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In silico models of aerosol delivery to the respiratory tract — Development and applications ☆

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ABSTRACT

This review discusses the application of computational models to simulate the transport and deposition of inhaled pharmaceutical aerosols from the site of particle or droplet formation to deposition within the respiratory tract. Traditional one-dimensional (1-D) whole-lung models are discussed briefly followed by a more in-depth review of three-dimensional (3-D) computational fluid dynamics (CFD) simulations. The review of CFD models is organized into sections covering transport and deposition within the inhaler device, the extrathoracic (oral and nasal) region, conducting airways, and alveolar space. For each section, a general review of significant contributions and advancements in the area of simulating pharmaceutical aerosols is provided followed by a more in-depth application or case study that highlights the challenges, utility, and benefits of *in silico* models. Specific applications presented include the optimization of an existing spray inhaler, development of charge-targeted delivery, specification of conditions for optimal nasal delivery, analysis of a new condensational delivery approach, and an evaluation of targeted delivery using magnetic aerosols. The review concludes with recommendations on the need for more refined model validations, use of a concurrent experimental and CFD approach for developing aerosol delivery systems, and development of a stochastic individual path (SIP) model of aerosol transport and deposition throughout the respiratory tract.

Contents

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1. Introduction

Modeling respiratory aerosol delivery requires an analysis of transport and deposition in the respiratory tract as well as an understanding of dynamics within the aerosol generation device, which often influence the flow field and deposition characteristics in the upper airways. Numerical models of particle deposition in the lungs were initially developed in the context of assessing the dosimetry of inhaled environmental and occupational pollutants, such as coal dust, cigarette smoke, and radionuclides. Decades of research on respiratory aerosol dosimetry were compiled in the ICRP [1,2] and NCRP [3] documents and corresponding models. Over time, these whole-lung dosimetry models, which were developed for ambient monodisperse particles, were expanded and applied to better understand the deposition of pharmaceutical aerosols in the airways [4]. *In silico* model results generally agreed well with *in vivo* studies for upper (fast clearance) and lower (slow clearance) deposition fractions considering stable monodisperse particles. However, these early whole-lung deposition models did not account for factors specific to respiratory drug delivery, such as inhaler spray momentum, droplet size change with dissolved solutes, and did not predict localized aerosol deposition. The advancement of computational fluid dynamics (CFD) technology has led to an alternative approach for dosimetry modeling in which aerosol transport and deposition is calculated from first principles in realistic three-dimensional (3-D) models of the inhaler and respiratory tract. CFD simulations can directly capture factors such as inhaler spray momentum [5], spray burst effect [6], turbulent inhaler jets [7], and droplet evaporation or hygroscopic growth [8,9]. Recent comparisons of CFD model predictions to *in vivo* [10] and *in vitro* [11,12] data show good agreement. As a result, applications of CFD models are progressing beyond providing an understanding of aerosol deposition mechanics and toward serving as an effective design and optimization tool for improving respiratory drug delivery. In this introductory section, types of numerical models are reviewed, advantages of CFD simulations are presented, and challenges related to the numerical modeling of respiratory aerosols are highlighted. This review then focuses on studies that contributed to the development of respiratory delivery models along with studies that applied these models to improve existing devices, target aerosol delivery to the lungs, and propose new aerosol delivery approaches.

1.1. Types of respiratory delivery models

Current whole-lung models of aerosol dosimetry in the respiratory tract typically account for deposition within individual sections of the airways using physical or empirical correlations. The individual sections considered may range in scale from general regions of the lungs, like the tracheobronchial airways, down to individual airway branches. However, only penetration depth into the lungs is considered in the most detailed of these simulations, such that they are often referred to as one-dimensional (1-D) models. Correlations for deposition may be dependent upon individual transport mechanisms (such as diffusion, sedimentation, and impaction) as reviewed by multiple previous studies [13,14], or may be empirically based [15,16]. While these models are generally developed for monodisperse ambient aerosols, studies have advanced their utility to evaluate the effects of size change [17,18], aerosol charge [19] and aerosol polydispersity [20]. Recently, *in vitro* experiments and CFD simulations were used to develop an empirical correlation for dry powder inhaler (DPI) deposition in the mouth–throat region as a function of jet and airway characteristics [7]. A similar correlation is not available for spray aerosols produced by metered dose inhalers (MDIs) and soft mist inhalers. Recent advances in whole-lung respiratory dosimetry models and the underlying correlations were reviewed by Finlay and Martin [16]. The related online Respiratory Deposition Calculator of the Aerosol Research Laboratory of Alberta provides a convenient method to determine the whole-lung deposition of pharmaceutical aerosols. The multiple path particle deposition model (MPPD) provided by the Hamner Institutes for Health Sciences and described by Asgharian et al. [21] is also a useful whole-lung modeling tool that can provide estimates of delivery to individual airway branches.

Strengths of 1-D whole-lung models are ease of use and the fact that deposition can be estimated throughout the respiratory tract. One disadvantage of these methods is that the available correlations may not cover all mechanisms related to pharmaceutical aerosol delivery from multiple platforms. A second disadvantage of these models is that the site of deposition is not well described; that is, deposition is predicted in general regions such as the mouth–throat or tracheobronchial airways. In general, 1-D models neglect the geometric complexity of the airways along with the associated complex flow physics, such that these models cannot directly capture a number of phenomena known to influence particle deposition.

In contrast with 1-D models, modern CFD simulations calculate flow and aerosol physics based on first principles in 3-D sections of the inhaler and respiratory tract. The flow field is determined using a solution of the Navier Stokes equations which may include approximations for turbulence, compressible flow, and heat/mass transfer [22,23]. The discrete particle or droplet phase is typically solved using Newton's second law accounting for all relevant forces acting on the discrete elements, such as drag, gravity, and Brownian motion, as well as heat and mass transfer with the continuous phase [9,24,25]. Recent studies have also developed very efficient models of particle motion using a continuous phase approach [26–28]. Simulations are conducted in idealized [29], patient specific [30], or characteristic models of the respiratory tract [31], as described later in this review.

A primary strength of CFD simulations is the use of general governing transport equations, such that the model can be applied to a wide range of airway geometries, aerosol conditions, and delivery devices without the need to develop empirical or semi-empirical deposition correlations. The CFD model provides a detailed description of the flow field at millions of representative points (control volume centers and nodes) and can predict deposition at very localized (sub-millimeter) levels [32–34]. Weaknesses of CFD