Efficient Nose-to-Lung (N2L) Aerosol Delivery with a Dry Powder Inhaler

P. Worth Longest, PhD,^{1,2,*} Laleh Golshahi, PhD,¹ Srinivas R.B. Behara, PhD,^{1,2} Geng Tian, PhD,¹
Dale R. Farkas, BS,¹ and Michael Hindle, PhD²

Abstract

Purpose: Delivering aerosols to the lungs through the nasal route has a number of advantages, but its use has been limited by high depositional loss in the extrathoracic airways. The objective of this study was to evaluate the nose-to-lung (N2L) delivery of excipient enhanced growth (EEG) formulation aerosols generated with a new inline dry powder inhaler (DPI). The device was also adapted to enable aerosol delivery to a patient simultaneously receiving respiratory support from high flow nasal cannula (HFNC) therapy.

Methods: The inhaler delivered the antibiotic ciprofloxacin, which was formulated as submicrometer combination particles containing a hygroscopic excipient prepared by spray-drying. Nose-to-lung delivery was assessed using *in vitro* and computational fluid dynamics (CFD) methods in an airway model that continued through the upper tracheobronchial region.

Results: The best performing device contained a 2.3 mm flow control orifice and a 3D rod array with a 3-4-3 rod pattern. Based on *in vitro* experiments, the emitted dose from the streamlined nasal cannula had a fine particle fraction $< 5 \mu\text{m}$ of 95.9% and mass median aerodynamic diameter of $1.4 \mu\text{m}$, which was considered ideal for nose-to-lung EEG delivery. With the 2.3-343 device, condensational growth in the airways increased the aerosol size to $2.5\text{--}2.7 \mu\text{m}$ and extrathoracic deposition was $< 10\%$. CFD results closely matched the *in vitro* experiments and predicted that nasal deposition was $< 2\%$.

Conclusions: The developed DPI produced high efficiency aerosolization with significant size increase of the aerosol within the airways that can be used to enable nose-to-lung delivery and aerosol administration during HFNC therapy.

Key words: active dry powder inhaler (DPI) system, enhanced condensational growth (ECG), excipient enhanced growth (EEG), high flow nasal cannula (HFNC), noninvasive ventilation (NIV)

Introduction

THE DELIVERY OF PHARMACEUTICAL AEROSOLS to the lungs through the nose using a nasal cannula is a recently proposed concept with a number of advantages for different medications and various patient groups.^(1,2) Applications of nose-to-lung (N2L) delivery include the convenient administration of medications with long delivery times or rapid clearance rates. The N2L approach may also be used to treat the entire respiratory tract with an antibiotic to prevent bacteria harbored in the nasal cavity from re-infecting the lungs. As an additional application, aerosols are currently delivered to pediatric patients less than 5 years of age through a face-mask interface.^(3,4) Delivery using facemasks is problematic

due to facial depositional loss, aerosol loss through leaks, low lung delivery rates, and noncompliance by the patient. However, targeted delivery of aerosols to children with only nasal cannula prongs has the potential to improve lung delivery efficiency,^(5,6) compliance of the child, and eliminate facial and ocular depositional losses.

For patients receiving noninvasive ventilation (NIV) with a nasal interface,⁽⁷⁾ delivering an aerosol to the lungs through the nose allows for the medication to be administered through the ventilation circuit and prevents the interruption of respiratory gas support.⁽⁸⁾ This can be especially useful in cases where administration times are long or for medications that require frequent delivery. High flow nasal cannula (HFNC) therapy is an increasingly popular form of

Departments of ¹Mechanical and Nuclear Engineering, and ²Pharmaceutics, Virginia Commonwealth University, Richmond, Virginia.

NIV due to its simplicity and positive outcomes.^(9,10) In this approach, heated and humidified air is delivered continually to the patient's nasal cavity with nasal cannula (also referred to as nasal prongs) that are not sealed at the nares.⁽¹¹⁾ The addition of heat and humidity allows for flow rates in the range of 10–60 LPM to be delivered comfortably.^(9,10) Advantages of this technique include improved oxygenation compared with a face mask⁽¹²⁾ and a reduction of the risks and costs associated with endotracheal tube intubation^(9,10) in common scenarios requiring ventilation support. However, aerosol delivery efficiency during all forms of NIV is typically poor, with values of approximately <10% in adults and children *in vitro* and even lower *in vivo*.^(8,13–15)

Previous studies have considered aerosol delivery through cannula systems using mesh nebulized aerosols.^(1,16) At a flow rate of 3 LPM, maximum aerosol delivery efficiency from an adult nasal cannula was approximately 25%.⁽¹⁾ Increasing the flow rate to 6 LPM and including heliox to reduce depositional losses resulted in approximately 5% delivery efficiency through a pediatric nasal cannula.⁽¹⁶⁾ These values represent output based on loaded nebulizer charge at the nasal cannula exit and do not include additional losses in the nasal airways. While these previous studies reported moderate drug throughput, it is important to note that the flow rates employed are lower than typically administered with HFNC in adults. Perry et al.⁽¹⁷⁾ considered aerosol delivery through a HFNC *in vitro* model with more common adult flow rates. For the adult size nasal cannula with flow rates of 10 LPM and above, drug delivery efficiencies were 0.6% and below with no drug being delivered at a commonly applied HFNC airflow rate of 40 LPM. As a result, HFNC systems appear to be a very challenging case for the simultaneous administration of pharmaceutical aerosols due to depositional losses in the delivery system and nasal airways.

