaneous delivery of respiratory gas support and therapeutic aerosols.^(2,4,8–10) Furthermore, inline DPIs are frequently used to deliver test aerosols to animals when evaluating the safety and efficacy of inhaled medications.^(11,12)

Based on the ability to deliver a positive pressure breath, inline DPIs have previously been proposed as stand-alone devices to deliver respiratory therapies to children. For example, Manion et al.⁽¹³⁾ proposed the Puffhaler™, which consists of a squeeze bulb, burst valve, blister powder storage, and reservoir mask. With spray-dried formulations, fine particle fractions (FPF) less than $5.8\ \mu\text{m}$ were 40%–60% and emitted dose (ED; as a percentage of loaded mass) was near 50%, with a majority of the aerosol lost in the

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optimized reservoir bag. Laube et al.⁽⁷⁾ reported use of the Solovent™ inline DPI that consists of an air syringe positive pressure gas source, capsule, spacer, and mask. With the Solovent connected directly to an infant nose-throat model and delivering air volumes of 50–200 mL, the percent of loaded drug found on the throat filter (which approximates lung delivery) was 0.28%–3.87%, with the majority of drug lost in the spacer reservoir. These findings indicate that a reservoir or spacer should be avoided if possible when delivering aerosols to children using inline DPIs. Hence, the aerosol should be generated very quickly during inhalation and require a much smaller volume of air for effective aerosolization.

The PennCentury™ DP-4 Dry Powder Insufflator is an inline DPI that has been used for over a decade to deliver aerosols to test animals and cell cultures. For the widely used mouse and rat PennCentury devices, the loaded dose is in the range of 1–5 mg of powder and recommended air volumes are 0.2 and 2 mL, respectively. Aerosolization performance depends on a wide range of factors, including the formulation, loaded mass, and air volume.^(12,14) For spray-dried formulations under optimal conditions, device retention is approximately 20% and emitted mass median aerodynamic diameters (MMAD) of mannitol powder approach values achieved by specialized lab testing equipment such as the Sympatec RODOS dispersion unit.⁽¹⁴⁾ Inclusion of a drug molecule such as tobramycin in the spray-dried formulation increases the PennCentury MMAD by a factor of approximately two compared with RODOS dispersion. Loading of the PennCentury device requires a small spatula and can be time consuming, highlighting the laboratory testing intent of this design. Furthermore, variability in performance increases as loaded dose increases beyond 1 mg.⁽¹⁴⁾

Studies of inline DPIs intended for human use have reported the delivery of albuterol sulfate (AS),^(3,15) mannitol,⁽²⁾ budesonide,^(1,16) surfactants,⁽¹⁷⁾ and various antibiotics.^(9,13) Tang et al.⁽²⁾ placed the Osmohaler DPI in an airtight container that enabled actuation with a manual ventilation bag and was connected to a straight endotracheal tube (ETT). The manual ventilation bag was used to generate peak flow rates in the range of 87–133 L/min (LPM) to aerosolize high dose capsules containing 40–80 mg of mannitol powder (Aridol™). Delivery efficiency to the distal end of the ETT was 50%–60% of the loaded dose and the associated MMAD was approximately 7 μ m. Based on this study, it appears that very high flow rates (~100 LPM) and large air volumes (multiple squeezes of an adult ventilation bag) are required to aerosolize high doses of powder.

For high dose surfactant aerosol delivery, Pohlmann et al.⁽¹⁷⁾ recently presented a design that passed pulses of air directly through a powder bed. Using pressure pulses consisting of 10–30 mL of air and a spray-dried surfactant formulation, high masses of powder could be aerosolized producing aerosols in the range of 3–3.5 μ m. These findings indicate that passing controlled volumes of air directly through a powder reservoir can effectively aerosolize a highly dispersible spray-dried formulation. However, the air delivery system of Pohlmann et al.⁽¹⁷⁾ appears complex and, as stated by the authors, the very high masses of aerosol require humidity to coat the particles with water before inhalation. Delivery efficiency to the end of a conducting tube and before nasal prongs was 55% of the aerosolized dose.⁽¹⁷⁾

Our group has recently developed a new inline DPI consisting of a flow control orifice, capsule chamber and three dimensional (3D) rod array.⁽³⁾ As described in Longest et al.,⁽¹⁸⁾ the 3D rod array maximizes aerosol deaggregation compared with other approaches for a set amount of input power by maximizing turbulent energy in the small turbulent eddies. The inline DPI is powered by a manual ventilation bag and the flow rate through the device is controlled by the orifice size. For a spray-dried excipient enhanced growth (EEG) formulation^(19,20) of AS, a device with a 2.3 mm flow control orifice and 3-4-3 rod array pattern (2.3–343 inline DPI) produced a flow rate of only 10 LPM with ED (as a percentage of loaded dose) and MMAD values of approximately 75% and 1.6 μ m.⁽³⁾ Longest et al.⁽⁹⁾ considered a spray-dried formulation of ciprofloxacin in the same device and reported an ED from a streamlined nasal cannula⁽²¹⁾ of approximately 70% with an MMAD of 1.4 μ m. Based on the EEG approach, the nasal deposition was <2% leading to high efficiency nose-to-lung (N2L) aerosol delivery. In the conference publication of Longest et al.,⁽¹⁵⁾ we reported a device with a 2.0 mm flow control orifice and 2-3-2 rod array pattern (2.0–232 inline DPI) that aerosolized AS at a flow rate of only 5 LPM for use with low flow nasal cannula oxygen.

Advantages of the previously developed 3D rod array inline DPI include high ED and excellent deaggregation.^(3,9,15) The capsule-based platform makes the device easy to load. Due to the use of the flow control orifice, the device is not sensitive to bag pressure above a nominal amount. However, as flow rate is reduced to 5 LPM and below, it becomes increasingly difficult to achieve an MMAD near 1.5 μ m,⁽¹⁵⁾ which is desirable for high efficiency nose-to-lung aerosol delivery and use of the EEG approach. The typical air volume for each of these devices was 1 L per actuation. Furthermore, performance is dependent upon capsule piercing pattern,⁽³⁾ and capsule piercing can be difficult inside a positive pressure device. Finally, higher masses of powder become more difficult to aerosolize at lower flow rates.

