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Performance of Combination Drug and Hygroscopic Excipient Submicrometer Particles from a Softmist Inhaler in a Characteristic Model of the Airways

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Abstract

Excipient enhanced growth (EEG) of inhaled submicrometer pharmaceutical aerosols is a recently proposed method intended to significantly reduce extrathoracic deposition and improve lung delivery. The objective of this study was to evaluate the size increase of combination drug and hygroscopic excipient particles in a characteristic model of the airways during inhalation using both *in vitro* experiments and CFD simulations. The airway model included a characteristic mouth-throat (MT) and upper tracheobronchial (TB) region through the third bifurcation (B3) and was enclosed in a chamber geometry used to simulate the thermodynamic conditions of the lungs. Both *in vitro* results and CFD simulations were in close agreement and indicated that EEG delivery of combination submicrometer particles could nearly eliminate MT deposition for inhaled pharmaceutical aerosols. Compared with current inhalers, the proposed delivery approach represents a 1–2 order of magnitude reduction in MT deposition. Transient inhalation was found to influence the final size of the aerosol based on changes in residence times and relative humidity values. Aerosol sizes following EEG when exiting the chamber (2.75–4.61 μm) for all cases of initial submicrometer combination particles were equivalent to or larger than many conventional pharmaceutical aerosols that frequently have MMADs in the range of 2–3 μm .

Keywords

Respiratory drug delivery; nanoaerosols; hygroscopic droplet growth; excipient enhanced growth; targeted aerosol deposition; characteristic airway model

INTRODUCTION

Current inhalers are inefficient at delivering pharmaceutical aerosols to the lungs due to high depositional losses in the device and extrathoracic airways. For widely used metered dose inhalers (MDIs) and dry powder inhalers (DPIs), mouth-throat (MT) depositional losses are typically in the range of 25 – 75% and higher, with the remaining drug fraction delivered to the lungs.^{15,21,37,52} Newly developed softmist inhalers have reduced MT deposition somewhat; however, high device deposition and retention remain an issue.^{22,38} High extrathoracic deposition results in increased side effects,¹⁹ reduced drug effectiveness, and increased costs of inhaled medications. A positive correlation also exists between high MT

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Conflicts of Interest

No conflicts of interest exist.

deposition and increased variability in lung dose.³ Moreover, high deposition fractions of pharmaceutical aerosols in the nasal airways typically eliminate the potential for delivering inhaled medications through the nose to the lungs. Despite these high extrathoracic deposition fractions of drugs, current orally inhaled medications such as bronchodilators and corticosteroids are clinically effective for treating respiratory conditions like COPD and asthma.³⁷ Improving the delivery efficiency of these medicines to the lungs will reduce side effects and treatment costs while improving patient compliance. In contrast, high MT deposition and intersubject variability are not acceptable for the delivery of many envisioned next generation inhaled medications such as antibiotics, insulin, vaccines, and chemotherapy.^{4,39} These next-generation medicines require more precise dosing to the airways and may require targeting the site of deposition within the lungs to minimize side effects for drugs with narrow therapeutic windows. As a result, improved aerosol drug delivery approaches are needed that are capable of significantly reducing extrathoracic drug loss, reducing intersubject variability, and targeting deposition within the lungs in order to make many envisioned inhaled medications a reality.

Controlled aerosol growth is a newly proposed method to significantly reduce extrathoracic losses and potentially target the site of aerosol deposition within the lungs using submicrometer and nanometer particles. With this method, pharmaceutical aerosols are inhaled orally or nasally as submicrometer or nanometer particles (or droplets). Due to the small size of the initial particles, in the range of approximately 40 – 1000 nm, extrathoracic deposition is significantly reduced⁴⁹ compared with conventional pharmaceutical aerosols. However, lung deposition and retention is also low for particles in this submicrometer size range. Two methods were recently described to increase submicrometer aerosol size *in vivo* following passage through the MT and thereby foster lung deposition and potentially target the deposition location. Longest et al.³⁰ presented the enhanced condensational growth (ECG) method, in which an initially submicrometer aerosol is inhaled with water vapor-saturated warm air to increase the particle size within the airways. Previous results indicate droplet diameters increasing to conventional-sized pharmaceutical aerosols, negligible MT deposition, and order of magnitude increases in upper and lower lung deposition compared with submicrometer particles.^{15,23,41} A second method to increase aerosol size *in vivo* is excipient enhanced growth (EEG), in which initially submicrometer particles are formed containing both an active agent and hygroscopic excipient.^{16,24} The natural relative humidity in the airways, which is typically considered to be 99.5%, interacts with the hygroscopic excipient causing condensational growth and significant size increase. Longest and Hindle²⁴ developed correlations to predict the size increase of initially submicrometer combination drug and hygroscopic excipient particles in the airways and demonstrated diameter growth ratios of up to 4.6 at excipient mass loadings of 50% and below. Hindle and Longest¹⁶ implemented *in vitro* experiments in a tubular geometry and demonstrated that it was possible to control the size growth ratio by altering the hygroscopic excipient, drug:excipient ratio, and drug. Longest and Hindle²⁵ implemented the same tubular geometry and developed a validated CFD model of combination aerosol size increase in comparison with *in vitro* data. The CFD model results revealed gradual size increase of the combination particles over the time scale of an inhalation cycle and aerosol growth from submicrometer to conventional pharmaceutical aerosol size that is expected to deposit in the lower tracheobronchial (TB) and alveolar airways by impaction and sedimentation.

As described above, previous studies have demonstrated that combination submicrometer particles composed of a drug and hygroscopic excipient can be used to increase aerosol size to a range that is expected to deposit within the lungs in a controlled manner. The studies of Hindle and Longest¹⁶ and Longest and Hindle²⁵ implemented a coiled tube geometry with pre-wetted and temperature controlled walls to simulate the thermodynamic and residence time conditions of the respiratory airways. Growth was observed to be continuous over the

time course of inspiration. However, the location of size increase within the airways was not reported because an anatomically accurate airway model was not implemented in these previous studies. Deposition was also not previously considered in EEG studies such that low MT and upper TB depositional losses have not been verified. In general, an *in vitro* and numerical test system is needed that can be used to explore the time course of size increase during EEG delivery within a characteristic model of the MT and TB regions and evaluate upper airway deposition.