A recently proposed set of methods to improve the delivery of pharmaceutical aerosols is the controlled condensational growth technique.^(18–21) In this approach, an aerosol is delivered to the respiratory tract with an initial sub-micrometer or sufficiently small size to minimize device and upper airway deposition. Droplet size increase through condensational growth allows for retention of the aerosol, which without growth would be exhaled. Techniques to produce the required size increase include enhanced condensational growth (ECG) and excipient enhanced growth (EEG). In the ECG approach, the aerosol is delivered with air saturated with water vapor a few degrees above body temperature, which creates supersaturated relative humidity (RH) conditions in the lungs to foster condensational growth of the droplets.^(18,22) Using the ECG approach, the aerosol may be nonhygroscopic or may contain a hygroscopic excipient to further enhance the rate of aerosol growth and final droplet size. With EEG, formulated particles contain a combination of a drug and a hygroscopic excipient and the natural RH in the lungs provides the water vapor source for aerosol size increase.^(19,20) Combination particles that contain both a therapeutic agent and hygroscopic excipient in order to create aerosol size increase in the airways are referred to as an EEG formulation.^(19,23)

The approach of controlled condensational growth has been successful at improving lung delivery rates for orally administered aerosols^(18,22–25) and for N2L delivery with nebulizer generated aerosols.^(2,5) Considering N2L delivery

with a nebulizer, Golshahi et al.⁽⁵⁾ previously demonstrated that both EEG and ECG approaches could reduce cannula and nasal depositional losses by an order of magnitude and deliver approximately 80% of the loaded dose to the lungs with steady flow. Using an aerosol mixer-heater system⁽²⁶⁾ combined with a mesh nebulizer, Golshahi et al.⁽²⁷⁾ demonstrated that synchronizing the aerosol delivery with patient breathing was important to achieve high efficiency aerosol delivery (~70%) in a HFNC system.

To advance the concept of controlled condensational growth delivery, Behara et al.⁽²⁸⁾ previously developed a DPI system that was actuated by a ventilation bag and connected to a streamlined nasal cannula interface.⁽²⁹⁾ The inline DPI contained a 3D rod array structure⁽³⁰⁾ to deaggregate the carrier-free EEG particle formulation. However, delivery of the aerosol through a nasal model and into the lungs was not considered. Furthermore, the growth characteristics of dry powder formulation aerosols delivered with EEG and ECG approaches through a nasal interface have not previously been considered. The bag-actuated system provides the advantage of coordinating aerosol administration with patient nasal inhalation. Further advantages of DPI aerosol delivery during HFNC therapy and other forms of NIV include stable formulations of drugs and rapid administration of the aerosol dose compared with nebulizer delivery.

The objective of this study is to evaluate the direct N2L delivery of EEG formulation aerosols generated with a new in-line DPI using a manual ventilation bag dispersion technique. As a second application, the in-line DPI system is used for N2L aerosol delivery during HFNC therapy with a modified nasal cannula interface. A combination of *in vitro* experiments and computational fluid dynamics (CFD) simulations is employed to concurrently analyze the N2L and N2L with HFNC delivery systems. Aerosol delivery is assessed using a realistic nose-mouth-throat (NMT) model that continues through the upper tracheobronchial (TB) region and is housed in a chamber to simulate realistic lung exposure times. Variables of interest include the initial aerosol characteristics exiting the nasal cannula, NMT and upper TB deposition, and aerosol growth exiting the lung chamber. Performance of inline devices is first assessed using *in vitro* experiments. Predictions of the CFD model are then validated using the *in vitro* results. Finally, the CFD model is used to explore realistic boundary condition effects that cannot be created in the *in vitro* model.

Materials and Methods

Materials

Ciprofloxacin hydrochloride (Cipro) was purchased from Spectrum Chemicals (Gardena, CA) and Pearlitol® PF-Mannitol 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).

Experimental setup

The experimental setup consisted of a manual ventilation bag, flow meter for experimental recording of flow rates, the

inline DPI, and previously developed nasal cannulas for N2L aerosol delivery during HFNC ventilation therapy. The inline DPI system was previously considered by Behara et al.⁽²⁸⁾ and is further evaluated in this study for a second formulation (Cipro) and with the addition of a respiratory model of the NMT extending through the upper TB airways. As described by Behara et al.,⁽²⁸⁾ the inline DPI is actuated manually using a firm and continuous pressure with two hands placed on the 1.0L ventilation bag (Adult Manual Resuscitator, Legend Medical Devices, South El Monte, CA). Additional pressure on the bag (i.e., squeezing as hard as possible) was found to have a negligible impact on increasing the flow rate through the system due to the use of a flow control orifice in the inline DPI. As illustrated by Behara et al.,⁽²⁸⁾ the size of the flow control orifice is used to modify the flow rate through the inline DPI device and has an effect on the resulting mass median aerodynamic diameter (MMAD) of the emitted aerosol.

The low pressure-drop flow meter (Sensirion SFM3000, Sensirion AG, Stafa, Switzerland) was included in the *in vitro* experiments to verify the root mean square (RMS) flow rate through the system as previously reported by Behara et al.⁽²⁸⁾ A different operator of the manual ventilation bag was used in the current experiments compared with the previous study⁽²⁸⁾ in order to evaluate potential inter-subject differences in the flow rate achieved through the system. Based on manual actuation of the ventilation bag supplying airflow to the inline DPIs, the flow rate waveforms contained accelerating, constant plateau, and decelerating phases. The root-mean-square (RMS) of the flow rate during the bag actuation was calculated, where the time points were recorded by the flow meter

with a typical sampling time of 0.02 sec. The beginning and end of the bag actuation were estimated to occur between the start of the accelerating and end of decelerating phases.

Inline DPI

As shown in Figure 1a, the inline DPI consists of the flow control orifice, capsule chamber and capsule, 3D rod array, and flow passage leading to various streamlined nasal cannulas with short nasal prongs. The flow control orifice provides a practical maximum to the flow rate that can be delivered with manual bag actuation and creates a jet of air to initially aerosolize the powder in the capsule. The capsules were pierced by hand with a 0.5 mm needle once in the head and once in the base using the optimal piercing locations for the inline device determined by Behara et al.⁽²⁸⁾ (Case 3 piercing). The 3D rod array then further deaggregates the particle agglomerates using a turbulence breakup mechanism. Briefly, it was previously shown that the 3D rod array provides maximum deaggregation of carrier-free submicrometer particle formulations.³⁰ The rod array consists of multiple rows of rods with a staggered arrangement such that flow accelerating between two rods impinges on a rod in the next row. Using this cascading process, turbulence for particle deaggregation is maximized, which is described by high turbulent energy levels in the small eddies.⁽³⁰⁾ The naming convention of the devices was based on the flow control orifice size and rod array structure. For example, the 2.3-343 device combined a 2.3 mm diameter flow control orifice with a rod pattern that had 3 rows containing 3, 4, and 3