There appears to be a need for an inline DPI device that can aerosolize relatively large (10 mg and above) masses of spray-dried powder formulations using very low dispersion air volumes (~10 mL per actuation). High powder masses are required for the aerosol delivery of most antibiotics, surfactants, nonsteroidal anti-inflammatories, and many biopharmaceuticals. These high doses are required in adults and children, where, for example, Morley et al.⁽²²⁾ delivered 25 mg capsules of dry powder surfactant to preterm infants with respiratory distress syndrome. Low dispersion air volume through the device enables application in both high flow and low flow settings. A 10 mL air volume is viewed as the upper end of ventilation that can be delivered to a late preterm infant.^(23–25) Furthermore, injection of 10 mL of air should not interfere with most noninvasive or invasive mechanical ventilation systems. The inline DPI device should be airtight and operate on positive pressure to allow connection to mechanical ventilation systems or sealed patient interfaces like streamlined nasal cannula^(21,26) or a face mask.⁽⁴⁾ Importantly, the device should be easy to load and minimize usage steps.⁽²⁷⁾

The objective of this study is to develop and characterize a new inline DPI for aerosolizing spray-dried formulations with powder masses of 10 mg and higher using an air volume of 10 mL per actuation. The device will be developed

FIG. 1. Axial cross section of the assembled ST device showing the inlet and outlet capillaries inside of the capsule. ST, straight-through.

based on knowledge gained from our previous work with high efficiency DPIs^(3,9,28,29) and rapid screening using 3D printing technology. *In vitro* aerosol experiments will be used to determine regional device retention, ED and to characterize the aerosol. Initial device performance will be based on 10 mg powder loading, and, for a lead design, a significantly higher powder mass will be tested. Aerosol plume size will also be assessed to aid in future incorporation of the device into positive pressure systems with low depositional losses. High efficiency performance is expected based on our previous DPI experience.^(3,9,28,29) Specifically, high efficiency performance for the delivery of EEG formulations will be defined by the production of an aerosol with the following characteristics: an MMAD of less than 1.5 μm , FPF less than 5 μm as a percentage of ED (FPF_{<5 μm /ED}) above 90%, FPF_{<1 μm /ED} above 30%, and an ED greater than 75%. The challenge is, clearly, to now achieve this level of DPI performance with a device that requires only 10 mL of dispersion air per actuation and is easy to load and operate.

Materials and Methods

Overview

In contrast with our previous inline DPIs that are intended to operate with relatively high dispersion air volumes,^(3,9) the low air volume (or LV) devices developed in this study pass all of the available airflow through a capsule dose containment unit. The air source is a simple syringe connected via a luer lock fitting and filled with 10 mL of room air that is operated manually. Based on experiments with a number of preliminary concepts, the two leading LV designs are presented as Figures 1 and 2, respectively. A common feature in both devices is that metal capillary tubes pierce the capsule when the device is closed, forming an airtight flow path through the device. In one design, the airflow pathway is in a single direction, or straight through (ST) the capsule and device (Fig. 1). In the second design, the capillary-based inlet and outlet are on a single side (SS) of the capsule, resulting in a near 180-degree turn in the airflow path. In both designs, the outlet capillary directs aerosol through a flow channel with a final diameter of 7 mm. These two leading designs are optimized and compared in this study based on modifications to the inlet and outlet capillary properties. To improve dispersion of the 10 mg powder mass, we also introduce the concept of a dispersion ball placed inside the capsule. Use of a

lightweight polytetrafluoroethylene (PTFE) dispersion ball is expected to create vibrational motion as observed in Farkas et al.⁽³⁰⁾ to enhance capsule emptying. As a representative EEG formulation, the new inline DPIs are tested with a previously described^(19,31) EEG formulation of AS. Using this formulation, previous inline DPIs have produced MMAD values as low as 1.47 μm with an ED value of 78.2% using high dispersion air volumes with approximately 1 L of air per actuation. The primary particle size of the EEG formulation is tested using a Sympatec (Sympatec GmbH, Clausthal-Zellerfeld, Germany) laser diffraction system with a RODOS aerosol dispersion accessory, which uses a pressure drop of 4 bar (400 kPa) to disperse a small amount of the powder. Aerosol characterization from the devices is based on drug quantification using high performance liquid chromatography (HPLC) analysis of the various DPI components to determine the ED and by cascade impaction using the Next Generation Impactor (NGI), to determine the FPF and MMAD. Further details of the devices, formulation, and characterization studies are provided in the following sections.

Materials

Albuterol sulfate (AS) USP was purchased from Spectrum Chemicals (Gardena, CA) and Pearlitol® PF-Mannitol was donated from Roquette Pharma (Lestrem, France). Poloxamer

FIG. 2. Axial cross section of the assembled SS device showing the inlet and outlet capillaries inside of the capsule. SS, single-sided.

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). Quali-V, Hydroxypropyl methylcellulose capsules (size 0) were donated from Qualicaps (Whitsett, NC).

Spray-dried AS EEG formulations were produced using the optimized method described by Son et al.⁽¹⁹⁾ Three batches of spray-dried formulations were employed for these studies. The primary particle size for each of the spray drying batches was determined using a laser diffraction method with a Sympatec ASPIROS/RODOS dry dispersing unit and HELOS laser diffraction sensor.

Inhaler design

Both inhaler designs (ST and SS) are opened at approximately midway the capsule chamber, the capsule is loaded into one of the halves, and the capillaries pierce the capsule when the device is reassembled. A bayonet fitting and o-rings have been employed to ensure an airtight seal in the capsule chamber. Both inhaler designs investigated in this study use a standard luer-lock to connect the syringe to deliver dispersion air through a single 0.6 mm inlet capillary and into a size 0 capsule that has a volume of 0.68 mL. The capillary remains in place during dispersion as the air inside of the syringe is forced through the capillary into the powder bed within the capsule. The powder is entrained and is carried through the outlet capillary configuration. Designs of the outlet capillaries are shown in cross section (to scale with respect to each other) in Figure 3. The ST design, shown in Figure 1, is designed with the inlet and outlet capillaries on opposite ends of the capsule, both centered on the capsule's longitudinal axis. The SS design, shown in Figure 2, is oriented with both the inlet and outlet capillaries piercing through the head of the capsule. The capillaries of the SS design are angled at ~ 8 degrees toward the centerline of the longitudinal axis of the capsule, so that the capillary central axes intersect halfway between the middle and the bottom of the capsule. This angle was selected to increase turbulent dispersion within the capsule.