The objective of this study is to evaluate the size increase of combination drug and hygroscopic excipient particles in a characteristic model of the airways during oral inhalation using both *in vitro* experiments and CFD simulations. The airway model includes a characteristic MT and upper TB region through the third bifurcation (B3) to accurately capture upper airway deposition and transition to fully humidified conditions. The model is housed in a chamber designed to produce residence times consistent with one inhalation cycle (i.e., 2 s). The resulting setup produces geometric realism through B3 and accurate thermodynamic exposure conditions for approximately 1 inhalation cycle. *In vitro* experiments are conducted with a state-of-the-art softmist inhaler modified to produce combination drug and excipient submicrometer aerosols.

Experimental results are used to demonstrate size increase within the airway model, deposition, and to validate the CFD simulations. CFD modeling is implemented to corroborate the experimental results and reveal the detailed time course of droplet size increase within the airways. The validated CFD model is then used to explore the influence of different excipients on size increase as well as the effects of steady state vs. transient inhalation conditions.

MATERIALS AND METHODS

Airway Model

The geometry considered in this study consisted of the MT for oral inhalation with a circular mouthpiece (2 cm inlet diameter), upper TB airways, and a cylindrical housing used to provide physiologically relevant thermodynamic exposure conditions and residence time. The MT geometry was the elliptical model proposed by Xi and Longest⁴⁸ and contained the oral cavity, pharynx, and larynx. This geometry was based on the oral airway cast reported by Cheng et al.⁵ and in-house CT data of the pharynx and larynx (Figure 1a). The upper TB airways were represented with an approximate model extending through the third bifurcation (Figure 1a). This asymmetrical model was based on the anatomical cast dimensions reported by Yeh and Schum.⁵¹ The complete lung model of Yeh and Schum⁵¹ (TB and alveolar airways) was scaled to a functional residual capacity (FRC) of 3.5 L, which is consistent with an adult male,¹⁸ and upper airway dimension from this scaled model were used in the present study. Further details about this model, including parameters used in constructing the physiologically realistic bifurcation units and locations of the lobar bronchi were provided in previous studies.^{41,42} Beginning with approximately the mid-trachea, the upper TB model was housed in a cylindrical chamber used to control thermodynamic exposure times and route the aerosol to an impactor for sizing in the *in vitro* experiments (Figure 1b). Preliminary CFD simulations were used to adjust the dimension of the cylinder to minimize deposition and provide a particle residence time of approximately 2 s before exiting the chamber, which is consistent with a typical inhalation cycle.¹⁸ Figure 1c illustrates particle residence times based on CFD simulations in the final chamber design and an average residence time in the geometry of approximately 2.0 s.

The airway geometry was constructed for the *in vitro* experiments using in-house rapid prototyping facilities. A Viper SLA machine (3D Systems, Valencia, CA) constructed an

exact replica of the airway geometry, including the chamber, out of clear Accura 60 plastic resin using a build layer thickness of 0.15 mm and a laser spot diameter of 0.25 mm. In the experiments, the aerosol inlet flow was provided by the aerosol inlet of the dual flow mouthpiece,¹⁵ and the chamber outlet was connected directly to an Andersen Cascade Impactor (ACI) for aerosol sizing. The mouth opening of the MT geometry was 2.2 cm with an inlet diameter for the aerosol stream of 1.1 cm (Figure 1b).

A numerical mesh (Figure 1d) of the airway geometry was constructed for CFD simulations using hexahedral elements to the extent possible, as specified by Vinchurkar and Longest.⁴⁵ Hexahedral mesh elements were used exclusively in the MT and TB regions of the model and multiple rows of hexahedral elements were used on the inner chamber surfaces where deposition may occur. However, due to the complexity of the geometry, some tetrahedral elements were required to fill the chamber area and create a continuous field. Final meshes of the MT-TB geometry and chamber contained 761,259 and 729,180 control volumes, respectively. Near-wall grid spacing of the MT-TB geometry and chamber was maintained to be less than 0.8 and 1.2 mm, respectively. Relative characteristic diameters of the MT-TB model and chamber are 1 cm and 11 cm, respectively. Comparison with a grid containing approximately 1.5 times more control volumes produced less than 3% relative difference in maximum velocity, outlet aerosol size, and particle deposition fractions.

Experimental Methods

In vitro experiments were conducted to generate submicrometer combination aerosols, determine the initial aerosol size distribution, evaluate aerosol growth in the model under EEG conditions, and evaluate drug deposition in the model. The initially submicrometer aerosol was generated using a Respimat Soft Mist™ Inhaler (Boehringer Ingelheim; Ingelheim, Germany)²² with a 80:20 v/v ethanol:water vehicle. Added to the ethanol:water mixture was 0.4% w/v drug (albuterol sulfate; AS) and 0.4% w/v hygroscopic excipient (citric acid; CA), where v is total volume of the mixture. In this manner, dried particles from the mixture consist of approximately 50% drug and 50% hygroscopic excipient. A 730 ml drying tube at the outlet of the Respimat was required to generate a consistent submicrometer aerosol. To evaluate EEG, walls of the model were pre-wetted and the model was housed in an environmental cabinet (Espec; Hudsonville, MI) to maintain a wall temperature of approximately 37 °C. After the walls were wetted, room air was pulled through the inhaler, drying tube, and airway model using a downstream vacuum pump at approximately 30 LPM with ambient conditions of 21 °C and 40% relative humidity (RH). The inhaler was actuated while the 30 LPM airstream was being pulled through the system. The size distribution of the aerosol was assessed both at the airway model inlet and at the outlet of the model after exposure to EEG conditions using either the MOUDI (MSP Corp, Shoreview, MN) or Andersen Cascade Impactor (ACI; Graseby-Anderson Inc.; Smyrna, GA), depending on the aerosol particle size followed by HPLC analysis of AS on each impactor stage. Specifically, the MOUDI was used to better resolve the initial submicrometer particle size, and the ACI was implemented to calculate the final aerosol size exiting the MT-TB growth chamber. Aerosol deposition on the MT-TB model surfaces was also determined using HPLC analysis. The deposition fraction was expressed as a percentage of the nominal emitted drug dose.

