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Variability in nose-to-lung aerosol delivery

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ABSTRACT

Nasal delivery of lung targeted pharmaceutical aerosols is ideal for drugs that need to be administered during high flow nasal cannula (HFNC) gas delivery, but based on previous studies losses and variability through both the delivery system and nasal cavity are expected to be high. The objective of this study was to assess the variability in aerosol delivery through the nose to the lungs with a nasal cannula interface for conventional and excipient enhanced growth (EEG) delivery techniques. A database of nasal cavity computed tomography (CT) scans was collected and analyzed, from which four models were selected to represent a wide range of adult anatomies, quantified based on the nasal surface area-to-volume ratio (*SA/V*). Computational fluid dynamics (CFD) methods were validated with existing *in vitro* data and used to predict aerosol delivery through a streamlined nasal cannula and the four nasal models at a steady state flow rate of 30 L/min. Aerosols considered were solid particles for EEG delivery (initial 0.9 μm and 1.5 μm aerodynamic diameters) and conventional droplets (5 μm) for a control case. Use of the EEG approach was found to reduce depositional losses in the nasal cavity by an order of magnitude and substantially reduce variability. Specifically, for aerosol deposition efficiency in the four geometries, the 95% confidence intervals (*CI*) for 0.9 and 5 μm aerosols were 2.3–3.1% and 15.5–66.3%, respectively. Simulations showed that the use of EEG as opposed to conventional methods improved delivered dose of aerosols through the nasopharynx, expressed as penetration fraction (*PF*), by approximately a factor of four. Variability of *PF*, expressed by the coefficient of variation (*CV*), was reduced by a factor of four with EEG delivery compared with the control case. Penetration fraction correlated well with *SA/V* for larger aerosols, but smaller aerosols showed some dependence on nasopharyngeal exit hydraulic diameter. In conclusion, results indicated that the EEG technique not only improved lung aerosol delivery, but largely eliminated variability in both nasal depositional loss and lung *PF* in a newly developed set of nasal airway models.

1. Introduction

Delivering inhaled medications to the lungs from a nasal interface has a number of advantages (Ari et al., 2011; Bhashyam et al., 2008; Dhand, 2012). For medications with long delivery times, frequent dosing routines, or those that require

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Nomenclature

95% *CI*	95% confidence interval
A	regional coronal cross-sectional area of the nasal cavity
A_{min}	minimum coronal cross-sectional area of the nasal cavity
AS	albuterol sulfate
C_{ca}	Cunningham correction factor for the aerodynamic diameter
CFD	computational fluid dynamics
CPAP	continuous positive airway pressure
CT	computed tomography
CV	coefficient of variation
d_c	characteristic diameter
d_{ae}	initial aerodynamic particle diameter
$d_{h,min}$	minimum coronal cross-sectional hydraulic diameter of the nasal cavity
$d_{h,nostril}$	average nostril hydraulic diameter
$d_{h,nasopharynx}$	nasopharynx hydraulic diameter
DE	deposition efficiency
DF	deposition fraction
ECG	enhanced condensational growth
EEG	excipient enhanced growth
HFNC	high flow nasal cannula
L_{CP}	central path length
LFNC	low flow nasal cannula
LRN	low Reynolds number
M	mean
MMAD	mass median aerodynamic diameter
MN	mannitol
MRI	magnetic resonance imaging
MT	mouth–throat
μ	dynamic viscosity
υ	kinematic viscosity
NIV	noninvasive ventilation
NMT	nose-mouth–throat
PF	penetration fraction
ρ	local density
ρ_a	air density
ρ_w	water density
R	correlation coefficient
Re	Reynolds number
RH	relative humidity
Q	flow rate
SA	surface area
SA/*V*	surface area-to-volume ratio
SD	standard deviation
St_k	Stokes number
V	volume
V_{total}	volume of the airway up to and including the larynx
τ_w	wall shear stress
y	distance from near wall node to wall
y^+	wall *y*-plus value

continuous nebulization, nose-to-lung delivery with a nasal cannula interface allows for convenient hands-free administration. Considering patients receiving noninvasive ventilation (NIV) with a nasal interface, high flow nasal cannula (HFNC) or low flow nasal cannula (LFNC) gas delivery, and continuous positive airway pressure (CPAP), nose-to-lung delivery allows for simultaneous administration of the aerosol and ventilation gas. Noninvasive ventilation, HFNC and LFNC gas delivery, and CPAP are increasingly popular forms of respiratory support (Aboussouan & Ricaurte, 2010; Brochard et al., 1995; Dhand, 2012; Lee et al., 2013; Lightowler et al., 2003; Parke et al., 2011; Ram et al., 2004). With each of these gas delivery systems, a nasal interface is typically implemented. Simultaneous administration of aerosol therapy through a nasal interface during gas delivery is needed so that the supply of gas does not need to be halted for the patient to receive respiratory medicines (Dhand, 2012).

A potential disadvantage of nose-to-lung aerosol delivery is the expected high depositional loss in the nasal cavity with conventional pharmaceutical aerosols. It is well known that one function of the nose is to filter inhaled particles. The deposition of toxicological and pharmaceutical aerosols in the nasal cavity has been assessed or reviewed by numerous *in vivo* (Bennett & Zeman, 2005; Cheng, 2003; Stahlhofen et al., 1989; Swift & Strong, 1996), *in vitro* (Garcia et al., 2009; Golshahi et al., 2011; Guilmette et al., 1994; Kelly et al., 2004a, 2004b; Longest et al., 2011; Storey-Bishoff et al., 2008), and *in silico* (Inthavong et al., 2011; Kimbell et al., 2007; Liu et al., 2007; Schroeter et al., 2006, 2011; Shanley et al., 2008; Shen et al., 2004; Xi & Longest, 2008b; Xi et al., 2011) studies. The results of these various studies typically provide correlations that can be used to estimate the deposition of aerosols in the nasal cavity. For example, pharmaceutical nebulizers generate droplets in the size range of 3–7 μm (Finlay, 1998; Kuhli et al., 2009). Considering a 5 μm aerosol inhaled through the nose with an airflow of 30 L/min, the *in vitro* study of Kelly et al. (2004b) predicts an average deposition of 40% based on nasal models created from a single subject. Under identical aerosol conditions, the *in vivo* nasal deposition correlation of Stahlhofen et al. (1989), which represents average deposition taken over multiple studies, predicts 80% nasal deposition. Based on a large majority of nasal deposition data, aerosol losses in the nasal cavity are unacceptably high for conventional aerosols delivered at typical nasal inhalation flow rates to achieve efficient nose-to-lung drug delivery.

In addition to high nasal losses, significant aerosol deposition is also expected in the delivery system and nasal interface during nose-to-lung administration. Studies by Bhashyam et al. (2008) and Ari et al. (2011) considered aerosol delivery through nasal cannulas with flow rates in the range of 3–6 L/min. Both studies reported depositional losses in the delivery system in the range of 75–98%, which did not include losses in a nasal cavity geometry. Longest et al. (2013b) reported the delivery of a nebulized aerosol with a mass median aerodynamic diameter (*MMAD*) of 4.7 μm through a commercial adult