The inhaler designs were created using Autodesk Inventor and exported as .STL files to be prototyped. The files were then prepared using Objet Studio preparation software and were built using a Stratasys Objet24 3D Printer (Stratasys Ltd., Eden Prairie, MN) using VeroWhitePlus material. Support material was cleaned away from the model material using a Stratasys waterjet cleaning station and the devices were allowed to fully dry before use. The capillaries used in the devices were custom cut from lengths of stainless steel (SAE 304) capillary tubing and were angled on one side to allow for easy piercing of the capsule upon insertion. The

capillaries were then secured into place using water-resistant epoxy and allowed to cure fully before use. It is noted that the sharpened capillaries are sufficiently recessed inside the capsule chamber of the device to facilitate safe operation.

Evaluation of LV devices

Aerosolization performance of the LV-DPIs was characterized using 10 mg of EEG-AS powder formulation, which was accurately weighed and manually filled into size 0 capsules. This mass of powder filled $\sim 3\%$ of the capsule volume. Capsules were then placed in one half of the LV-DPI device and the capsule was pierced when the two halves were sealed together. After the devices were assembled, a 10 mL syringe was filled with room air and then connected via the luer lock onto the LV-DPI inlet. To maintain a consistent distance from the outlet of the devices to the inlet of the NGI for aerosol sizing a custom adaptor was fabricated, which held the LV-DPIs ~ 3 cm away from the NGI preseparator inlet. The powders were aerosolized with the LV-DPI in a horizontal position as shown in Figures 1 and 2 with the gravity vector pointing down the page. As minimal size change is expected in the aerosol under ambient temperature and relative humidity (RH) conditions, experiments were conducted with ambient air ($T = 22^\circ\text{C} \pm 3^\circ\text{C}$ and $\text{RH} = 50\% \pm 5\%$) with the NGI at room temperature. To allow for horizontal positioning of the inhaler, the NGI was positioned on its side (oriented vertically) to test both the ST and SS devices. The NGI was operated at 45 L/min and the preseparator and individual stages were coated with MOLYKOTE[®] 316 silicone spray (Dow Corning, Midland, MI) to minimize particle bounce and re-entrainment. The flowrate of 45 LPM was chosen to ensure collection of the aerosol, which exited the device 3 cm away from the preseparator inlet, and maintain reasonable stage cutoff diameters for evaluating a small size aerosol. To actuate the DPI, the plunger of the syringe was depressed quickly (~ 0.2 seconds to empty) to aerosolize the powder into the inlet of the NGI. The syringe was then disconnected from the inhaler, refilled with room air, and reconnected to the device for a total of five actuations. Using the optimized device, an additional study was performed using 50 mg of powder to evaluate the effect of higher powder mass loadings. A slower syringe emptying test (~ 0.5 seconds to empty) was also made with a 10 mg loaded mass using the optimized device to simulate extreme variability between users. Syringe emptying times were determined using a single operator and high speed photography (1000 frames/sec). All measurements were made with three replicates for each design configuration.

Aerosol performance characterization methods

After aerosolization, drug masses retained in the capsule, device, and the drug collected on the preseparator, impaction plates, and the filter of the NGI were recovered by washing with appropriate volumes of deionized water and quantified by HPLC analysis. The mass of AS retained in the capsule and device, determined by HPLC, was expressed as a percentage of the nominal AS dose. The ED was calculated by subtracting the mass of AS retained in the capsule and device from the nominal AS dose.

FIG. 3. Cross-sectional view of the outlet capillaries with the following internal diameters: (a) 0.6 mm, (b) 1.17 mm, (c) 4×0.6 mm, and (d) 0.89 mm.

To determine the nominal dose of AS in the EEG-AS formulation, known masses of the formulation were dissolved in 100 mL of water and the mean amount of AS per mg of formulation was determined using HPLC analysis. For each aerosolization experiment, the measured formulation AS content and the mass of formulation loaded into the capsule was used to determine the nominal dose of AS.

The cutoff diameters of each NGI stage at the operating flow rate of 45 LPM were calculated using the formula specified in USP 35 (Chapter 601, Apparatus 5) and were used to calculate MMAD and FPF of the delivered aerosol. FPF of the EEG formulation ($\text{FPF}_{<5\mu\text{m}/\text{ED}}$) and sub-micrometer FPF ($\text{FPF}_{<1\mu\text{m}/\text{ED}}$) were defined as the fraction less than 5 μm and 1 μm , respectively, expressed as a percentage of the ED. MMAD, $\text{FPF}_{<5\mu\text{m}/\text{ED}}$, and $\text{FPF}_{<1\mu\text{m}/\text{ED}}$ were calculated by linear interpolation using a plot of cumulative percentage drug mass versus cutoff diameter.

Aerosol plume characterization

The plume characteristics of aerosols generated by the different studied outlet orientations were also investigated. To measure the plume characteristics, the device was loaded and actuated as described above (evaluation of LV devices). The outlet of the device was positioned such that the aerosol was emitted against a black background labeled with marks in both the vertical and horizontal directions to provide a scale. A camera (Pentax K-30) was positioned to capture images at 30 fps. For comparison, a still image recorded when the plunger was fully depressed and was used to determine the horizontal and vertical spreads of the plume, which were calculated using the scale marks. This information will help with future implementation of the device

into a continuous flow path for use in an inhaler or for aerosol administration during mechanical ventilation.