CFD Simulations

Computational fluid dynamics simulations of fluid flow, heat and mass transport, along with droplet trajectories, size change, and deposition were considered using a combination of a commercial code (Fluent 12, Ansys Inc.) and user-supplied routines. Some level of turbulence within the airway model was expected based on a maximum Reynolds number range of 8081 to 15627 for all inhalation conditions considered, based on the hydrodynamic

diameter of the glottis. To effectively address both laminar and turbulent flow conditions, a low Reynolds number (LRN) $k-\omega$ turbulence model was selected. This model has previously been well tested, and found to provide good estimates of aerosol transport and deposition in upper airway geometries.⁵⁰ To evaluate the variable temperature and RH fields in the MT-TB model, interconnected relations governing the transport of heat and mass (water vapor) were also included. These governing equations were previously presented in detail by Longest and Xi³² and Longest et al.²⁶ and are included as an appendix to this study.

To simulate droplet trajectories, including hygroscopic size change, a Lagrangian model was implemented that accounted for drag, gravitational, and Brownian motion effects as previously described in the study of Longest and Hindle.²³ To model the effect of turbulent fluctuations on droplet trajectories, or turbulent dispersion, a random walk method was implemented that included a previously described correction for near-wall anisotropic turbulence.²⁶ Deposition predictions of this model were previously shown to agree well with *in vitro* experiments for ambient aerosols, pharmaceutical sprays, and powders delivered from inhalers.^{22,26,27,31,42} The Lagrangian tracking equations are provided in detail in the appendix of this study.

The droplet evaporation and condensation model employed in this study was similar to previous approximations for salts^{8,9,17} and multicomponent aerosols.²³ The heat and mass transfer relations for multicomponent hygroscopic droplets in the respiratory airways were previously reported by Longest and Xi,³² and are briefly reviewed here. The droplet heat and mass transfer model is based on continuum mechanics with corrections for non-continuum effects, as presented by Longest and Xi,³² which is appropriate for the droplet size range considered in this study (500 nm - 5 μ m). The droplet model accounts for interdependent heat and mass transfer, which results in droplet heating during condensation and cooling during evaporation as a function of the surrounding temperature. Mass and heat fluxes at the droplet surface are modified for non-continuum effects using the Knudsen correlation,¹⁰ and blowing velocity effects were also considered.³² A full description of the droplet heat and mass transfer model including all relevant equations is provided in Longest and Xi³² as well as the appendix of this study.

The mass fraction of water vapor on the droplet surface is a critical variable, which is significantly influenced by both temperature and drug concentration. For a combination particle of soluble drug and excipient, the surface mass fraction of water vapor $Y_{v,surf}$ is calculated as

$$Y_{v,surf} = \frac{S K P_{v,sat}(T_d)}{\rho_{air} R_v T_d} \quad (1)$$

where $P_{v,sat}(T_d)$ is the temperature dependent saturation pressure of water vapor, calculated from the Antoine equation,¹³ ρ_{air} is the density of air, R_v is the gas constant of water vapor, and T_d is the droplet temperature. The influence of the Kelvin effect on the droplet surface concentration of water vapor is expressed as

$$K = \exp \left[\frac{4\sigma(T_d)}{d_d \rho_d R_v T_d} \right] \quad (2)$$

where $\sigma(T_d)$ is the temperature dependent surface tension of the droplet, d_d is the droplet diameter, and ρ_d is the droplet density. In Eq. (1), the water activity coefficient, S , describes how dissolved molecules affect the surface concentration of water vapor, i.e., the hygroscopic effect, and can be expressed as

$$S = \left(1 + \frac{i_{drug} \chi_{drug} + i_{ex} \chi_{ex}}{\chi_w} \right)^{-1} \quad (3)$$

for a drug and hygroscopic excipient (*ex*) combination particle where χ represents the mole fraction of each component. The i coefficients account for the effect of molecular dissociation during dissolution and are sometimes referred to as van't Hoff factors. The i values of the solutes were previously determined experimentally by Longest and Hindle²⁴ for use in Eq. (3). At high concentrations of drug and excipient, the available water may not be sufficient to dissolve all of the material. In these cases, χ_{drug} and χ_{ex} are replaced by the mole fraction solubility limits of each compound in water. This approach assumes an initial droplet model of a solid core of un-dissolved material surrounded by a layer of liquid with a saturated concentration of each solute. This representation persists until there is enough water to fully dissolve the drug and excipient. In either case, the mole fraction of water in the droplet is calculated as

$$\chi_w = 1 - \chi_{drug} - \chi_{ex} \quad (4)$$

It is noted that the van't Hoff factors along with the solubility limits for the drug and excipient were determined individually and may be influenced by the presence of multiple solutes. The current model neglects these interaction effects and assumes that multiple dissolved species can be considered using Eq. (3). The quality of this assumption in relation to condensational growth will be assessed by comparing the *in vitro* results and CFD predictions of final particle size.

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 the dissolved drug and excipient, and the effect of droplet temperature on surface vapor pressure. In simulating aerosol evaporation and growth, the effect of the droplets on the continuous phase was typically neglected, resulting in a one-way coupled approach. One-way coupled simulations are expected to be accurate in this study due to the presence of wetted walls. However to assess the validity of this assumption, the effects of the discrete aerosol phase on the continuous heat and water vapor fields was also included in some simulations, which is referred to as two-way coupling. An analytically estimated concentration of 5.5×10^5 particles/cm³ for the *in vitro* generated aerosol (after mixing with the gas flow stream) was employed to assess the two-way coupling effects. Heat and mass transfer equations that account for two-way coupling effects were previously reported in the study of Longest and Hindle²³ and are included in the appendix.