FIG. 1. Aerosol generation and delivery devices including the (a) inline dry powder inhaler (DPI) with 3D rod array connected to the nasal cannula, (b) cannula for N2L delivery with a single inlet for aerosol administration with ambient room air, and (c) cannula for N2L delivery during HFNC therapy with two inlets allowing for the aerosol and HFNC gas to be administered to separate nostrils. In panels (b) and (c), the dark shading illustrates the streamlined flow passage for the aerosol. The nasal prongs from the cannula device are short and enter the nostrils only several millimeters.

rods, respectively. In this study, a short streamlined flow passage was implemented between the 3D rod array and nasal cannula to minimize depositional loss. Based on the study of Behara et al.,²⁸ the two best performing inline DPIs for an albuterol sulfate (AS) EEG formulation were 3.1–565 and 2.3–343 with average (RMS) flows of 27.2 and 14.7 LPM, respectively. These two devices achieved MMADs near 1.5 μm with emitted doses (ED) greater than 70% from the nasal cannula and $\text{FPF}_{<5\mu\text{m}}$ based on ED greater than 65%, and will be further explored in this study.

Nasal cannula

The inline DPI devices were tested with previously developed nasal cannula for nose-to-lung (N2L) delivery and N2L delivery during HFNC therapy (Fig. 1b and 1c). Both cannulas implement a streamlined design for the aerosol flow passage, which was previously shown to significantly improve aerosol delivery.^(26,29) To administer the aerosol for N2L delivery, the single inlet cannula was used (Fig. 1b). Once inhaled, the EEG hygroscopic aerosol formulation interacts with the natural relative humidity in the airways causing size increase and deposition of the aerosol droplets. With N2L delivery during HFNC therapy, a divided nasal cannula is employed (Fig. 1c) such that the aerosol and heated/humidified airflow are delivered to separate nostrils. As described by Longest et al.,² these controlled condensational growth approaches allow the aerosol to remain at a

small size in the nasal airways and then experience rapid growth in the lungs likely resulting in full lung retention of the droplets. In the experiments, the heated and humidified HFNC gas was supplied by a VapoTherm 2000i device (VapoTherm, Stevensville, MD). The VapoTherm delivery temperature was set to 43°C and previous measurements of humidity from the outlet of this system have resulted in RH values near 99%–100%.⁽⁵⁾

Airway models

The airway geometry consisted of a characteristic NMT model, upper TB region, and a chamber to simulate residence time of the aerosol in the lungs (Fig. 2). The characteristic NMT model was previously described and implemented in the study of Golshahi et al.⁽⁵⁾ Briefly, the NMT model included the nasal geometry of Guilmette et al.,⁽³¹⁾ which has been implemented in numerous *in vitro* and numerical studies.^(32–37) Smoothing of the initial Guilmette et al.⁽³¹⁾ data was employed to produce a physiologically realistic looking surface. The nasopharynx, pharynx, and larynx were developed from the anatomical CT data used in the previous study of Xi and Longest.⁽³⁸⁾ The oral cavity region was also based on the previous CT data and approximates a nearly closed mouth position. Airflow is not included through the mouth opening, consistent with a subject breathing nasally.

A realistic model of the upper TB airways was employed, which was recently developed by Walenga et al.⁽³⁹⁾ The

FIG. 2. The composite airway model employed in the *in vitro* experiments and CFD simulations composed of a nose-mouth-throat (NMT) geometry, upper tracheo-bronchial (TB) model, and a lung chamber designed to provide a 1.6–2.0 sec exposure time of the particles to controlled thermodynamic conditions prior to exiting the right angle arm leading to the impactor for size measurement.

FIG. 3. Illustration of the (a) N2L and (b) N2L during HFNC therapy nasal cannulas positioned in the nostrils. Only the internal flow passages of the cannulas are shown without the exterior support structure.

model begins at the tracheal inlet and continues through the third respiratory bifurcation (B3), with the trachea and main bronchi representing B1. As described by Walenga et al.,⁽³⁹⁾ this model was developed to represent the average airway anatomy of an adult male based on comparisons to a database of upper airways from 21 individuals. For the upper TB model, average airway hydraulic diameters in the trachea, right main bronchus, and left main bronchus were 19.4, 14.9, and 11.6 mm, respectively.

Finally, the upper TB model was housed in a cylindrical lung chamber with a volume of 2.0 L. The chamber volume and dimensions in addition to the NMT-TB geometry provide an approximate 1.9 sec residence time for the particles at a flow rate of 45 LPM before exiting the right-angle arm configuration and entering the impactor for sizing. At a flow rate of 60 LPM, used with the 3.1-565 device, the total aerosol residence time in the chamber was 1.6 sec.

Delivery scenarios

Aerosol and gas delivery scenarios employed in the *in vitro* experiments are described in Table 1. The initial particle size of the aerosol exiting the 2.3-343 device was determined. The 2.3-343 device was also then tested for both N2L delivery (Fig. 3a) and N2L delivery during HFNC therapy (Fig. 3b). The 3.1-565 device was tested for N2L delivery during HFNC therapy.

For each experiment, the ventilation bag was operated with ambient room air, which was assumed to be approximately 25°C and 40% RH. As described, the Vapotherm 2000i was used to produce HFNC therapy gas in the case of N2L delivery with the HFNC device. During aerosol deposition and size change experiments, the NMT-TB model was housed in an environmental cabinet (Espec, Hudsonville, MI) and maintained at 37°C and 100% RH. Prior to the experiments, the *in vitro* airway model was allowed to equilibrate to 37°C within the chamber and the inner surfaces of the model were pre-wetted. Due to these environmental conditions, the inline DPI and cannula were inserted into the model immediately prior to actuation of the device to avoid unrealistic exposure of the DPI to the high RH. In practical use, the inline DPI and cannula would be exposed to normal environmental temperature and RH conditions. Delivery scenarios with the 2.3-343 devices used a constant tracheal inhalation of 45 LPM. The tracheal inhalation flow rate was increased to 60 LPM for use with the 3.1-565 inline DPI due to the increased flow rate through the DPI. During an *in vitro* experiment, air enters the model from both the cannula and the chamber (37°C and 100% RH) as it is inhaled through the nostrils in the space surrounding the nasal prongs (Table 1).