Results

EEG formulation dispersion characterization

The dispersion characteristics and primary particle size for each of the batches of AS-EEG formulation employed in this study was determined using a Sympatec laser diffraction setup. When comparing the novel LV-DPIs over a period of time, it was important to determine the batch to batch consistency of the AS-EEG powder formulation using a consistent method of dispersion (ASPIROS/RODOS unit). For comparison to the aerosolization performance determined by the NGI, the geometric sizes determined by the laser diffraction method were converted to aerodynamic diameters using a theoretical AS-EEG particle density of 1.393 g/cm³.⁽³²⁾ Figure 4 shows the mean particle size distribution for the three batches of AS-EEG formulation used in this study. The mean (SD) MMAD and FPF values were calculated from this data and are also shown in Figure 4. The overall mean MMAD was 1.29 μm calculated from the laser diffraction sizing with the ASPIROS/RODOS dispersion unit. The coefficient of variation for the MMAD for the three batches was 7% indicating the relative reproducibility of the spray drying process to produce a small sized powder formulation. The mean $\text{FPF}_{<5\mu\text{m}/\text{ED}}$ and $\text{FPF}_{<1\mu\text{m}/\text{ED}}$ across batches were found to be 99.3% and 33.8%, respectively with coefficients of variability of 0.8% and 7.6%, respectively. These results represent very high efficiency aerosol dispersion that was achieved using a benchtop dispersion unit operating at relatively high pressure. Low coefficients

FIG. 4. Average cumulative particle size distribution of the three powder batches as a function of aerodynamic diameter (converted based on a formulation density of 1.393 g/cm³). Average MMAD and fine particle fractions (bottom right) are shown with standard deviations (SD) given in parentheses. MMAD, mass median aerodynamic diameters.

of variability provided further confidence that batch-to-batch variability is low for the powder formulations employed in this study.

Effect of outlet on ST design

The ST design is the simplest of the two investigated, with a single inlet and outlet centered on the longitudinal axis of the capsule. A single 0.6 mm inlet capillary was used for each design to create a high velocity jet to aid in powder dispersion. The performance results of the ST design are provided in Table 1. The first outlet tested, shown in Figure 3a, used a 0.6 mm capillary identical to the inlet capillary. This outlet produced a small aerosol, with a mean MMAD ($n=3$) of $1.57\ \mu\text{m}$, but almost half (49.6%) of the powder stayed inside the capsule, with only 44.8% of the total loaded powder mass emitted from the device. Increasing the outlet capillary size was expected to increase the ED while reducing the amount of deaggregation that was achieved. However, when the diameter was increased to 1.17 mm (shown in Fig. 3b), the MMAD was not significantly different ($1.64\ \mu\text{m}$) while the ED significantly increased to 57.3% (Table 1) compared to the 0.6 mm outlet. Four 0.6 mm outlet capillaries (Fig. 3c) were then placed in a circular pattern around the longitudinal axis of the capsule, as close together as possible. The four-fold increase in cross-sectional area versus the single 0.6 mm outlet was expected to increase the ED while the small diameter of each individual capillary would improve deaggregation. The mean $\text{FPF}_{<5\ \mu\text{m}/\text{ED}}$ and $\text{FPF}_{<1\ \mu\text{m}/\text{ED}}$ values of 96.4% and 24.2%, respectively, and an MMAD of $1.57\ \mu\text{m}$ mirrored that of the single 0.6 mm outlet (Table 1) and were not significantly different. The ED was significantly increased to 55.9% with four outlets from 44.8% with one 0.6 mm outlet, but the capsule retention was still very high. The addition of a small PTFE ball, 2.4 mm in diameter, inside the capsule was incorporated to help decrease the capsule powder retention by increasing vibration to prevent powder sticking to the walls. The ball addition resulted in a 6% absolute increase in ED without changing the emitted aerosol particle size (Table 1) compared to four outlets and no ball. A statistical comparison (*post-hoc* Tukey) of the $4 \times 0.6\ \text{mm}$ outlet case with and without the ball indicated no change ($p \geq 0.05$). The ST design with $4 \times 0.6\ \text{mm}$ outlet and ball performed the best in terms of ED while maintaining good powder dispersion. However, the capsule drug retention (28.9%) was still high

and the ED was lower (61.9%) than the performance requirement of 75% that was initially set.

Effect of outlet on SS design

To help with increasing the ED, a more complex design was tested with the inlet and outlet on the same end of the capsule. This SS device, with performance results shown in Table 2, was designed to use the same 0.6 mm inlet as the ST design, and the same outlet configurations. Only the orientation of the capillaries piercing the capsule was changed to assist in ED, and to potentially prevent a negative effect on the emitted aerosol particle size. Using the single 0.6 mm outlet in the SS design, the ED increased by more than 30% (absolute difference; compared to ST), resulting in 77.7% of the dose being emitted after five actuations. However, the mean MMAD increased to $2.19\ \mu\text{m}$ with the SS design from $1.57\ \mu\text{m}$ with the ST design. Capsule retention was 17.8% with the SS 0.6 mm outlet, which still appeared relatively high. Increasing the outlet capillary diameter to 1.17 mm for the SS device successfully decreased the capsule retention to 5.8% (Table 2). However, the FPF values decreased significantly compared to the 0.6 mm outlet, corresponding with an increased MMAD value of $3.12\ \mu\text{m}$. The $4 \times 0.6\ \text{mm}$ outlet with and with the PTFE ball were also tested with this configuration in an attempt to lower the particle size without compromising ED. Using these outlet configurations did not significantly alter the ED or MMAD compared to the 0.6 mm outlet. Also, with the SS configuration, addition of the ball did not have a significant effect on the ED or the MMAD when comparing the results of the $4 \times 0.6\ \text{mm}$ outlet with and without the ball. To find a compromise between the ED produced by the 1.17 mm outlet and the dispersion produced by the 0.6 mm outlet, an outlet diameter of 0.89 mm was selected. The 0.89 mm diameter outlet capillary was able to emit 84.8% of the loaded powder, which was not significantly different than the ED from the 1.17 mm outlet. Powder dispersion was also comparable to the 0.6 mm outlet with an MMAD of $2.13\ \mu\text{m}$. An $\text{FPF}_{<5\ \mu\text{m}/\text{ED}}$ of 89.3% and an $\text{FPF}_{<1\ \mu\text{m}/\text{ED}}$ value of 14.7% was observed with the 0.89 mm outlet.