Inlet conditions for the computational geometry compared with the *in vitro* experiments contained the aerosol inlet of the dual-flow mouthpiece¹⁵ with a diameter of 1.1 cm at the MT inlet. For the remaining simulations, the flow field was initialized at the 1.1 cm diameter MT inlet. Blunt velocity and particle profiles were assumed at the inlets. It is known that inhaler flow dynamics affect aerosol transport in the MT region.^{27,28} However, the Respimat inhaler was connected to a drying chamber and the dual-flow mouthpiece in this study in order to produce submicrometer aerosols.

Boundary conditions of the numerical model included walls saturated with water vapor and maintained at 37 °C to match the *in vitro* experiments. More detailed reports of airway temperature are available; however, these temperature profiles could not be reproduced in the experimental model. Inlet air conditions matched the ambient experimental conditions (21 °C and 40% RH) and included steady state flow through the model at 30 LPM. To assess

the effects of realistic transient inhalation waveforms on deposition and growth, previously developed slow and deep (SD) and quick and deep (QD) breathing profiles consistent with pharmaceutical inhalers were employed.^{31,42} Briefly, the SD waveform was characterized by a peak inspiratory flow rate (PIFR) of 61.4 LPM, an average flow rate of 37 LPM, and a time fraction to PIFR of 1/4. The QD waveform was characterized by a PIFR of 122.2 LPM, an average flow rate of 75 LPM, and a time fraction to PIFR of 1/6. Both profiles delivered 3 L of air with inhalation times for the SD and QD waveforms of 4.9 s and 2.4 s, respectively. Enclosure of the upper TB model in a chamber with a single outlet creates a boundary condition of constant pressure among the B3 outlets in both the CFD and *in vitro* geometries. Droplets were assumed to impact and remain deposited upon initial contact with the wall. The aerosol was initially introduced at $t = 0$ and injected continually for 1 s and 0.5 s with the SD and QD inhalations, respectively.

In performing the CFD simulations with Fluent 12, previously established best-practices were implemented to provide a high quality solution. All transport equations were discretized to be at least second order accurate. For the convective terms, a second order upwind scheme was used to interpolate values from cell centers to nodes. The diffusion terms were discretized using central differences. A segregated implicit solver was employed to evaluate the resulting linear system of equations. This solver uses the Gauss-Seidel method in conjunction with an algebraic multigrid approach. The SIMPLEC algorithm was employed to evaluate pressure-velocity coupling for the steady state simulations. For the transient simulations, PISO pressure-velocity coupling was implemented along with second order implicit time advancement and a time step size of 0.02 s. Convergence of the flow field solution was assumed when the global mass residual had been reduced from its original value by five orders of magnitude and when the residual-reduction-rates for both mass and momentum were sufficiently small. To improve accuracy and to better resolve the significant change in flow scales during deposition, all calculations were performed in double precision. In order to produce convergent deposition results, 90,000 initial droplets were released for each of the cases considered. Mass median aerodynamic diameters after growth were calculated based on the ACI stage midpoint diameters. Doubling the number of droplets considered had a negligible impact on both total and sectional deposition results.

RESULTS

In Vitro Experiments and Comparison with CFD Results

The mean (SD) initial mass median aerodynamic diameter (MMAD) of the 50:50 AS and CA combination particles was 0.43 (0.1) μm after drying based on measurements at the inlet of the MT model using cascade impaction with the MOUDI (Table 1). In the *in vitro* experiments, this aerosol was passed through the MT-TB model with an inhalation flow rate of 30 LPM at inlet conditions of 21 °C and 40% RH. The final mean aerosol MMAD determined using the ACI at the chamber outlet was 1.53 μm (SD = 0.05) resulting in a final to initial MMAD growth ratio of 3.56. Experimental analysis of deposited drug in the MT-TB model and chamber resulted in mean deposition fractions of <1% and 5.44%, respectively. At this very low deposition fraction, it was not practical to further resolve MT vs. TB deposition using the HPLC method employed in the experiments. While chamber deposition is not important physiologically, it is reported for validation of the CFD model and to ensure that only a small fraction of the aerosol is lost and does not significantly affect aerosol sizing.

Computational fluid dynamics simulations of the *in vitro* test conditions are reported in Table 1 and illustrated in Figure 2. To match the experimental setup, the aerosol inlet of the dual flow mouthpiece was included in the validation simulations. As an approximation, the experimentally determined MMAD at the model inlet was used as an initial monodisperse

size of the combination AS and CA particles in the simulations. Based on a wall temperature of 37 °C and CFD predicted estimates of air density near the boundary, the saturated mass fraction of water vapor at the model walls was calculated to be 0.03838. Simulation results indicate that submicrometer size of the aerosol is maintained through a majority of the MT-TB geometry (Figure 2). The predicted chamber exit MMAD of the aerosol was 1.54 μm , which is in very close agreement with the experimental result (<1% relative error). The CFD model predicted a drug deposition fraction of 0.84% in the MT-TB model, which is consistent with the <1% value determined in the experiments. Similarly, the predicted chamber deposition fraction of 5.22% was within a 5% relative error of the *in vitro* results (Table 1). Simulation of two-way coupling between the discrete and continuous phases for the AS:CA aerosol resulted in a less than 10% relative reduction in final droplet size. As a result, one-way coupling was assumed for all other simulations. Based on these comparisons, it appears that the CFD model provides an excellent approximation of *in vitro* conditions in terms of both final aerosol size and deposition.

Continuous Field Variables

Contours of the velocity field and RH values are illustrated in Figure 3 for cross-sectional slices under steady state (30 LPM) and transient (SD and QD) inhalation conditions. The steady state velocity field highlights a core of high velocity flow that enters the mouth inlet and strikes the back of the throat (Figure 3a). Impaction due to this jet-type flow is typically responsible for high MT deposition. The magnitude of the velocity is also observed to change by over an order of magnitude between the glottis and chamber regions, which creates a difficult system to model. Relative humidity values at a steady flow rate of 30 LPM indicate a rapid increase from 40% inlet conditions to 90–100% in the trachea (Figure 3b). At steady state, limited regions of RH > 100% are observed. For SD inhalation, the MT-TB contours of RH appear very similar to steady state conditions, especially in terms of transitioning to > 90% in the trachea (Figure 3c). However, RH is elevated in the chamber compared with steady state likely due to increased convection from the walls. In contrast, the QD inhalation profile is observed to result in slightly reduced RH levels in the MT and TB compared with SD and steady state, which may affect the growth rate of the aerosol (Figure 3d).