In all cases, a 2 mg dose of spray dried powder was loaded into the size 3 HPMC capsules and aerosolized. Four actuations of the manual ventilation bag were implemented

TABLE 1. INLET AND BOUNDARY CONDITIONS FOR TESTING NOSE-TO-LUNG (N2L) AND N2L DURING HIGH FLOW NASAL CANNULA (HFNC) THERAPY AEROSOL DELIVERY WITH *IN VITRO* EXPERIMENTS AND CFD VALIDATION SIMULATIONS

Cases	Initial d_{ae} (μm) ^a	Aerosol inlet	Humidity inlet (HFNC)	Additional nasal inhalation ^b	Wall conditions
2.3-343-N2L Growth	1.4	13.9 L/min, 40% RH, 25°C	NA	31.1 L/min, 100% RH, 37°C	100% RH, 37°C
2.3-343-N2L-HFNC Growth	1.4	13.4 L/min, 40% RH, 25°C	20 L/min, 100% RH, 43°C	11.6 L/min, 100% RH, 37°C	100% RH, 37°C
3.1-565-N2L-HFNC Growth	1.4	22.0 L/min, 40% RH, 25°C	20 L/min, 100% RH, 43°C	18.0 L/min, 100% RH, 37°C	100% RH, 37°C

^aInitial aerodynamic diameter (d_{ae}) of the monodisperse aerosol used in the CFD simulations based on MMAD measurements from the *in vitro* experiments.

^bAdditional airflow entering the nose around the nasal prongs to accommodate the tracheal inhalation flow rate for the 2.3-343 (45 LPM) and 3.1-565 (60 LPM) devices.

requiring approximately 2.5 sec each for the 2.3-343 device and approximately 1.5 sec each for the 3.1-565 device. At a tracheal inhalation flow rate of 45 LPM, an inhalation time of 2.5 sec results in an inhaled volume of 1.9 L per breath, which is well within the total inhaled volume limit of an adult.⁽⁴⁰⁾ Similarly at an inhalation flow rate of 60 LPM, an inhalation time of 1.5 sec results in an inhaled volume of 1.5 L, which is also acceptable. Behara et al.⁽²⁸⁾ previously reported high ED and low variability with the inline devices after two bag actuations; however, four actuations further reduced the variability in ED.

Several limitations of the *in vitro* setup include the inhalation of chamber air by the model and the use of 37°C wall temperatures throughout. The CFD model is first validated under these physiological conditions with comparisons to the *in vitro* results. Additional simulations are then conducted to evaluate the effects of more realistic nasal inhalation conditions and wall temperatures, as described in Table 2. Specifically, ambient room air was inhaled around the nasal prongs (25°C and 40% RH) to satisfy the tracheal inhalation flow rate and the physiologically correct nasal surface temperature was assumed to be 33°C.⁽⁴¹⁾

Powder formulation

Excipient enhanced growth formulation combination particles were engineered as described by Son et al.⁽²³⁾ Briefly, a 20% ethanol in water mixture containing 0.5% w/v of solutes consisting of Cipro, mannitol, 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 μ m nozzle diameter at 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 of the spray dryer and was stored in a desiccator until it was used. The powder yield was about 50%–60%. Approximately 1 mg powder was dissolved in 100 mL of deionized water and analyzed for content uniformity ($n=3$) of Cipro in the formulation using the USP HPLC method for Cipro.

Emitted dose, initial particle size, NMT deposition, and aerosol growth determinations

For each experiment, the powders were aerosolized with the DPIs in a horizontal position. After aerosolization, the drug mass retained in the capsule, capsule chamber (CC), flow passage with 3D array and cannula was determined by

washing each part with de-ionized water. Drug mass of Cipro was determined in each region using the USP HPLC assay for Cipro and expressed as a percentage of the loaded dose. The emitted dose (ED) was calculated by subtracting the measured Cipro mass retained in the capsule, CC, flow passage, and cannula from the loaded dose, where the loaded dose was determined from the initial weight of the powder and percent of drug content in the EEG formulation.

The initial particle size of the aerosol at the exit of the cannula was determined using cascade impaction in a Next Generation Impactor (NGI; MSP Corp., Shoreview, MN) operated at a constant flow rate of 45 LPM for the 2.3-343 device and 60 LPM for the 3.1-565 device. The prongs were positioned centrally at the entrance of the pre-separator (without an adaptor or induction port) allowing the aerosol to be entrained into the impactor. All measurements were made with at least three replicates. The stages of the impactor were coated with silicone spray (Molykote® 316, Silicone Release Spray, Dow Corning, Midland, MI) to minimize particle bounce and re-entrainment. Drug mass was determined by washing with de-ionized water and collecting drug from the pre-separator, impactor plates, and the filter for quantitative determination by HPLC. Fine particle fraction (FPF) of the DPI aerosol ($FPF_{<5\mu m/ED}$) and submicrometer FPF ($FPF_{<1\mu m/ED}$) were defined as the percent mass of Cipro less than 5 μ m and 1 μ m, respectively, based on the mass percent ED. The Cipro mass median aerodynamic diameter (MMAD) was obtained for the drug mass entering the impactor. MMAD, $FPF_{<5\mu m/ED}$ and $FPF_{<1\mu m/ED}$ were calculated from linear regression equations resulting from cumulative percentage mass vs. natural logarithm of the cut-off diameter for the respective NGI stages.

Deposition of drug mass in the airway model was determined with experiments conducted within the environmental chamber. Cipro deposition was evaluated in the combined airway model (NMT-TB) and lung chamber and reported as a deposition fraction based on loaded dose for the inline DPI. Following each experiment the model was washed with deionized water and the deposition in the NMT model and lung chamber was quantitatively determined by HPLC. The combined airway model was washed in 20 mL of deionized water whereas each device component and each NGI plate was washed with 10 mL each.

Finally, an assessment of the aerosol particle size following passage through the NMT model was performed using the NGI, which was connected to the right angle arm leading out of the lung chamber. Determination of the Cipro particle size distribution and data analysis was performed as described previously for the initial particle size distribution.