Comparison of ST and SS devices

The best performing ST and SS devices were then analyzed in a side-by-side comparison, shown in Table 3. The ST device was able to produce an aerosol with a significantly smaller MMAD ($1.56\ \mu\text{m}$ vs. $2.13\ \mu\text{m}$) and with a significantly higher $\text{FPF}_{<1\ \mu\text{m}/\text{ED}}$ value (25.1% vs. 14.7%), compared

TABLE 1. OPTIMIZATION OF STRAIGHT-THROUGH LOW AIR VOLUME DRY POWDER INHALER DEVICE OUTLET INTERNAL DIAMETER

Description	0.6 mm	1.17 mm	$4 \times 0.6\ \text{mm}$	$4 \times 0.6\ \text{mm w/ball}$
ED (%) ^a	44.8 (4.8)	57.3 (4.9) ^b	55.9 (4.2) ^b	61.9 (2.0) ^b
Capsule (%) ^a	49.6 (4.9)	35.0 (6.0) ^b	35.6 (2.6) ^b	28.9 (2.2) ^b
Device (%)	5.6 (0.3)	7.7 (1.6)	8.5 (1.6)	9.2 (1.5)
$\text{FPF}_{<5\ \mu\text{m}/\text{ED}}$ (%)	95.7 (1.2)	93.7 (1.3)	96.4 (0.3)	95.2 (1.4)
$\text{FPF}_{<1\ \mu\text{m}/\text{ED}}$ (%)	22.4 (0.9)	23.8 (6.0)	24.2 (0.7)	25.1 (2.8)
MMAD (μm)	1.57 (0.04)	1.64 (0.09)	1.57 (0.01)	1.56 (0.03)

Mean aerosol characteristics with standard deviations (SD) shown in parenthesis [$n=3$].

^a $p < 0.05$ significant effect of device outlet diameter on % ED and % capsule drug retention (one-way ANOVA).

^b $p < 0.05$ significant difference compared to 0.6 mm outlet (*post-hoc* Tukey).

ED, emitted dose; FPF, fine particle fraction; MMAD, mass median aerodynamic diameters.

TABLE 2. OPTIMIZATION OF SINGLE-SIDED LOW AIR VOLUME DRY POWDER INHALER DEVICE OUTLET INTERNAL DIAMETER

Description	0.6 mm	0.89 mm	1.17 mm	4×0.6 mm	4×0.6 mm w/ball
ED (%)	77.7 (6.3)	84.8 (3.0)	87.9 (2.4)	82.0 (7.3)	80.3 (4.4)
Capsule (%) ^a	17.8 (5.7)	8.8 (2.0) ^b	5.8 (1.1) ^b	9.5 (5.5)	10.6 (3.1)
Device (%) ^a	4.5 (1.4)	6.4 (1.7)	6.3 (1.3)	8.5 (2.0)	9.1 (1.5) ^b
FPF _{<5μm/ED} (%) ^a	83.2 (3.8)	89.3 (0.5)	61.6 (8.9) ^b	67.2 (4.5) ^b	68.5 (2.3) ^b
FPF _{<1μm/ED} (%) ^a	14.1 (1.1)	14.7 (1.1)	9.6 (1.4) ^b	11.8 (1.1)	12.4 (0.9)
MMAD (μm) ^a	2.19 (0.18)	2.13 (0.07)	3.12 (0.40) ^b	2.80 (0.23)	2.72 (0.11)

Mean aerosol characteristics with standard deviations (SD) shown in parenthesis [*n* = 3].

^a*p* < 0.05 significant effect of device outlet on % capsule and device drug retention, FPF_{<5μm/ED}, FPF_{<1μm/ED}, and MMAD (one-way ANOVA).

^b*p* < 0.05 significant difference compared to 0.6 mm outlet (*post hoc* Tukey).

to the SS device. However, capsule retention was 20% lower (absolute difference) with the SS device, resulting in a significantly larger ED (84.8% vs. 61.9%). Although not all of the desired performance metrics were achieved with the SS-0.89 mm device, it was chosen as a best case in this study for further investigation.

Comparison of SS-0.89 mm device using varying actuation conditions

Using the SS-0.89 mm device as the leading design for this study, further testing was conducted in terms of increased powder mass and increased actuation time. A high dose test of 50 mg of the same AS-EEG powder formulation was conducted, and a test using the original 10 mg loaded dose, but with a slower depression of the syringe lasting approximately 0.5 seconds (vs. ~0.2 sec originally). The results of these tests are presented in Tables 4 and 5 alongside the original data from the optimized device. With the larger loaded mass, ED increased ~8%, but this also resulted in a 0.9 μm increase in MMAD (Table 4). This increase in MMAD also corresponded in a decrease in FPF values. Slower actuation of the device resulted in a 10% absolute increase in ED and a 0.6 μm increase in MMAD (Table 5). Fine particle fraction (FPF_{<5μm/ED}) decreased as expected with a larger aerosol, but FPF_{<1μm/ED} did not change from the original value.

Effect of outlet on plume size

Using the SS device, each outlet configuration was tested delivering the aerosol into an open environment. Powder

was aerosolized with the outlet facing vertically upward and captured on video, with the frames at the point in time that the syringe plunger was fully depressed used to measure the plume characteristics (Fig. 5). A vertical orientation was implemented such that maximum entrainment of the plume acting against gravity could be determined in future analysis. Particle size experiments with the device oriented vertically and with the impactor suspended upside down indicated a negligible change in aerosol size compared with a horizontal device orientation. From the images in Figure 5, the measurements of the plume dimensions were taken and simplified to show height, width and angle, and these simplified diagrams are shown in Figure 6. The 0.6 mm outlet produced the largest plume, in terms of both height and width, while the 4×0.6 mm outlet produced the smallest. Since the cross-sectional area of the 4×0.6 mm outlet is four times larger, the velocity of the particles leaving the device should be four times less, carrying them away from the outlet slower as was observed. However, the velocity of the 1.17 mm outlet should be slower than the 0.89 mm outlet, but the results of the test show that the plume is closer to the device for the smaller of the two outlets at the moment the syringe is empty. This may be due to inaccuracy of this visual measurement method, or complexity of a transient multiphase turbulent jet entering a quiescent environment.

Discussion

The primary outcome of this study is the development of an easy to use DPI powered by only a small volume of air. This

TABLE 3. COMPARISON OF STRAIGHT-THROUGH AND SINGLE-SIDED OPTIMIZED DEVICES

Description	ST-4×0.6 mm w/ball	SS-0.89 mm
ED (%)	61.9 (2.0)	84.8 (3.0) ^a
Capsule (%)	28.9 (2.2)	8.8 (2.0) ^a
Device (%)	9.2 (1.5)	6.4 (1.7)
FPF _{<5μm/ED} (%)	95.2 (1.4)	89.3 (0.5) ^a
FPF _{<1μm/ED} (%)	25.1 (2.8)	14.7 (1.1) ^a
MMAD (μm)	1.56 (0.03)	2.13 (0.07) ^a

Mean aerosol characteristics with standard deviations (SD) shown in parenthesis [*n* = 3].

