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# Deposition of particles in the alveolar airways: Inhalation and breath-hold with pharmaceutical aerosols

Navvab Khajeh-Hosseini-Dalasm [a], P. Worth Longest [a,b,*]

[a] Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA, USA
[b] Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, USA

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ABSTRACT

Previous studies have demonstrated that factors such as airway wall motion, inhalation waveform, and geometric complexity influence the deposition of aerosols in the alveolar airways. However, deposition fraction correlations are not available that account for these factors in determining alveolar deposition. The objective of this study was to generate a new space-filling model of the pulmonary acinus region and implement this model to develop correlations of aerosol deposition that can be used to predict the alveolar dose of inhaled pharmaceutical products. A series of acinar models was constructed containing different numbers of alveolar duct generations based on space-filling 14-hedron elements. Selected ventilation waveforms were quick-and-deep and slow-and-deep inhalation consistent with the use of most pharmaceutical aerosol inhalers. Computational fluid dynamics simulations were used to predict aerosol transport and deposition in the series of acinar models across various orientations with gravity where ventilation was driven by wall motion. Primary findings indicated that increasing the number of alveolar duct generations beyond 3 had a negligible impact on total acinar deposition, and total acinar deposition was not affected by gravity orientation angle. A characteristic model containing three alveolar duct generations (D3) was then used to develop correlations of aerosol deposition in the alveolar airways as a function of particle size and particle residence time in the geometry. An alveolar deposition parameter was determined in which deposition correlated with $d^2t$ over the first half of inhalation followed by correlation with $dt^2$, where $d$ is the aerodynamic diameter of the particles and $t$ is the potential particle residence time in the alveolar model. Optimal breath-hold times to allow 95% deposition of inhaled 1, 2, and 3 μm particles once inside the alveolar region were approximately $>10$, 2.7, and 1.2 s, respectively. Coupling of the deposition correlations with previous stochastic individual path (SIP) model predictions of tracheobronchial deposition was demonstrated to predict alveolar dose of commercial pharmaceutical products. In conclusion, this study completes an initiative to determine the fate of inhaled pharmaceutical aerosols throughout the respiratory airways using CFD simulations.



* Corresponding author at: Department of Mechanical and Nuclear 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).

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## 1. Introduction

The alveolar surface of the lungs represents a very large and thin barrier separating inhaled gases and particles from the blood (Weibel et al., 2005). Knowledge of aerosol deposition in the alveolar region is important for the toxicological assessment of inhaled pollutants (ICRP, 1994). Similarly, the alveolar region is the target for the deposition and absorption of systemically acting inhaled medications (Patton & Byron, 2007). Examples of inhaled medications intended for alveolar delivery and systemic absorption include proteins and peptides (e.g., inhaled insulin), some antibiotics (e.g., anti-tuberculosis drugs), and inhaled pain medications (e.g., rapid acting migraine medications). In contrast, the alveolar deposition of medications intended for the tracheobronchial region can represent a source of unwanted systemic exposure and increased side effects. As a result, it is critical to predict the deposition of inhaled aerosol in the alveolar region in an accurate manner for the assessment of both inhaled pollutants and inhaled pharmaceutical products.

Due to the extremely small size of individual alveoli (characteristic dimension $\sim$180 μm), both computational fluid dynamics (CFD) analysis and scaled-up *in vitro* models provide effective tools for analyzing the fluid flow and associated aerosol transport. It is not possible to construct complete models of the alveolar airspace or even a single acinar unit considering the small size of the alveoli and total number of alveoli in the lungs [$\sim$480 million (Ochs et al., 2004)]. An understanding of general transport within the alveolar region has been gained from the analysis of individual alveolus models consisting of a single hemispherical shell or single alveolus attached to a tube (Balashazy et al., 2008; Haber et al., 2000, 2003; Lee & Lee, 2003; Sznitman et al., 2007a, 2009). From these individual alveolus approaches, geometric complexity has increased to include channels with multiple attached hemispheres (Tsuda et al., 1992), 3D tubular models (Darquenne & Paiva, 1996; Karl et al., 2004), bifurcating models with rectangular alveoli compartments (Harrington et al., 2006; Ma et al., 2009), tubular bifurcating models with attached hemispheres (Ma & Darquenne, 2012), tubes or bifurcating networks using a honeycomb or polyhedral structure of attached alveoli (Fung, 1988; Kumar et al., 2009; Sznitman et al., 2009), and cast or image-based geometries (Berg et al., 2010; Sznitman et al., 2010). Typical findings from these studies are summarized as follows:

