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Technical note

An idealized branching airway geometry that mimics average aerosol deposition in pediatric central conducting airways

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ABSTRACT

The objective of this work was to design an idealized pediatric central conducting airway model that mimics average total particle deposition in the airways of 4–8 year old children. Dimensions of the idealized model were selected based on analytical prediction of deposition in scaled versions of existing adult airway geometries. Validation experiments were then conducted using steady inhalation air flow rate to measure the deposition of monodisperse particles with mass median diameters (MMD) of 3.5, 4.5, 5 and 5.2 μm in the idealized pediatric model. The total deposition of particles was measured using gravimetry. Experimental data confirmed that aerosol deposition in the idealized pediatric central conducting airway geometry was consistent with the average deposition previously measured in 10 realistic airway replicas for children 4–8 years old.

1. Introduction

The use of idealized, representative upper airways geometries that mimic average aerosol deposition in various populations has proven indispensable in the development and assessment of devices used to deliver inhaled pharmaceutical aerosols (Below, Bickmann, & Breitkreutz, 2013; Bickmann, Wachtel, Kroger, & Langguth, 2008; Byron et al., 2010; Delvadia, Longest, & Byron, 2012; Golshahi & Finlay, 2012; Longest, Tian, Walenga, & Hindle, 2012; Oldham, Mannix, & Phalen, 1997; Wachtel, Bickmann, Breitkreutz, & Langguth, 2010). Such idealized geometries exist as a result of extensive fundamental investigation of air flow and aerosol deposition in the upper airways (Grgic, Finlay, & Heenan, 2004; Heenan, Finlay, Matida, & Pollard, 2003; Zhang, Gilbertson, & Finlay, 2007; Zhou, Sun, & Cheng, 2011). For many pharmaceutical aerosol delivery devices, physical phenomena that can influence upper airways deposition are sufficiently complex to model that *in vitro* testing on the bench top remains commonplace in research and development. Such phenomena include fluidization and deagglomeration of multi-component powders used in dry powder inhalers (DPIs) and rapid deceleration and evaporation of propellant droplet sprays emitted from pressurized metered-dose inhalers (pMDIs). When evaluating aerosol delivery *in vitro* using upper airways geometries, the fraction of active drug penetrating the geometry is commonly interpreted as the lung dose (Borgstrom, Olsson, & Thorsson, 2006). For the vast majority of inhalers in use and in development, the fraction of drug inhaled into the lung and subsequently exhaled is negligible, such that this interpretation is acceptable. Accordingly, current *in vitro* methods using idealized upper airways geometries permit average *in vivo* total lung dose to be predicted

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with a reasonable assurance of accuracy (Delvadia et al., 2012; Ruzycki, Golshahi, Vehring, & Finlay, 2014; Zhang et al., 2007; Zhou et al., 2011).

In addition to the total, aggregate lung dose, for many inhaled drugs the location of deposition *within* the lungs is suspected to influence therapeutic efficacy. Targeting delivery of albuterol to the central conducting airways has been associated with increased bronchodilation in asthmatics (Usmani, Biddiscombe, & Barnes, 2005), whereas targeting inhaled dornase alfa to the small airways improved treatment response for cystic fibrosis patients (Bakker et al., 2011). Likewise, phenotypes of COPD and asthma have been characterized by inflammation affecting the small peripheral airways, such that targeting inhaled drugs to small airways has potential to improve treatment (van den Berge, ten Hacken, Cohen, Douma, & Postma, 2011; Lahzami & King, 2008; Usmani & Barnes, 2012). Determining the distribution of lung dose between central and peripheral airways generally requires *in vivo* imaging experiments with radiolabelled formulations, interpretation of *in vivo* pharmacokinetic data, or use of mathematical models or correlations to predict regional lung doses based on aerosol size distributions measured *in vitro*. Unfortunately, *in vivo* approaches are expensive and time-consuming in early development, while models or correlations often fail when presented with phenomena or conditions outside the bounds of the model, or outside the range of experimental data from which the correlation was developed.

Recently, the Alberta Idealized Throat was uniformly scaled down by applying a scale factor of 0.62 to develop the Idealized Child Throat (Golshahi & Finlay, 2012). That geometry mimics average exrathoracic aerosol deposition in children 6–14 years old. In contrast, here we explore an idealized geometry for deposition in the proximal conducting airways of the lung.

For adults, idealized geometries representing the central conducting airways, down to the third lung generation, have been developed (Delvadia et al., 2012; Zhang & Finlay, 2005) and used to predict the regional distribution of aerosols delivered from commercial inhalers (Delvadia et al., 2012). Though earlier in development than upper airway geometries that terminate at the trachea, these conducting airway geometries offer the potential to distinguish between formulations and devices that preferentially deposit drug in central branching airways *versus* those for which aerosol predominantly penetrates to the peripheral airways. The emergence of validated, representative conducting airway geometries would present a valuable tool for early-stage development of delivery systems designed to target central or peripheral airway deposition.

To date, equivalent idealized conducting airway geometries for children are not widely available, largely due to limited aerosol deposition data in children's airways upon which to develop and validate such a geometry. In a recent study, aerosol particle deposition was measured in physical replicas of central conducting airway geometries obtained from segmented computed tomography (CT) scans of school-aged children (Borojeni, Noga, Vehring, & Finlay, 2014). The age range of the study was 2–8 years old; in general, higher deposition was measured in airway replicas of younger subjects. Variation in deposition was also observed between subjects of the same age, due to intersubject variability in airway geometry. This presents a drawback on the use of any single realistic airway replica as representative of a larger population, unless deposition data for that replica are known to lie along a specific percentile within the range of the population data (*e.g.* the mean).

This article describes the development and validation of a pediatric idealized branching airway geometry. The idealized geometry was designed to yield deposition efficiency over a representative range of flow rates and aerodynamic particle sizes equivalent to the average deposition measured in 10 realistic central conducting airway replicas of children aged 4–8 years (Borojeni et al., 2014). We have restricted our exploration to this limited age range because of significant variation of deposition with age in young children.

2. Materials and methods

2.1. Idealized model development

We have recently reported good agreement between aerosol deposition measured in physical replicas of pediatric central conducting airways and analytical predictions made using the Chan and Lippmann (1980) correlation, which was originally developed based on experimental measurements of aerosol deposition performed in casts of adult airways. The Chan and Lippmann (1980) correlation predicts the deposition efficiency, η, for a given airway generation to be:

$$\eta = 1.606Stk + 0.0023 \tag{1}$$

where Stk is the particle Stokes number defined as follows:

$$Stk = \frac{2\rho_p d_p^2 C_c Q}{9\pi\mu D^3} \tag{2}$$

where ρ_p is the aerosol particle density; d_p is the particle diameter; μ is the dynamic viscosity of air; C_c is the Cunningham slip correction factor; D is the airway diameter; and Q is the flow rate of air.

In using Eqs. (1) and (2) to predict deposition in pediatric airways, size differences between child and adult airways are accounted for through incorporation of airway diameter in the particle Stokes number. The ability of the Chan and Lippmann (1980) correlation to predict deposition in pediatric airways suggests that the main geometrical features affecting deposition in child and adult central conducting airways are similar. Consistent with this suggestion, in the present work, an