^a*p* < 0.05 significant difference between ST-4×0.6 mm w/ball and SS-0.89 mm (Student's *t*-test)

TABLE 4. COMPARISON OF OPTIMIZED SINGLE-SIDED DEVICE USING THE ORIGINAL 10 MG DOSE AND A HIGHER DOSE OF 50 MG

Description	10 mg	50 mg
ED (%)	84.8 (3.0)	92.5 (2.7) ^a
Capsule (%)	8.8 (2.0)	4.6 (2.0) ^a
Device (%)	6.4 (1.7)	2.9 (0.7) ^a
FPF _{<5μm/ED} (%)	89.3 (0.5)	74.2 (6.2) ^a
FPF _{<1μm/ED} (%)	14.7 (1.1)	9.2 (0.8) ^a
MMAD (μm)	2.13 (0.07)	3.01 (0.21) ^a

Mean aerosol characteristics with standard deviations (SD) shown in parenthesis [*n* = 3].

^a*p* < 0.05 significant difference between 10 mg and 50 mg (Student's *t*-test)

TABLE 5. COMPARISON OF OPTIMIZED SINGLE-SIDED DEVICE USING THE ORIGINAL 0.2 SECONDS ACTUATION AND WITH A SLOWER DEVICE ACTUATION (0.5 SECONDS)

Description	10 mg-0.2 sec	10 mg-0.5 sec
ED (%)	84.8 (3.0)	95.6 (2.0) ^a
Capsule (%)	8.8 (2.0)	3.0 (1.4) ^a
Device (%)	6.4 (1.7)	1.3 (0.6) ^a
FPF _{<5μm/ED} (%)	89.3 (0.5)	73.0 (1.7) ^a
FPF _{<1μm/ED} (%)	14.7 (1.1)	13.4 (1.0)
MMAD (μm)	2.13 (0.07)	2.71 (0.04) ^a

Mean aerosol characteristics with standard deviations (SD) shown in parenthesis [*n* = 3].

^a*p* < 0.05 significant difference between 10 mg-0.2 seconds and 10 mg-0.5 seconds (Student's *t*-test)

device has the potential to be implemented in several types of delivery systems because of its use of a positive pressure air source to create an aerosol of very high quality. The optimum device that emerged from this study was a capsule-based LV-DPI with a single inlet, designed to be connected to a standard luer-lock syringe, and an aerosol single outlet that was 7 mm in diameter at the distal end (Fig. 2), to decrease loss of the exiting particles. An inlet capillary 0.6 mm in diameter and an outlet capillary 0.89 mm, located on the same end of the capsule, were used to pierce the

FIG. 5. Still images taken at the moment of complete syringe actuation showing plume of aerosol particles leaving the SS device for each outlet case: (a) 0.6 mm, (b) 0.89 mm, (c) 1.17 mm, and (d) 4 × 0.6 mm.

FIG. 6. Simplified images showing height, width, and approximate angle of particle plume after device actuation based on visual inspection of pictures: (a) 0.6 mm, (b) 0.89 mm, (c) 1.17 mm, and (d) 4 × 0.6 mm.

capsule while remaining in place to administer the five actuations of 10 mL air volume through the capsule containing the powder to be aerosolized.

Even with the combination of the best performing inhaler design and the AS-EEG powder formulation, the optimized device was not able to meet all of the desired performance metrics with the five actuations of 10 mL air volume in this study. However, the SS device was able to emit almost all of the loaded dose with close to 90% being smaller than a 5 μm aerodynamic diameter. Best case performance with a 10 mg loaded dose of powder included an ED of 84.8%, MMAD of 2.13 μm, FPF_{<5μm/ED} of 89.3%, and FPF_{<1μm/ED} of 14.7%. In comparison, the targeted ideal design characteristics were an ED of greater than 75%, MMAD of 1.5 μm, FPF_{<5μm/ED} of greater than 90%, and FPF_{<1μm/ED} greater than 30%.

An inline device developed by Pohlmann et al.⁽¹⁷⁾ was able to emit 55% of the loaded powder mass to produce an aerosol with an MMAD of 3.16 μm using 14 mL compressed air volume. However, FPFs were much lower than those that are required for the EEG aerosol applications (less than 10% FPF_{<1μm/ED}). The ability of the Pohlmann et al.⁽¹⁷⁾ device to store and deliver a larger powder mass (up to 3 g) could partially offset the larger depositional losses generated by the particle size, but this would mean more wasted medication. By comparison, the Puffhaler was able to emit 60% of the loaded dose using a manually operated squeeze bulb, but was only able to achieve a maximum of 21% of the particles under 3.3 μm.⁽¹³⁾ The FPF_{<3.3μm/ED} for the SS-0.89 mm device in this study was calculated to be 79%.

The PennCentury insufflator (DP-4M) was designed to deliver small amounts of drug using less than 2 mL of air for

dispersion. While device drug retention and particle size varied greatly depending on powder formulation, the device was shown to have the ability to emit $\sim 90\%$ of loaded powder masses in the range of 1–3 mg.⁽¹⁴⁾ The DP-4M was able to disperse some powder formulations to a size resembling that of the RODOS dispersed aerosol. However, with the addition of drug to the formulation, effectiveness of the device to disperse the aerosol was decreased. The best reported performance of the DP-4 device from Hoppentocht et al.,⁽¹⁴⁾ with a powder formulation containing drug was obtained using a spray-dried formulation of colistimethate sodium. With an air volume of 1 mL from the pressurized air pump and a powder mass of 3 mg, this device/formulation combination produced an ED close to 90% and a median particle size of approximately 4 μm .

The recently developed 3-4-3 3D rod array device proposed by our group was able to produce a high quality aerosol with a loaded dose of 2 mg and an air volume of 1 L per actuation.⁽³⁾ An ED of 75%, coupled with an MMAD of 1.6 μm , produced by the 3D rod array device indicate very good performance, but $\text{FPF}_{<5\mu\text{m}/\text{ED}}$ and $\text{FPF}_{<1\mu\text{m}/\text{ED}}$ values of 65% and 21%, respectively, were lower than targeted.⁽³⁾ In comparison, the SS-0.89 mm device was able to emit 10% more of the loaded dose with a higher percentage of the dose smaller than 5 μm . It is noted that the SS-0.89 mm device aerosolized five times the amount of powder using 1% of the air volume of the 3-4-3 3D rod array device per actuation (5% of the total dispersion air volume).