Effect of Hygroscopic Excipient

Size increase of drug only and 50:50 by mass combination particles of AS:CA and AS:NaCl are presented in Figure 4 based on CFD simulations. Initial monodisperse particles were simulated with a geometric diameter of 900 nm starting at the MT inlet. All other conditions were identical to the experimental validations. Mean geometric sizes (d_{geo}) of the polydisperse aerosols at the chamber exit are reported. Albuterol sulfate demonstrates some size increase; however, a final size of 1.72 μm results in a diameter growth ratio of less than 2. In contrast, inclusion of hygroscopic excipients CA and NaCl increase the final size to above 2 μm at the chamber outlet, which will likely result in significant lung retention. As predicted by Longest and Hindle,²⁴ NaCl has a higher hygroscopic parameter than CA resulting in a larger final droplet size. Within the airways, little size increase is observed at the MT exit (Table 2). At the exit of B3, the mean sizes of the AS:CA (1.34 μm) and AS:NaCl (1.68 μm) aerosols are noticeably different. This size difference may be used to control deposition within the TB airways and target local delivery based on the type of excipient and initial drug:excipient mass ratio. Deposition of drug mass in the MT-TB region was approximately 1% or below for all cases considered.

Effects of Transient Inhalation

Simulation results of size increase are reported for transient SD and QD inhalation profiles in Figures 5 and 6, respectively. The initial aerosol geometric diameter was 900 nm and the

particles were composed of drug and hygroscopic excipient at a mass ratio of 50:50 for both AS:CA and AS:NaCl. In addition to sizes at the chamber outlet, mean geometric diameters at the MT exit and B3 exit are provided in Tables 3 and 4 for SD and QD inhalation, respectively. Aerosol growth was observed to be affected by a combination of residence time and RH within the geometry under different inhalation conditions. Average residence times for the SD and QD inhalation profiles were 2.05 s and 1.89 s, respectively. In general, exit sizes for SD inhalation are larger than with QD conditions. This is expected because SD provides higher MT-TB RH values (Figure 3c) and longer residence times. Compared with steady state inhalation, the SD results are similar through the TB exit. Thereafter, SD inhalation produces larger size increases than steady state conditions. For both transient inhalation profiles, the chamber exit sizes are greater than 3 μm for AS:CA and greater than 4 μm for AS:NaCl. These final size droplets are larger than the MMAD of many conventional pharmaceutical aerosols and are expected to be fully retained in the lungs. Deposition of drug mass in the MT-TB region was approximately 1% or below for both inhalation waveforms.

DISCUSSION

Both *in vitro* results and CFD simulations indicate that EEG delivery of combination particles, generated using the Respimat spray inhaler platform, could nearly eliminate unwanted MT deposition for the delivery of orally inhaled pharmaceutical aerosols. Compared with current MDIs and DPIs,³¹ the proposed delivery approach represents a 1–2 order of magnitude reduction in MT deposition. The CFD simulations demonstrated excellent agreement with the *in vitro* experiments in terms of predicting the deposition and final aerosol size of combination particles exposed to the characteristic airway model. Aerosol growth was observed to occur gradually over the MT-TB region with submicrometer aerosols exiting the MT in nearly all cases. The type of excipient was found to influence the particle size at different locations within the MT-TB geometry, which was expected based on previous studies in a tubular geometry.^{16,24,25} Combination particles exiting B3 ranged from 1.2 to 1.7 μm , depending on the type of hygroscopic excipient and inhalation conditions. Transient inhalation was found to influence the final size of the aerosol based on changes in residence times and relative humidity values. However, steady state estimates of size were consistently lower than with SD or QD inhalation, indicating that steady state simulations provide a conservative estimate of final size. Aerosol sizes exiting the chamber (2.75–4.61 μm) for all cases of combination particles were equivalent to or larger than conventional pharmaceutical aerosols that frequently have MMADs in the range of 2–3 μm .³¹ As a result, full lung retention is expected, which is generally observed for conventional inhaled products. Furthermore, the large difference in size increase associated with different excipients may be effective for targeting the site of deposition within the lower TB and alveolar airways.

An interesting phenomenon was observed in the relative humidity field plots where RH values greater than 100% (supersaturated conditions) were observed close to the airway walls and within the chamber. Previous studies have indicated that a cool airstream flowing through tubes with warmer and wet walls can produce supersaturated conditions. This phenomenon is the basis for one type of condensation particle counter that uses water as the working fluid.¹⁴ The non-dimensional Lewis number can be defined as the ratio of thermal to mass (water vapor) diffusivities, i.e., α/D . For the temperature range considered in this study (21 – 37 °C), the Lewis number describing transport from the wall ranges from approximately 0.88 – 0.89. Values less than one indicate that mass diffusion at the wall is greater than thermal diffusion. As a result, it is reasonable that greater mass diffusion from the wall compared with thermal diffusion results in supersaturated conditions in the near-wall region, as observed in the CFD predictions. Related to EEG delivery, these regions of

supersaturation will produce accelerated droplet growth compared with RH values of 100%.³⁰ As a result, final particle size with EEG in the lungs may be even greater than previously estimated with numerical models that assume a maximum RH of 100% in the airways, as with Longest and Hindle.²⁴