TABLE 2. INLET AND BOUNDARY CONDITIONS FOR TESTING N2L AND N2L DURING HFNC AEROSOL DELIVERY USING CFD SIMULATIONS WITH IMPROVED REALISM

Cases	Initial d_{ae} (μ m)	Aerosol inlet	Humidity inlet (HFNC)	Additional nasal inhalation	Nasal wall conditions	MT-TB walls
2.3-343-N2L	1.4	13.9 L/min, 40% RH, 25°C	NA	31.1 L/min, 40% RH, 25°C	100% RH, 33°C	100% RH, 37°C
2.3-343-N2L-HFNC	1.4	13.4 L/min, 40% RH, 25°C	20 L/min, 100% RH, 43°C	11.6 L/min, 40% RH, 25°C	100% RH, 33°C	100% RH, 37°C

CFD simulations

A CFD model was implemented that can accurately simulate local temperature and humidity fields, together with droplet trajectories, droplet size change, and deposition within the cannula and airway model during aerosol delivery. To address both laminar and turbulent flow conditions effectively, a low Reynolds number (LRN) $k-\omega$ turbulence model was selected.⁽⁴²⁾ This approach has previously been well tested and found to provide good estimates of aerosol transport and deposition in airway models provided that near-wall corrections are included.^(43–46) To evaluate the variable temperature and RH fields in the conducting airway geometry, interconnected relations governing the transport of heat and mass (water vapor) were also included. These governing equations were presented in detail by Longest and Xi⁽⁴⁷⁾ and Longest et al.⁽⁴⁵⁾

Particle transport

To model droplet trajectories, growth, and deposition, previously developed and tested commercial code (ANSYS Fluent 12, ANSYS Inc.) and user functions were implemented. User routines were employed to better model near-wall conditions and to simulate multicomponent aerosol condensation and evaporation in the complex three-dimensional temperature and humidity fields. Previous studies have shown that the isotropic turbulence approximation, which is assumed with the LRN $k-\omega$ model, can over predict aerosol deposition.⁽⁴⁸⁾ As a result, a user routine was employed to account for anisotropic near-wall turbulence, as described by Longest et al.⁽⁴⁵⁾ Other additions to the particle tracking model included (i) a correction to better predict the Brownian motion of submicrometer aerosols and (ii) improved near-wall interpolation of fluid velocities.⁽⁴⁹⁾

A user routine was employed to model interconnected droplet temperature and size change resulting from condensation and evaporation. This droplet model accounts for the Kelvin effect, hygroscopicity arising from multiple soluble components, and the effect of droplet temperature on surface vapor pressure.⁽²¹⁾ In simulating aerosol evaporation and growth, the effect of the droplets on the continuous phase was neglected, resulting in a one-way coupled approach. One-way coupled simulations are expected to be accurate in this study due to the use of submicrometer aerosols and wetted walls.⁽⁵⁰⁾

In performing the CFD simulations, previously established best-practices were implemented to provide a high quality solution.⁽⁴⁴⁾ To solve the transport governing equations, the CFD package ANSYS Fluent 12.0, (ANSYS Inc.) coupled with user-defined functions was employed. All transport equations were discretized to be at least second order accurate in space. As part of a best-practices approach, convergence of the solution was verified in terms of both mass and momentum residuals and number of particles simulated. Grid convergence was established by successively increasing the grid resolution. Checks on all types of convergence resulted in a less than 3% relative change in maximum flow velocities, final aerosol sizes, and regional depositional values.

In the simulations, the initial particles were composed of the same materials in the same proportions as used in the *in vitro* experiments. L-leucine and poloxamer 188

were considered nonhygroscopic and nonsoluble in water. The hygroscopic parameters of Cipro and mannitol were calculated using the methods described by Longest and Hindle.⁽²⁰⁾ In the simulations, the complex DPI geometry was replaced by a 10 mm diameter tube and the particles were introduced at the site of the DPI outlet. The cannula geometry was reproduced from the experiments in terms of dimensions and positioning. The initial particle size in the simulations was based on the experimentally measured MMAD exiting the cannula prior to humidity exposure in the airway model. Small aerosol size change between the cannula inlet and outlet is expected to be negligible due to very low cannula deposition fractions.⁽²⁹⁾ The initial aerosol size distribution was assumed monodisperse with the aerodynamic diameter of the aerosol (d_{ac}) equal to the experimentally measured MMAD. This assumption is based on an expected monomodal size distribution and small geometric standard deviation (GSD) of the aerosol *in vitro*.⁽²⁸⁾

Statistical analysis

In the current investigation, the data were expressed as the mean $\pm$ standard deviation (SD) based on at least three replicates of each experiment. The statistical significance was determined using Student's *t*-test at a *p*-value of 0.05 using JMP Pro (Version 10.0.2, SAS Institute, Cary, NC, USA).

Results

In vitro experiments

Characteristics of the Cipro formulation aerosol exiting the nasal cannula using the 2.3-343-N2L device are reported in Table 3. The device was actuated with four bag squeezes using ambient air and the aerosol entered the NGI preseparator for determination of the initial particle size distribution following dispersion using the inline DPI (this aerosol was not exposed to the airway model and growth conditions). The average RMS flow rate through the device was measured to be 13.9 LPM. The emitted dose from the 2.3-343-N2L device was 67% with the highest device drug retentions observed in the flow passage (14.3%) and capsule chamber (11.7%). Deposition in the flow passage includes the 3D rod array, short connector, and streamlined nasal cannula. Aerosol dispersion of the formulation appears excellent with $FPF_{<5\mu m/ED}$ and $FPF_{<1\mu m/ED}$ values of 95.9% and 25.3%, respectively, leaving the nasal cannula. The resulting aerosol has an MMAD of 1.4 μm , which is expected to pass through the nasal cavity with low depositional loss making it suitable for nose to lung delivery.

Simulated *in vitro* exposure and growth results are also reported in Table 3 and represent performance of the inline DPI connected to the airway geometry and maintained at physiological conditions of 37°C and 100% RH, as described in Table 1. As with the initial size experiments, ambient air (20°–25°C and 30%–45% RH) was used to actuate the device. Compared with the initial size experiments, ED and device retention characteristics are unchanged when the device is connected to the airway geometry. Drug deposition in the NMT and TB region is <5% of the loaded dose due to the minimal impaction losses of the small aerosol generated by the inline DPI. Lung delivery efficiency for the N2L method is observed to be 62% of the loaded dose.