A potential concern with the device is exposure of the EEG hygroscopic powder to humidity and connection of the device to humidified ventilation systems. As implemented in this study, the device and EEG powder performed well when operated with room condition air ($T=22^\circ\text{C}\pm 3^\circ\text{C}$; $\text{RH}=50\%\pm 5\%$) as intended. Performance of the device with excess humidity air in the syringe (e.g., $\text{RH}>70\%$) was not considered. It is noted that the device is intended to be used in pressurized and humidified systems, when needed. The 10 mL syringe containing room air provides the device air source and prevents backflow of humidified air through the device. Future designs of the device will prevent the need to remove the syringe with each air refilling. As a result, the device can be connected to a positive pressure humidified system without water vapor entering the capsule and degrading the powder quality. A similar positive pressure device operated with a manual ventilation bag (containing room air) was used in the study of Walenga et al.⁽⁴⁾ by our group in which a 3D rod array inline DPI was connected to a noninvasive positive pressure ventilation mask that was supplied with humidified airflow. The device performed well even in the presence of the humidified ventilation flow. Furthermore, the aerosol was delivered into the airways at an adequate velocity that prevented significant size growth before entry into the lungs.⁽⁴⁾

A potential shortcoming of the newly developed LV-DPIs is the ability to control the plume size exiting the device for use in future delivery systems. If the momentum of the particles generated by the device is too high, depositional losses will increase significantly before the aerosol can be carried to the patient. Slowing of the air flow through the syringe was shown to have a negative effect on the overall size of the aerosol (MMAD increase of 0.6 μm ; Table 5), but also showed an increase in ED with a similar fraction of

submicrometer particles. Another potential limitation of this active style DPI is the requirement to coordinate actuation with inhalation. However, this coordination can be signaled or automated and will depend on the application in which the device is used. Future improvements in filling of the air syringe to increase ease of use are planned.

Syringe emptying times may be partially dependent on the operator of the device. To maintain a simple low-cost device, the air syringes were emptied by hand in all cases. The fast emptying time of 0.2 seconds was easy to achieve by the operator depressing the air syringe as quickly as possible. In contrast, the operator had to practice with the device to reliably produce the slower 0.5 seconds emptying time. However, difficulty with producing an emptying time of 0.5 seconds is not a concern given that the fast emptying time of 0.2 seconds performed better. A flow control orifice as in the study of Behara et al.⁽³⁾ can be used on future designs if it becomes necessary to limit variability in syringe emptying time among operators.

Additional limitations present in this study will be further explored in the future. Delivery to a realistic lung model was not investigated, but will be considered after developing a delivery system and interface to administer the aerosol to a patient. Further optimization of the device will also be considered when implementing the delivery system, but it is expected that only small changes are needed, if any, to improve aerosol penetration through the delivery system. Only a single drug formulation was tested in this study, AS-EEG, but other EEG formulations, such as ciprofloxacin have been used in previous DPI development studies with similar performance to AS.⁽³⁰⁾

Conclusion

The results of this study show that a high quality aerosol can successfully be generated using a low volume of air on the order of approximately 10 mL. While the results do not meet all of the desired performance metrics for EEG aerosol delivery, this device provides a substantial advance. The device successfully outperformed more complex devices,^(2,14,17) while still being easy to load and operate. The LV devices also compared well with the inline DPIs our group has developed, with improved ED and $\text{FPF}_{<5\mu\text{m}/\text{ED}}$ values higher than obtained with current 3D rod array inline devices while using two orders of magnitude less air.⁽³⁾ Higher drug masses on the order of 50 mg marginally decreased aerosol performance; however, it is expected that improved performance can be obtained by optimizing the device for operation with a known mass of powder for a specific application. Furthermore, we expect that a quantitative analysis and design approach^(33,34) implementing computational fluid dynamics⁽¹⁸⁾ and additional prototyping can be used to meet all of the high performance aerosol delivery metrics that were initially set. Future studies will be performed to integrate this device into delivery systems to deliver aerosols to both adults and children to take advantage of the flexible nature of this technology.

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Author Disclosure Statement

Virginia Commonwealth University is currently pursuing patent protection of EEG aerosol delivery, LV-DPI aerosol generation devices, and patient interfaces, which if licensed may provide a future financial interest to the authors.