- Gravity dominates the deposition of particles $\geq$3 μm whereas smaller particles (but above $\sim$400 nm) are controlled by both gravity and convection (Haber et al., 2003).
- Wall motion, which drives alveolar airflow, is an important component (Balashazy et al., 2008; Lee & Lee, 2003; Sznitman et al., 2007b).
- Unsteady flow has a large effect on transport dynamics (Haber et al., 2000; Sznitman et al., 2007a; Tippe & Tsuda, 2000).
- The presence of multiple alveoli in a model has an effect on the flow field and particle trajectories (Sznitman et al., 2009; Tsuda et al., 1992).
- Bifurcations and complexity of the airway geometry strongly influence aerosol deposition (Berg & Robinson, 2011; Fung, 1988; Harrington et al., 2006; Karl et al., 2004; Ma & Darquenne, 2012).

These findings have provided an excellent understanding of alveolar transport and aerosol deposition. However, aerosol deposition correlations that take these features into account have previously not been developed. Clearly, the generation of a model to predict alveolar deposition needs to include these reported aspects of transport dynamics.

As reviewed by Longest and Holbrook (2012), regional lung deposition is often predicted using whole-lung one-dimensional (1D) models (Asgharian et al., 2001a; Koblinger & Hofmann, 1990; Martonen, 1982; Yeh & Schum, 1980). These models implement analytic approximations of the various particle transport mechanisms to predict deposition at the level of individual bifurcations throughout the airways (Isaacs et al., 2005). The correlations used for alveolar deposition are typically based on aerosol sedimentation in a fixed inclined tube during steady flow (Finlay, 2001; Heyder & Gebhart, 1977). However, this approach omits a number of factors that were determined to be important for accurately capturing alveolar transport and deposition, as described above. For example, Kojic and Tsuda (2004) showed the importance of considering oscillating flow in determining gravitational sedimentation in a simple pipe model. Kim (2009) and Choi and Kim (2007) demonstrated that airway wall motion was important to accurately match *in vivo* alveolar deposition data with 1D model predictions. Despite the limitations of current 1D models, these approaches show reasonable agreement with *in vivo* determined slow clearance ($>$24 h) from the lung (Hofmann & Koblinger, 1990, 1992). Still, the slow clearance of deposited aerosol mass as measured by gamma scintigraphy and used for alveolar model validation is not synonymous with alveolar deposition (Asgharian et al., 2001b). There is often a significant tracheobronchial fraction that clears slowly, possibly due to macrophage uptake, entrapment in the cilia, binding to epithelial cells, intersubject variability, and airway paths of different lengths (Asgharian et al., 2001b; ICRP, 1994). Furthermore, pulmonary predictions of deposition are typically of lowest accuracy in the range of 1–3 μm particle diameter, which is the expected range of pharmaceutical aerosols that reach the alveolar airways. Improved alveolar deposition correlations are needed that take into account recent findings related to alveolar transport and deposition. The benefits of these correlations can be determined through comparisons with the currently implemented inclined straight tube models.

In a series of studies, a CFD approach has recently been developed to simulate the delivery of pharmaceutical aerosols throughout the conducting airways (Longest et al., 2012a, 2012b; Tian et al., 2011). Using this approach, CFD simulations are used to capture spray and jet effects of the inhaler (Longest et al., 2008) and the inhalation profile (Byron et al., 2013) in