Limitations of the current study in relation to *in vivo* conditions include use of a chamber geometry, 100% RH at the walls, and evaluation of one-way coupling between the continuous and discrete phases. The model considered is only intended to provide geometric similarity with the airways through B3. Thereafter, only thermodynamic equivalence and residence time equivalence with the airways are assumed. However, heat and mass transfer is expected to be enhanced in the bronchi beyond B3 compared with chamber conditions, which will accelerate the rate of size increase. Therefore, the chamber model is expected to provide a conservative estimate of growth in branches distal to B3. Some physiological details of the MT and upper TB model were not included in the characteristic geometry, such as the presence of the nasopharynx⁴⁹ and tracheal curvature; however, these features are not expected to significantly influence the deposition of aerosols as reported in this study. Compared with the assumption of 100% RH on the walls of the CFD and *in vitro* model, isotonic mucus lining the airway is expected to be at 99.5% RH. This difference may decrease the rate of aerosol growth, as reported by Longest and Xi.³² Finally, the current simulations were conducted using a one-way coupled assumption based on the findings of Longest and Hindle.²⁵ However, two-way coupling may become more important for aerosols growing above approximately 3 or 3.5 μm .^{23,25}

Based on the results of this study, negligible MT deposition and significant size increases associated with full lung retention are possible with EEG delivery. Future studies are needed to evaluate growth in lower TB airways and the alveolar region using models similar to those of Tian et al.,⁴² Longest et al.,³¹ and Sznitman.⁴⁰ Experimentally, the EEG concept needs to be tested *in vivo* using humans or animal models. Studies are currently underway to develop inhalers capable of delivering submicrometer aerosols using both spray (softmist and MDI) and DPI approaches. Ultimately, the proposed concepts may deliver nearly 100% of an inhaled drug dose to the deep lung and potentially target the site of deposition within the airways.

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APPENDIX

This appendix provides additional equations describing the heat and mass transfer analysis of the MT-TB model system during EEG aerosol delivery.

Continuous Phase Transport and Two-Way Coupling

The mass transport of water vapor in the continuous phase is governed by the convective-diffusive equation including turbulent dispersion, as follows:²

$$\frac{\partial Y_v}{\partial t} + \frac{\partial u_j Y_v}{\partial x_j} = \frac{\partial}{\partial x_j} \left[\left(\tilde{D}_v + \frac{\nu_T}{Sc_T} \right) \left(\frac{\partial Y_v}{\partial x_j} \right) \right] + S_v \quad (A1)$$

In the above expression, Y_v is the mass fraction of water vapor, $\tilde{D}_v$ is the binary diffusion coefficient of water vapor in air, ν_T is the turbulent viscosity ($\sim$ turbulent kinetic energy (k)/specific dissipation rate (ω)), and Sc_T is the turbulent Schmidt number, which is taken to be $Sc_T = 0.9$.² The water vapor source term S_v is used to account for the increase (or decrease) in continuous phase water vapor mass fraction from evaporating (or condensing) droplets. For the two species considered, the mass fraction of air was evaluated as $Y_a = 1.0 - Y_v$. The binary diffusion coefficient $\tilde{D}_v$ was determined on a temperature dependent basis using the correlation of Vargaftik.⁴⁴

To determine the temperature field in the model geometry, the constant property thermal energy equation is expressed as

$$\rho C_p \frac{\partial T}{\partial t} + \rho C_p \frac{\partial u_j T}{\partial x_j} = \frac{\partial}{\partial x_j} \left[\left(\kappa_g + \frac{\rho C_p \nu_T}{Pr_T} \right) \left(\frac{\partial T}{\partial x_j} \right) \right] + \sum_s h_s \left(\rho \tilde{D}_v + \frac{\rho \nu_T}{Sc_T} \right) \frac{\partial Y_s}{\partial x_j} + S_e \quad (A2)$$

In this conservation of energy statement, ρ is mixture density, C_p is the constant specific heat, κ_g is the gas conductivity, and Pr_T is the turbulent Prandtl number, which is taken to be $Pr_T = 0.9$.² The enthalpy of each species is represented as h_s , and the two species are air and water vapor. On the right-hand-side of Eq. (A2), the first term represents conductive transport due to molecular and turbulent mechanisms while the second term accounts for energy transport due to species diffusion. Finally, S_e is the continuous phase energy source (or sink) term due to the presence of the discrete phase. The relative humidity of the continuous phase is based on both the amount of water vapor present and the air temperature. Relative humidity of the ideal gas mixture can be expressed

$$RH = \frac{P_v}{P_{v,sat}} = \frac{Y_v \rho R_v T}{Y_{v,sat} \rho R_v T} = \frac{Y_v}{Y_{v,sat}} \quad (A3)$$

where R_v is the gas constant of water vapor and ρ is the mixture density. The temperature dependent saturation pressure of water vapor ($P_{v,sat}$) was evaluated from the Antoine equation.¹³ The mass flux of water vapor at the wall is based on saturated (wet-walled) conditions and is calculated as

$$n_{v,wall} = \frac{-\rho \tilde{D}_v \frac{\partial Y_v}{\partial n} \big|_{wall}}{(1 - Y_{v,wall})} \quad (A4)$$

To evaluate droplet condensation and evaporation, cases with one-way or two-way coupling with the continuous phase were considered. In one-way coupling, condensation and evaporation at the droplet surface do not affect the continuous phase. This assumption is valid if the droplet concentration is sufficiently dilute such that water gain or loss from the continuous phase can be neglected. Two-way coupling considers the effect of the droplets on the continuous phase. Evaporation or condensation at the droplet surface results in a mass and energy source or sink in the continuous phase. These effects are expressed using the mass (S_v) and energy (S_e) source or sink terms in Eqs. (A1) and (A2). In this study we are primarily concerned with condensation, so that the mass term will be considered as a continuous phase sink and the energy term will be considered as a continuous phase source. This discussion is equally valid for evaporation where mass is added to the continuous phase.