TABLE 3. EMPTYING, NMT AND UPPER TB DEPOSITION, AND AEROSOL CHARACTERISTICS OF CIPROFLOXACIN HYDROCHLORIDE (CIPRO) RESULTING FROM FOUR BAG SQUEEZES FOR N2L DELIVERY WITH THE INLINE DPIS

Description	2.3-343-N2L Initial Size	2.3-343-N2L Growth	2.3-343-N2L during HFNC Growth	3.1-565-N2L during HFNC Growth
Emitted dose (%) ^a	67.4 (0.6)	66.5 (3.5)	71.3 (3.0)	69.5 (2.7)
Capsule retention (%)	6.6 (1.0)	8.2 (0.8)	7.3 (1.3)	8.8 (1.6)
Capsule chamber retention (%)	11.7 (0.6)	10.7 (3.1)	7.7 (1.6)	6.4 (0.1)
Flow passage retention (%) ^b	14.3 (0.6)	14.6 (0.7)	13.7 (0.4)	15.4 (1.2)
NMT-TB (%)	N/A	4.4 (0.6)	7.6 (0.9)**	12.1 (1.4)#
<i>In vitro</i> lung dose (%)	N/A	62.2 (3.1)	63.7 (2.6)	57.4 (3.9)
FPF _{<5μm/ED} (%)	95.9 (0.8)	83.7 (0.7)*	77.4 (1.1)**	72.0 (0.7)#
FPF _{<1μm/ED} (%)	25.3 (2.4)	5.8 (0.3)*	5.2 (0.4)	7.0 (0.6)#
MMAD (μm)	1.4 (0.04)	2.5 (0.05)*	2.7 (0.1)**	2.4 (0.1)#
GSD	1.8 (0.03)	1.7 (0.02)	1.7 (0.03)	1.6 (0.02)

* $p < 0.05$ significant difference between 2.3-343-N2L initial and 2.3-343-N2L growth (Student's *t*-test); ** $p < 0.05$ significant difference between 2.3-343-N2L growth and 2.3-343-N2L during HFNC growth (Student's *t*-test); # $p < 0.05$ significant difference between 2.3-343-N2L during HFNC growth and 3.1-565-N2L during HFNC growth (Student's *t*-test).

^aPercentage of the loaded dose leaving the nasal cannula; ^bIncludes the 3D rod array, short connector, and streamlined nasal cannula. Measurements were made for initial sizing at ambient conditions where the dose directly entered the preseparator and for growth where the aerosol passed through the NMT-TB and lung chamber with controlled thermodynamic conditions (Table 1). [$n = 3$; Mean (SD)].

Furthermore, significant size increase of the aerosol is observed with the FPF_{<1μm/ED} falling from an initial value of 25.3% to 5.8% and the MMAD increasing to 2.5 μm from 1.4 μm. The geometric standard deviation (GSD) of the aerosol is similar between the initial and growth sizes with a value of 1.7–1.8, which represents a relatively monodisperse pharmaceutical aerosol.

Comparison of the N2L delivery in the presence of HFNC therapy is shown following delivery through the airway model with growth conditions in Table 3. The flow rate through the N2L with HFNC device (13.4 LPM) was nearly identical to that measured for the N2L system, as expected. As a result, ED (71.3%) was similar to the N2L delivery approach. Due to the inclusion of additional humidity and the potential for accelerated aerosol size increase in the pharyngeal and TB model, NMT-TB deposition was higher with HFNC therapy compared to the N2L delivery, but remained below 10%. This increase in aerosol growth can be observed with the MMAD, where the N2L during HFNC therapy approach produced a statistically larger value of 2.7 μm. Practically, such a small change would not be expected to be clinically significant. The overall lung delivery efficiency was high with 64% of the loaded dose being delivered to the airways.

Table 3 also shows the performance of the 3.1-565-N2L with HFNC device. As expected, the 3.1-565 device with the larger 3.1 mm diameter flow control orifice produced a higher flow rate of 22 LPM with manual bag actuation. To accommodate the HFNC humidity flow delivery rate of 20 LPM (Table 1), the tracheal flow rate through the impactor was increased to 60 LPM. Despite the increase in flow rate, the ED and regional device retention values were not statistically different from the 2.3-343 case. Due to the higher flow rate, NMT-TB deposition increased to 12.1% while MMAD exiting the lung chamber decreased to 2.4 μm.

It appears that the best device considered for N2L aerosol delivery is the 2.3-343 inline DPI, which is suitable for use alone or during HFNC therapy. Use of HFNC therapy during N2L delivery increases NMT-TB deposition (7.6 vs.

4.4%), but also increases the final aerosol size exiting the lung chamber (2.7 vs. 2.5 μm). The CFD model will be used to determine the fraction of NMT-TB deposition that is in the nose vs. in the TB region.

Validation of CFD model

CFD simulations were conducted for N2L and N2L during HFNC therapy aerosol delivery with the 2.3-343 device under flow and thermodynamic conditions that were consistent with the *in vitro* experiments (Table 1). For N2L delivery, gradual size increase of the aerosol is observed through the upper airway model resulting in a final aerosol MMAD of 2.4 μm exiting the lung chamber (Fig. 4a). This value is in very close agreement with the experimentally measured value of 2.5 μm. Similarly, deposition predictions in the NMT-TB and lung chamber geometries were in close agreement with the *in vitro* predictions (Fig. 4b). For the case of N2L delivery during HFNC therapy, both the CFD model and experimental results predicted an MMAD exiting the lung chamber of 2.7 μm (Fig. 5a). Deposition results are again in close agreement between the simulations and experiments (Fig. 5b). Therefore, the CFD model is highly accurate in predicting both growth and deposition of the EEG formulation aerosol in the NMT-TB airway and lung chamber geometries. These results are impressive, considering that the model must account for laminar to turbulent flows, multiple species (air and water vapor), heat transfer, hygroscopic and multiple solute effects, and droplet deposition in a highly complex geometry. Furthermore, agreement between the CFD and *in vitro* results indicates that the one-way coupled assumption is sufficient for the conditions evaluated.