References

1. Everard ML, Devadason SG, and LeSouef PN: In vitro assessment of drug delivery through an endotracheal tube using a dry powder inhaler delivery system. *Thorax*. 1996; 51:75–77.
2. Tang P, Chan HK, Rajbhandari D, and Phipps P: Method to introduce mannitol powder to intubated patients to improve sputum clearance. *J Aerosol Med Pulm Drug Deliv*. 2011; 24:1–9.
3. Behara SRB, Longest PW, Farkas DR, and Hindle M: Development of high efficiency ventilation bag actuated dry powder inhalers. *Int J Pharm*. 2014;465:52–62.
4. Walenga RL, Longest PW, Kaviratna A, and Hindle M: Aerosol drug delivery during noninvasive positive pressure ventilation: Effects of intersubject variability and excipient enhanced growth. *J Aerosol Med Pulm Drug Deliv*. 2017;30:190–205.
5. Goralski JL, and Davis SD: Breathing easier: Addressing the challenges of aerosolizing medications to infants and preschoolers. *Respir Med*. 2014;108:1069–1074.
6. Rubin BK: Pediatric aerosol therapy: New devices and new drugs. *Respir Care*. 2011;56:1411–1421.
7. Laube BL, Sharpless G, Shermer C, Sullivan V, and Powell K: Deposition of dry powder generated by solovent in Sophia Anatomical infant nose-throat (SAINT) model. *Aerosol Sci Technol*. 2012;46:514–520.
8. Dhand R: Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. *Respir Care*. 2005;50:1331–1344.
9. Longest PW, Golshahi L, Behara SRB, Tian G, Farkas DR, and Hindle M: Efficient nose-to-lung (N2L) aerosol delivery with a dry powder inhaler. *J Aerosol Med Pulm Drug Deliv*. 2015;28:189–201.
10. Hess DR: Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. *Respir Care*. 2015;60:880–893.
11. Grainger CI, Alcock R, Gard TG, Quirk AV, van Amerongen G, de Swart RL, and Hardy JG: Administration of an insulin powder to the lungs of cynomolgus monkeys using a Penn Century insufflator. *Int J Pharm*. 2004;269: 523–527.
12. Duret C, Wauthoz N, Merlos R, Goole J, Maris C, Roland I, Sebti T, Vanderbist F, and Amighi K: In vitro and in vivo evaluation of a dry powder endotracheal insufflator device for use in dose-dependent preclinical studies in mice. *Eur J Pharm Biopharm*. 2012;81:627–634.
13. Manion JR, Cape SP, McAdams DH, Rebitts LG, Evans S, and Sievers RE: Inhalable antibiotics manufactured through use of near-critical or supercritical fluids. *Aerosol Sci Technol*. 2012;46:403–410.
14. Hoppentocht M, Hoste C, Hagedoorn P, Frijlink HW, and De Boer AH: In vitro evaluation of the DP-4M Penn-Century insufflator. *Eur J Pharm Biopharm*. 2014;88:153–159.
15. Longest PW, Behara SRB, Farkas DF, and Hindle M: Efficient generation and delivery of dry powder aerosols during low flow oxygen administration. *Drug Delivery to the Lungs - DDL 24*. 2014;http://ddl-conference.com/files/DDL24Abstracts/oral/05.Hindle.pdf
16. Pornputtapitak W, El-Gendy N, Mermis J, O'Brein-Ladner A, and Berkland C: NanoCluster buudesonide formulations enable efficient drug delivery driven by mechanical ventilation. *Int J Pharm*. 2014;462:19–28.
17. Pohlmann G, Iwatschenko P, Koch W, Windt H, Rast M, Gama de Abreu M, Taut FJH, and De Muynck C: A novel continuous powder aerosolizer (CPA) for inhalative administration of highly concentrated recombinant surfactant protein-C (rSP-C) surfactant to preterm neonates. *J Aerosol Med Pulm Drug Deliv*. 2013;26:370–379.
18. Longest PW, Son Y-J, Holbrook LT, and Hindle M: Aerodynamic factors responsible for the deaggregation of carrier-free drug powders to form micrometer and sub-micrometer aerosols. *Pharm Res*. 2013;30:1608–1627.
19. Son Y-J, Longest PW, and Hindle M: Aerosolization characteristics of dry powder inhaler formulations for the excipient enhanced growth (EEG) application: Effect of spray drying process conditions on aerosol performance. *Int J Pharm*. 2013;443:137–145.
20. Hindle M, and Longest PW: Condensational growth of combination drug-excipient submicrometer particles for targeted high efficiency pulmonary delivery: Evaluation of formulation and delivery device. *J Pharm Pharmacol*. 2012; 64:1254–1263.
21. Longest PW, Golshahi L, and Hindle M: Improving pharmaceutical aerosol delivery during noninvasive ventilation: Effects of streamlined components. *Ann Biomed Eng*. 2013;41:1217–1232.
22. Morley CJ, Miller N, Bangham AD, and Davis JA: Dry artificial lung surfactant and its effect on very premature babies. *Lancet*. 1981;317:64–68.
23. Walsh BK, and DiBlasi RM: Mechanical ventilation of the neonate and pediatric patient. In: BK Walsh, MP Czerwinski, and RM DiBlasi, (eds). *Perinatal and Pediatric Respiratory Care*. Saunders Elsevier, St. Louis, pp. 325–347, 2010.
24. Jauernig J, Mitchell J, Berg E, Dennis J, Kreher C, Lamb P, Karlsson M, and Tservistas M: Position paper: Recommendation on the adoption of breathing patterns for infants and small children in General Chapter 2.9. 44. Preparations for Nebulisation. *Pharmeur Sci Notes*. 2008; 2008:31–32.
25. Sunbul F, Fink JB, Harwood R, Sheard MM, Zimmerman RD, and Ari A: Comparison of HFNC, bubble CPAP and SiPAP on aerosol delivery in neonates: An in-vitro study. *Pediatr Pulmonol*. 2015;50:1099–1106.
26. Longest PW, Walenga RL, Son Y-J, and Hindle M: High efficiency generation and delivery of aerosols through nasal cannula during noninvasive ventilation. *J Aerosol Med Pulm Drug Deliv*. 2013;26:266–279.
27. Smith II, Bell J, Bowman N, Everard M, Stein S, and Weers JG: Inhaler devices: What remains to be done? *J Aerosol Med Pulm Drug Deliv*. 2010;23:S25–S37.
28. Behara SRB, Farkas DR, Hindle M, and Longest PW: Development of a high efficiency dry powder inhaler: Ef-

- fects of capsule chamber design and inhaler surface modifications. *Pharm Res.* 2014;31:360–372.
29. Behara SRB, Longest PW, Farkas DR, and Hindle M: Development and comparison of new high-efficiency dry powder inhalers for carrier-free formulations. *J Pharm Sci.* 2014;103:465–477.
30. Farkas DR, Hindle M, and Longest PW: Characterization of a new high-dose dry powder inhaler (DPI) based on a fluidized bed design. *Ann Biomed Eng.* 2015;43:2804–2815.
31. Son Y-J, Longest PW, Tian G, and Hindle M: Evaluation and modification of commercial dry powder inhalers for the aerosolization of submicrometer excipient enhanced growth (EEG) formulation. *Eur J Pharm Sci.* 2013;49:390–399.
32. Longest PW, and Hindle M: Numerical model to characterize the size increase of combination drug and hygroscopic excipient nanoparticle aerosols. *Aerosol Sci Technol.* 2011; 45:884–899.
33. Longest PW, and Hindle M: Quantitative analysis and design of a spray aerosol inhaler. Part 1: Effects of dilution air inlets and flow paths. *J Aerosol Med Pulm Drug Deliv.* 2009;22:271–283.
34. Hindle M, and Longest PW: Quantitative analysis and design of a spray aerosol inhaler. Part 2: Improvements in mouthpiece performance. *J Aerosol Med Pulm Drug Deliv.* 2013;26:237–247.

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