Journal of Aerosol Science 42 (2011) 781–799

Contents lists available at ScienceDirect

Journal of Aerosol Science

journal homepage: www.elsevier.com/locate/jaerosci

Development of a stochastic individual path (SIP) model for predicting the tracheobronchial deposition of pharmaceutical aerosols: Effects of transient inhalation and sampling the airways

Geng Tian [a], P. Worth Longest [a,b,*], Guoguang Su [a], Ross L. Walenga [a], Michael Hindle [b]

[a] Department of Mechanical Engineering, Virginia Commonwealth University, 401 West Main Street, P.O. Box 843015, Richmond, VA 23284-3015, USA
[b] Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, USA

ARTICLE INFO

Article history:
Received 27 April 2011
Received in revised form
1 July 2011
Accepted 8 July 2011
Available online 19 July 2011

Keywords:
Stochastic lung modeling
Dry powder inhalers
Respiratory drug delivery
Aerosol deposition
Transient inhalation waveforms
Respiratory dosimetry

ABSTRACT

While a number of studies have considered the dynamics of ambient or environmental particles in the respiratory tract, far fewer have evaluated the transport and deposition of pharmaceutical aerosols from inhalers in the mouth-throat (MT) and tracheobronchial (TB) airways. The objective of this study was to develop a new stochastic individual path (SIP) modeling approach for simulating the MT and TB deposition of a pharmaceutical aerosol from a dry powder inhaler and to evaluate the effects of transient vs. steady state conditions and sampling of the airways. In the SIP approach, representative models of the MT and upper TB geometries are considered through the third respiratory bifurcation (B3; approximately lobar bronchi). Stochastic individual paths are then evaluated extending from B4 to the terminal bronchioles (B15) in which one branch of each bifurcation is continued and one is not. Three SIP geometries were considered extending into the lower right lung lobe through the end of the conducting airways. A commonly prescribed dry powder inhaler (DPI) was connected to the MT geometry and the deposition of drug mass from a realistic polydisperse pharmaceutical aerosol was evaluated. Predictions of deposited drug mass in the MT and upper TB geometries were found to be in good agreement with concurrent experimental results. Transient inhalation was shown to influence the deposition of particles in the MT and upper TB airways through B3, where the Womersley number is greater than 1. In contrast, transient conditions were found to have little influence on deposition in the TB region starting with B4, where steady state simulations provided a good representation of total, regional, bifurcation-averaged, and localized deposition. Furthermore, a single SIP model was shown to characterize both regional and highly localized deposition within a lung lobe assuming mean airway dimensions. The resulting SIP model provides a highly efficient method to simulate the regional and local deposition of pharmaceutical aerosols throughout the conducting airways. In comparison with performing fully transient simulations of all branches in the regions considered, the SIP modeling approach reduces computational effort by a factor of approximately 3×10^5 while predicting regional and local deposition values to within approximately 5%.

* Corresponding author at: Department of Mechanical Engineering, Virginia Commonwealth University, 401 West Main Street, P.O. Box 843015, Richmond, VA 23284-3015, USA. Tel.: +1 804 827 7023; fax: +1 804 827 7030.
E-mail address: pwlongest@vcu.edu (P.W. Longest).

0021-8502/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jaerosci.2011.07.005

1. Introduction

Predicting the fate of inhaled particles in the lungs is important in order to improve the performance of inhaled pharmaceutical aerosols and to make accurate dose predictions of inhaled environmental pollutants. Considering pharmaceutical aerosols, the effectiveness of inhaled medications is related to the site of deposition within the airways (Patton & Byron, 2007). Common bronchodilators and corticosteroids are intended to deposit in the tracheobronchial (TB) airways in order to alleviate airway constriction and reduce inflammation associated with asthma and COPD (Newman & Busse, 2002). Doses of these medications that deposit in the alveolar region are believed to have little clinical benefit and may be associated with adverse side effects (Kamada et al., 1996). In contrast, inhaled proteins and peptides, like inhaled insulin, are likely to have a greater systemic bioavailability if they are deposited in the lower TB and alveolar airways where absorption is more efficient (Weers et al., 2010). Algebraic whole-lung models have previously been shown to effectively predict the total lung deposition of inhaled aerosols (Asgharian et al., 2001; ICRP, 1994; Kim, 2009; Martin & Finlay, 2007). However, these models cannot effectively predict localized deposition in the lung, and often do not account for factors associated with pharmaceutical aerosols such as spray momentum and inhaler air jets (Finlay & Martin, 2008; Longest et al., 2008b). As a result, the application of these models to predict and improve the delivery of pharmaceutical aerosols to the lungs is limited. In contrast, computational fluid dynamics (CFD) models can directly simulate the physics of pharmaceutical aerosol delivery and deposition within the airways (Kleinstreuer et al., 2008). Advances in CFD models have led to reports of simulating increasing regions of the extrathoracic (Longest et al., 2011; Zhang & Kleinstreuer, 2011), TB (Lambert et al., 2011; Tian et al., 2011), and alveolar (Sznitman et al., 2009) airways. However, a method to effectively simulate the delivery of pharmaceutical aerosols in a composite model of the mouth-throat (MT) and TB airways through the terminal bronchioles (i.e., the conducting airways) has previously not been reported.