To evaluate mass and energy sinks and sources due to two-way coupling, the Strength of representative droplet trajectories in units of particles/s is calculated as

$$Strength = \frac{n \cdot NF \cdot Q}{\text{number of particles in bin}} \quad (A5)$$

where n is the particle number density in part/cm³, NF is the number fraction in each particle size bin, and Q is the total inlet flow rate in cm³/s of the aerosol inlet. The number of size bins is either based on the number of impactor stages used for initial size evaluation or unity for the evaluation of a monodisperse initial size assumption. Within each bin, a finite number of droplets is computed to avoid simulating all of the droplets in the physical system. As shown in Eq. (A5), the Strength is divided by this number of computational droplets in each bin resulting in the number of particles per second (part/s) along each computational trajectory. Based on the Strength calculation, the mass of water vapor removed from a control volume during condensation is calculated for a single computational trajectory as

$$\dot{m}_p = \Delta m \cdot Strength \quad (A6)$$

where Δm is the droplet mass change within the computational cell. The sign of $\dot{m}_p$ is positive for evaporation and negative for condensation. The vapor sink term for use in Eq. (A1) is then calculated as

$$S_v = \frac{\dot{m}_p}{V_{cv} \rho} \quad (A7)$$

where V_{cv} is the volume of the current computational cell (control volume) and ρ is the density of the air-vapor mixture. Based on $\dot{m}_p$, S_v is negative for condensation (resulting in a vapor sink) and positive for evaporation (resulting in a vapor source).

The energy source term in two-way coupling can be expressed as

$$S_e = -\frac{\dot{m}_p L_v}{V_{CV}} - \frac{\dot{m}_p C_p}{V_{CV}} (T_d - T_{CV}) \quad (\text{A8})$$

where L_v is the latent heat of vaporization and C_p is the specific heat at constant pressure for water. The droplet and surrounding (control volume) temperatures are expressed as T_d and T_{CV} , respectively. This source term represents energy transfer to the continuous phase from the aerosol as a result of mass exchange. For condensation, $\dot{m}_p$ is negative resulting in a positive latent heat term and energy gain, which increases the surrounding temperature. The second term in Eq. (A8) accounts for the energy required to heat the discrete phase. This convective term has the opposite sign of the latent heat term making it negative during condensation. However, the convective term is typically much smaller than the latent heat term resulting in continuous phase heat gain during condensation.

Discrete Phase Transport Equations

Based on experimental evidence, mean droplet sizes from 300 nm to approximately 3 μm and greater are expected in the current EEG system. To address this broad range of aerosol sizes and to accommodate the calculation of aerosol evaporation and condensation, a Lagrangian particle tracking method was employed. The Lagrangian transport equations can be expressed

$$\frac{dv_i}{dt} = \frac{f}{\tau_p} (u_i - v_i) + g_i (1 - \alpha) + f_{i,Brownian} \quad \text{and} \quad \frac{dx_i}{dt} = v_i(t) \quad (\text{A9})$$

Here v_i and u_i are the components of the particle and local fluid velocity, g_i denotes gravity, and α is the ratio of mixture to droplet density ρ/ρ_d . The characteristic time required for a particle to respond to changes in fluid motion, or the particle relaxation time, is expressed as $\tau_p = C_c \rho_d d_d^2 / 18\mu$, where C_c is the Cunningham correction factor for submicrometer aerosols based on the expression of Allen and Raabe¹ and μ is the absolute viscosity. The pressure gradient or acceleration term for aerosols was neglected due to small values of the density ratio. The drag factor f , which represents the ratio of the drag coefficient to Stokes drag, is based on the expression of Morsi and Alexander.³⁶ The effect of Brownian motion on the trajectories of submicrometer particles has been included as a separate force per unit mass term at each time-step. This force has been calculated as

$$f_{i,Brownian} = \frac{\zeta_i}{m_d} \sqrt{\frac{1}{\tilde{D}_d} \frac{2k^2 T^2}{\Delta t}} \quad (\text{A10})$$

where ζ_i is a zero mean variant from a Gaussian probability density function, k is the Boltzmann constant, Δt is the time-step for particle integration, and m_d is the mass of the droplet. Assuming dilute concentrations of spherical particles, the Stokes-Einstein equation was used to determine the diffusion coefficients $\tilde{D}_d$ for various size droplets.¹⁷

To model the effects of turbulent fluctuations on particle trajectories, a random walk method was employed.^{7,12,33,35} The primary limitation of this eddy interaction model in conjunction with the RANS equations is that it does not account for reduced turbulent fluctuations in the wall-normal direction, which may result in an over-prediction of deposition.^{20,34,35,43} To better approximate turbulent effects on particle deposition, an anisotropic turbulence model was applied where the near-wall fluctuating velocity is calculated as^{34,46}

$$u'_n = f_n \xi_n \left(\frac{2}{3} k \right)^{1/2} \quad \text{where} \quad f_n = 1 - e^{-0.02n^+} \text{ and } n^+ = u_\tau n / \nu \quad (\text{A11})$$

In the above equations, u' is the fluctuating component of the instantaneous velocity, n is the wall-normal coordinate, and u_τ is the turbulent friction velocity.⁴⁷ The wall-normal damping function (f_n) is typically evaluated from the wall to a maximum n^+ value ranging from 10 to 100; otherwise it is assumed to be 1.0. In this study, f_n was evaluated for n^+ values ranging from 0 to a maximum of 60.

Conservation of energy for an immersed droplet, indicated by the subscript d , under rapid mixing model (RMM) conditions can be expressed²⁹

$$\frac{dT}{dt} m_d C_{pd} = - \int_{surf} q_{conv} dA - \int_{surf} n_v L_v dA = - \bar{q}_{conv} \cdot A - \bar{n}_v L_v \cdot A \quad (\text{A12})$$

In the above equation, m_d is the droplet mass, C_{pd} is the composite liquid specific heat, q_{conv} is the convective heat flux, n_v is the mass flux of the evaporating water vapor at the droplet surface, and L_v is the latent specific heat of the water vapor component. The integrals are performed numerically over the droplet surface area, A .