CFD simulations with improved realism

Additional CFD simulations were conducted with a physiologically realistic nasal surface temperature (33°C)⁽⁴¹⁾ and inhalation of additional ambient air around the nasal prongs, as described in Table 2. Deposition and final aerosol size

FIG. 4. CFD predictions for the 2.3-343-N2L device of (a) particle trajectories colored according to droplet size and (b) deposition fractions and locations with comparisons to *in vitro* experimental data. In these simulations the flow and thermodynamic conditions were identical to the *in vitro* experiments (Table 1). Close agreement is observed between the CFD predictions and *in vitro* results in terms of MMAD exiting the lung chamber and regional deposition fractions.

predictions with these highly realistic boundary conditions are provided in Table 4. Considering comparisons with the *in vitro* conditions, both final size and regional deposition are very similar with both delivery methods. For example, both sets of boundary conditions with N2L delivery resulted in a CFD predicted final size of $2.4 \mu\text{m}$ and approximately 6% NMT-TB deposition. Similarly for N2L delivery during HFNC therapy, the final MMAD exiting the lung chamber was not changed due to the more realistic boundary conditions with CFD predictions. As a result, it does not appear significant to maintain the exact nasal surface temperature of

33°C in the *in vitro* model considering that a majority of the airway is expected to be at 37°C and 100% RH.

The CFD results provide the additional advantage of determining more localized deposition patterns. For example, with the highly realistic boundary conditions, nasal depositions are only 0.5 and 1.2% for the N2L and N2L with HFNC 2.3-343 devices, respectively. Similarly, values for upper TB deposition for the two methods are 2.9 and 3.6%, respectively, which are considered part of the lung deposition fraction. Therefore, a significant fraction of the *in vitro* reported NMT-TB deposited dose is successfully delivered to the lungs.

FIG. 5. CFD predictions for the 2.3-343-N2L with HFNC device of (a) particle trajectories colored according to droplet size and (b) deposition fractions and locations with comparisons to *in vitro* experimental data. In these simulations the flow and thermodynamic conditions were identical to the *in vitro* experiments (Table 1). Close agreement is observed between the CFD predictions and *in vitro* results in terms of MMAD exiting the lung chamber and regional deposition fractions.

TABLE 4. CFD PREDICTIONS OF REGIONAL AEROSOL DEPOSITION FRACTION (%) AND MMAD EXITING THE LUNG CHAMBER WITH THE 2.3-343 DEVICE AND HIGHLY REALISTIC BOUNDARY CONDITIONS (TABLE 2)

	2.3-343- N2L growth	2.3-343- N2L during HFNC growth
Nose	0.5	1.2
Mouth-Throat	2.3	3.6
Upper TB	2.9	3.6
NMT-TB	5.7	8.4
Lung Chamber	3.0	3.4
MMAD (μm)	2.4	2.7

Discussion

A primary outcome of this study was the high efficiency aerosolization and lung delivery achieved using a combination of the inline DPI with ventilation bag actuation and the EEG particle formulation with Cipro as the active pharmaceutical ingredient. The 2.3-343 device produced a 70% ED of the loaded drug mass from the nasal cannula with an initial MMAD $< 1.5 \mu\text{m}$. Deposition in the NMT-TB geometry for the 2.3-343 device was $< 5\%$ for N2L and $< 10\%$ for N2L during HFNC therapy, which equates to lung delivery efficiencies of 62.2% and 63.7% of the loaded dose, respectively. For the 3.1-565 device, NMT-TB deposition was near 12% with a lung delivery of 57.4%; however, it is important to realize that these *in vitro* estimates of NMT-TB deposition include the dose delivered to the upper TB model (first three bifurcations).

CFD predictions (Table 4) indicated that 40% or more of the total NMT-TB dose was in the TB geometry. Therefore, it is reasonable to state that the NMT deposition was $< 10\%$ for all cases, which is also consistent with CFD predictions. This depositional loss amount is significantly less than with orally administered DPIs with conventional drug:lactose binary mixture formulations, where approximately 30%–90% of the drug is lost in the oropharynx.^(51,52) Significant growth of the EEG formulation containing Cipro was observed throughout the airway model. Final aerosol MMADs ranged from 2.4–2.7 μm , which are expected to be fully retained in the lungs and not exhaled when administered with instructions for deep inhalation. Size increase of the aerosol can also be used to target the region of aerosol deposition within the lungs. A study by Tian et al.⁽⁶⁾ recently showed that compared with orally inhaled commercial products, N2L delivery with EEG formulation aerosols could enhance deposition in the lower TB airways by factors as large as 35. This improvement in regional drug delivery may enhance the treatment of diseases affecting the lower TB and small airways, such as pulmonary fibrosis⁽⁵³⁾ and COPD.⁽⁵⁴⁾

Considering the 2.3-343 device, results of this study allow for a comparison of N2L and N2L delivery during HFNC therapy. As expected from previous studies,^(5,6) N2L delivery during HFNC therapy resulted in more rapid size increase of the aerosol and a slightly larger final aerosol size. Both methods resulted in a final size $\geq 2.5 \mu\text{m}$, which is expected to be retained within the airways. Previous CFD simulations by Tian et al.⁽⁶⁾ indicated that N2L delivery during HFNC therapy could more efficiently target the total TB region, with

deposition approximately 6-fold greater than with conventional oral DPIs. In contrast, in the absence of the additional humidity, the N2L approach alone could efficiently target the lower TB region and alveoli, where alveolar regional delivery was over two times greater than with a conventional oral DPI. Additional methods that can be used to target aerosol delivery with controlled condensational growth include modifying the amount of hygroscopic excipient within the combination particles, selecting alternative hygroscopic excipients, modifying the inhalation flow rate, and altering the initial aerosol size.^(19,20,25) Nose-to-lung delivery during HFNC therapy allows for simultaneous aerosol and ventilation gas administration, which may be advantageous in certain clinical situations. In the absence of HFNC therapy, the N2L approach allows for convenient administration of the aerosol with only the inline DPI system described in this study.