Considering deposition in the MT region, a number of computational studies have evaluated ambient aerosols in the nanometer (Xi & Longest, 2008; Zhang et al., 2005), submicrometer (Longest & Xi, 2008), and micrometer (Sosnowski et al., 2007; Xi & Longest, 2007; Zhang et al., 2002b) size regimes. Far fewer studies have simulated the MT deposition of aerosols from pharmaceutical devices including metered dose inhalers (MDIs), dry powder inhalers (DPIs), and softmist inhalers. Longest et al. (2008a) considered the deposition of an MDI and two softmist inhalers in a representative MT model. CFD results were found to be in good agreement with concurrent *in vitro* experiments for all three inhalers considered based on an analysis of deposited drug mass for the polydisperse aerosols. Kleinstreuer et al. (2007) simulated the deposition of MDI aerosols in a MT and upper TB bifurcation model. Good agreement was found between the CFD simulations, *in vitro* data (Cheng et al., 2001), and *in vivo* results (Leach et al., 1998). Considering DPIs, CFD simulations have shown good agreement with *in vitro* data, provided that turbulence is correctly modeled with either near-wall anisotropic simulations or large eddy simulations (LES) (Matida et al., 2006, 2004). Softmist spray inhalers were considered by Longest and Hindle (2009a; Longest et al., 2009, 2007), and simulations were shown to agree well with concurrent *in vitro* results based on deposited drug mass for polydisperse aerosols. Longest et al. (2008b) demonstrated a four-fold increase in the MT deposition of a spray inhaler aerosol vs. ambient particles of the same size due to spray momentum and induced turbulence. Considered together, these studies indicate that the MT deposition of pharmaceutical aerosols is largely dependent upon inlet air profiles from the inhaler (Longest & Hindle, 2009b), spray momentum (Longest et al., 2008b), high velocity jets (Matida et al., 2003), and turbulence (Longest et al., 2008b; Matida et al., 2006). However, propagation of these flow features into the TB airways is largely unexplored.

A number of recent CFD studies have considered the deposition of ambient particles in the upper TB airways, typically extending to approximately the 5th respiratory generation. Jin et al. (2007) used a LES approach to model micrometer particles in a simple model of the MT and the first two TB bifurcations. Transient inhalation was shown to increase deposition in comparison to steady state flow conditions. Li et al. (2007) conducted simulations of microparticles in a TB model without a MT geometry and highlighted the complex interconnections of particle release time, flow rate, and transient inhalation on final deposition locations. Xi et al. (2008) studied the significant impact of the laryngeal jet, and importance of including this anatomical feature, on the deposition of nanometer and micrometer particles in a realistic model of the TB airways extending to approximately generation G7. Ma & Lutchen (2009) conducted simulations in a patient-specific MT-TB model through the 10th generation for steady state flow and found good agreement with existing algebraic correlations for deposition using micrometer particles. Lambert et al. (2011) constructed a similar patient-specific MT-TB model and reported that flow field characteristics (and not lung ventilation distribution) caused more particles to enter the left lung based on LES.

In comparison with these TB and MT-TB studies for ambient particles, far fewer analyses have considered the transport and deposition of pharmaceutical aerosols from spray devices and DPIs in the TB airways. The study of Kleinstreuer et al. (2007), which considered conditions through the first bifurcation, is the only CFD simulation of an MDI in a MT-TB model. Hindle & Longest (2010) considered the transport, condensational growth, and deposition of submicrometer pharmaceutical aerosols from a small particle aerosol generator in a MT-TB model through generation G5. Inthavong et al. (2010) considered the effects of tidal vs. inhaler-type breathing on microparticle aerosol deposition in a TB model without the inclusion of an oral and laryngeal geometry. Effects of MDI and DPI inhalers on the flow field were also ignored in this study.

Recent studies by several groups have proposed methods to simulate aerosol transport and deposition throughout the TB airways. Gemci et al. (2008) developed a CFD model of airflow in all generations ($\sim$17) of the TB region. However, the