Conservation of mass for an immersed droplet based on the evaporating flux can be expressed as

$$\frac{d(m_d)}{dt} = - \int_{surf} n_v dA = - \bar{n}_v \cdot A \quad (\text{A13})$$

For a semi-empirical RMM solution, the area-averaged heat flux is evaluated from

$$\bar{q}_{conv} = \frac{Nu \kappa_g C_T}{d_p} (T_d - T_\infty) \quad (\text{A14})$$

where Nu is the Nusselt number, κ_g is the thermal conductivity of the gas mixture, and T_∞ is the temperature condition surrounding the droplet. In the expression for heat flux, the term C_T represents the Knudsen correlation for non-continuum effects given by^{10,11}

$$C_T = \frac{1 + Kn}{1 + \left(\frac{4}{3\alpha_T} + 0.377 \right) Kn + \frac{4}{3\alpha_T} Kn^2} \quad (\text{A15})$$

In this expression, Kn is the Knudsen number, defined as $Kn = 2\lambda/d_p$, where λ is the mean free path of air. The factor α_T is an accommodation coefficient, which is assumed to be unity.^{10,17}

Considering mass transfer, the area-averaged mass flux is

$$\bar{n}_v = \rho \frac{Sh \tilde{D}_v C_M}{d_p} \frac{Y_{v,surf} - Y_{v,\infty}}{1 - Y_{v,surf}} \quad (\text{A16})$$

where Sh is the non-dimensional Sherwood number, ρ is the gas mixture density, and $Y_{v,\infty}$ is the water vapor mass fraction surrounding the droplet. This expression includes the effect of droplet evaporation on the evaporation rate, which is referred to as the blowing velocity.²⁹ In Eq. (A16), C_M is the mass Knudsen number correction, which is equivalent to Eq. (A15) with a mass-based accommodation coefficient $\alpha_M = \alpha_T = 1$.

The non-dimensional Nusselt and Sherwood numbers employed in Eqs. (14 & 16), respectively, for droplet surface heat and mass transfer are based on the empirically derived expression of Clift et al.⁶

$$Nu = 1 + (1 + Re_p Pr)^{1/3} \max [1, Re_p^{0.077}] \quad (A17a)$$

$$Sh = 1 + (1 + Re_p Sc)^{1/3} \max [1, Re_p^{0.077}] \quad (A17b)$$

These correlations are valid for droplet Reynolds numbers up to 400 and include blowing velocity effects.

Equations for calculating the water vapor mass fraction on the droplet surface ($Y_{v,surf}$) accounting for hygroscopic effects are provided in the main body of the article as Eqs. (1) – (4).

Figure 1.

Airway models evaluated using *in vitro* experiments and CFD simulations including (a) the characteristic mouth-throat (MT) and tracheobronchial (TB) geometry for an adult, (b) the MT-TB model enclosed in a chamber used to expose the aerosol to thermodynamic conditions of the lungs, (c) evaluation of residence time within the MT-TB and chamber geometry, and (d) computational mesh of the system used for CFD simulations.

Figure 2.

Computational fluid dynamics (CFD) predictions of droplet trajectories colored according to droplet diameter for AS:CA combination particles delivered through a mouthpiece inlet (with a diameter of 1.1 cm available for flow) at a steady state flow rate of 30 LPM. The submicrometer aerosol was inhaled with ambient air (21 °C and 40% RH) and the initial drug to excipient mass ratio of the particles was 50:50. Predicted MMAD of the aerosol exiting the chamber based on CFD was in very close agreement with the *in vitro* experiments (Exp).

Figure 3.

Contours of continuous field variables for the MT-TB and chamber geometry shown as 2D slices including (a) the velocity field and RH conditions for (b) steady state inhalation at 30 LPM as well as (c) slow and deep (SD) and (d) quick and deep (QD) inhalation.

Figure 4.

CFD predictions of droplet trajectories colored according to diameter during steady state inhalation of 30 LPM for initially dry 900 nm particles composed of (a) AS, (b) AS:CA, and (c) AS:NaCl. Initial drug and hygroscopic excipient mass ratios were 50:50. The mean geometric diameter (d_{geo}) is reported at the chamber outlet.

Figure 5. CFD predictions of droplet trajectories colored according to diameter during SD inhalation for initially dry 900 nm particles composed of (a) AS:CA and (b) AS:NaCl. Initial drug and hygroscopic excipient mass ratios were 50:50. The mean geometric diameter (d_{geo}) is reported at the chamber outlet.

Figure 6.

CFD predictions of droplet trajectories colored according to diameter during QD inhalation for initially dry 900 nm particles composed of (a) AS:CA and (b) AS:NaCl. Initial drug and hygroscopic excipient mass ratios were 50:50. The mean geometric diameter (d_{geo}) is reported at the chamber outlet.

Table 1

Comparison of experimental (mean $\pm$ SD) and CFD growth and deposition characteristics for combination particles initially composed of AS:CA at a mass ratio of 50:50.

	Experimental Results	CFD Results
Initial size MMAD (μ m)	0.43 $\pm$ 0.1	0.43
Final size MMAD (μ m)	1.53 $\pm$ 0.05	1.54
MMAD Growth Ratio	3.56	3.58
Deposition Fractions		
MT-TB (%)	<1	0.84
Chamber (%)	5.44 $\pm$ 0.84	5.22

Table 2

CFD predictions of mean geometric aerosol size at different positions in the MT-TB chamber model for steady state inhalation conditions of 30 LPM and an initial particle size of 900 nm at the MT inlet.

	AS	AS:CA	AS:NaCl
MT _{exit} (μm)	0.93	1.02	1.03
MT-TB _{exit} (μm)	0.94	1.34	1.68
Chamber _{exit} (μm)	1.72	2.75	3.38

Table 3

CFD predictions of mean geometric aerosol size at different positions in the MT-TB chamber model for SD inhalation conditions and an initial particle size of 900 nm at the MT inlet. The drug (AS) to excipient (CA or NaCl) mass ratio in the initial particles was 50:50.

	AS:CA	AS:NaCl
MT _{exit} (μm)	1.01	1.49
MT-TB _{exit} (μm)	1.23	1.61
Chamber _{exit} (μm)	3.92	4.61

Table 4

CFD predictions of mean geometric aerosol size at different positions in the MT-TB chamber model for QD inhalation conditions and an initial particle size of 900 nm at the MT inlet. The drug (AS) to excipient (CA or NaCl) mass ratio in the initial particles was 50:50.

	AS:CA	AS:NaCl
MT _{exit} (μm)	0.94	0.96
MT-TB _{exit} (μm)	1.19	1.50
Chamber _{exit} (μm)	3.78	4.52