Considering initial aerosolization with the 2.3-343 device, both the current study with Cipro and the study of Behara et al.⁽²⁸⁾ with AS EEG formulations produced high quality aerosols. However, some differences are observed between the aerosolization of these two powders. For example, the Cipro formulation had a slightly lower ED from the cannula (67.4% vs. 75.3%) and higher FPF _{$< 5 \mu\text{m}$ /ED} (95.9% vs. 65.4%) compared with the AS formulation. The MMAD was smaller with Cipro compared with the AS formulation (1.4 vs. 1.6 μm), which will likely reduce NMT deposition but also reduces final particle size. These variations are due to the significant physicochemical differences between Cipro and AS. However, results of this study indicate that EEG formulations can be developed and efficiently aerosolized using multiple therapeutics. Furthermore, it should be noted that the manually generated flow rates observed in the Cipro and AS independent studies with the inline devices were similar. For example, the 2.3-343 and 3.1-343 device flow rates were 13.4 and 22.0 LPM in the current study vs. 14.7 and 27.2 LPM in the study of Behara et al.⁽²⁸⁾ As a result, actuation of the bag does not appear to be highly dependent on the operator, especially for the 2.3-343 device.

As described in the Introduction, several other studies have considered aerosol delivery during HFNC therapy or with active DPI systems for use in mechanical ventilation. Considering HFNC delivery, the study of Perry et al.⁽¹⁷⁾ implemented typical flow rates and cannula sizes used for adults and demonstrated suboptimal delivery efficiencies of $< 1\%$ to the patient at flow rates of 10 LPM and above. In contrast, the approach implemented in the current study allows for tracheal inhalation flow rates of 45–60 LPM with cannula EDs of 70% and nasal depositional losses of $< 10\%$. A recent study by Pornputtapitak et al.⁽⁵⁵⁾ considered a NanoCluster budesonide formulation delivered with inline DPIs in an *in vitro* model of invasive mechanical ventilation including a 5 mm diameter endotracheal tube connected to an impactor. Emitted doses through the 5 mm tube were approximately 65%–68% with MMADs of 2.2 and 1.7 μm for a commercial and custom inline DPI, respectively, at a ventilation humidity of 51%. This represents a significant improvement in aerosol delivery during mechanical ventilation compared with conventional devices⁽⁸⁾ and a previous inline DPI.⁽⁵⁶⁾ The study of Pornputtapitak et al.⁽⁵⁵⁾ also considered bag actuated delivery and demonstrated that aerosolization performance was better with an automated mechanical ventilation system. An advantage of the NanoCluster budesonide formulation is the lack of excipients. However, this

formulation does not provide the added targeted delivery and lung retention advantages provided with the EEG approach.

Additional important findings of the current study include an insensitivity to reduced nasal surface temperatures and the adequacy of one-way coupled simulations. In the *in vitro* experiments, it is not possible to maintain the nasal surface at a temperature of 33°C and the remainder of the airway model at 37°C. However, the CFD results revealed that capturing this temperature difference does not significantly affect deposition in the NMT-TB model and the associated final aerosol size. Furthermore, nasal surface temperatures during HFNC therapy are not known. As a result, it appears appropriate to simulate the entire airway at a physiological approximation of 37°C and 100% RH. Agreement between the *in vitro* results and CFD predictions provides confidence that the one-way coupled simulations are appropriate for the dose and initial particle size considered.

This study has demonstrated the potential of N2L delivery using a DPI with low losses in the device and extrathoracic airways. As described by Behara et al.,⁽⁵⁷⁾ ED may be further improved with surface coatings as well as continued airflow through the device. The system described can be directly applied to improving aerosol delivery simultaneously with HFNC therapy. The realization of envisioned N2L applications without HFNC therapy will, however, require additional research. For example, the administration of medications with extended delivery times will require adjusting the device for prolonged release of the powder by a continuous gas source. Treating the nasal and lung airways simultaneously with an antibiotic, such as Cipro, will require designing the EEG technique in a manner that produces deposition leading to nearly equal airway surface liquid concentrations of the drug. Use of the device in pediatric applications to replace facemasks will require adjustments in the cannula design and flow rate.

In this study, Cipro was considered as a model inhalable antibiotic formulation. However, the dose considered may be significantly lower than what is needed to have a biological effect.⁽⁵⁸⁾ Some reduction from currently proposed inhaled doses may be possible due to improved lung delivery with controlled condensational growth, however further studies will be required. It may also be necessary to consider improved local delivery in determining the appropriate initial dose in a dose escalation study with EEG formulations. For example, Tian et al.^(6,25) indicated an order of magnitude increase in lower TB dose with N2L delivery compared with conventional DPIs. Future studies will explore performance of the inline bag actuated DPIs with increasing dosages of antibiotics like Cipro. However, the current results indicate excellent aerosolization performance of a baseline dose for EEG formulation delivery.

Conclusions

In conclusion, the new inline DPIs provided high efficiency aerosolization and lung delivery of a new Cipro EEG formulation powder. Extrathoracic depositional losses with N2L delivery were less than 10% for all cases and the initially small aerosol increased in size due to hygroscopic growth throughout the airway model to MMADs of 2.4 µm or greater. Compared with aerosol delivery during HFNC therapy in studies that employed typical flow rates used in

adults,⁽¹⁷⁾ lung delivery of the aerosol was improved by multiple orders of magnitude. The CFD results agreed well with *in vitro* experiments and provided more refined estimates of nasal deposition with values less than 2%. An additional advantage of EEG formulation and controlled condensational growth delivery is the ability to target the region of lung deposition, with previous studies indicating dramatic increase in dose to the small airways. Future studies are needed with antibiotics to determine realistic doses for clinical effects and to test the aerosolization of these doses with the inline DPI for effective N2L aerosol delivery.

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Author Disclosure Statement

Virginia Commonwealth University is currently pursuing patent protection of EEG aerosol delivery and the 3D rod array device used for deaggregation, which if licensed, may provide a future financial interest to the authors.

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Reviewed by:
Philip Kwok
Yung-Sung Cheng

Address correspondence to:
P. Worth Longest, PhD
Virginia Commonwealth University
401 West Main Street
P.O. Box 843015
Richmond, VA 23284-3015

E-mail: pwlolongest@vcu.edu