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An adaptable model for growth and/or shrinkage of droplets in the respiratory tract during inhalation of aqueous particles

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ABSTRACT

The site of deposition of pulmonary delivered aerosols is dependent on the aerosol's droplet size distribution, which may change during inhalation. The aim of this study was to develop a freely accessible and adaptable model that describes the growth (due to condensation) and shrinkage (due to evaporation) of inhaled droplets as a function of the distance from the airway wall during various inhalation conditions, for a laminar flow scenario. This was achieved by developing a model with which the evaporation of water from a droplet surface or condensation of water onto the droplet surface can be calculated. This model was then applied to a second model that describes the heat and mass transfer from the airway wall to the inhaled aerosol. The latter was based on the Weibel model. It was found that the growth and shrinkage of inhaled droplets markedly differs, depending on the distance from the airway wall. Droplets near the wall start to grow immediately due to fast water vapor transfer from the wall to the cold inhaled air. This growth continues until the air reaches body temperature and is fully saturated. However, droplets in the center of the airway first evaporate partly, due to a delay in water vapor transfer from the airway wall, before they start to grow. Depending on the conditions during inhalation, the droplet size distribution can widen considerably, which may affect the lung deposition and thereby the efficacy of the inhalation therapy. In conclusion, the model was able to show the effect of the conditions in the respiratory tract on the growth and shrinkage of inhaled droplets during standard inhalation conditions. Future developments can be aimed at expanding the model to include turbulent flow and hygroscopic growth, to improve the accuracy of the model and make it applicable to both droplets of solutions and dry particles.

1. Introduction

Inhalation of drugs is widely applied in the treatment of asthma and COPD. Furthermore, the pulmonary route is currently targeted for the treatment of diseases that are not directly located or even associated with the respiratory tract. Due to the proximity of the capillaries and blood vessels with the lining in the respiratory tract and the leaky nature of the pulmonary membranes (especially in the alveoli), the absorption of active pharmaceutical ingredients can be extremely rapid (Patton, 1996; Rabinowitz et al., 2006). However, the rate and amount of absorption heavily depend on the location of

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deposition of the inhaled substance (Labiris & Dolovich, 2003; Usmani, Biddiscombe & Barnes, 2005; Zanen, Go & Lammers, 1994).

During a standard inhalation procedure, the largest particles (either dry powder or droplets, although in this paper only aqueous droplets will be considered) are deposited in the mouth and the back of the throat, meaning their effect is essentially lost. The rest of the particles are deposited throughout the respiratory tract, where the spread of deposition is mainly dependent on the particle size distribution of the liquid aerosol or dry powder. This aerosol's particle size distribution is ideally tailored to obtain deposition at a location where it is desired for a specific application. As a general rule of thumb, particles with an aerodynamic diameter larger than 5 μm are deposited in the throat and smaller than 1 μm are exhaled after inhalation (Labiris & Dolovich, 2003). Anything in between is deposited in the lung, with smaller particles having a higher chance to reach the peripheral parts of the lung and even the alveoli and larger particles being deposited more centrally in the respiratory tract. However, in reality it is more complex.

When particles are inhaled, they are subjected to quickly changing conditions. When the particles exit the inhaler together with the ambient air, conditions surrounding the particles closely match those of the ambient air, which means relatively low relative humidity and room temperature. During the passage through the respiratory tract, the relative humidity quickly increases as well as the temperature. For both dry powder and liquid aerosols, this could affect their aerodynamic diameter, as the increased humidity could cause the dry powder particles to get wet and grow, while droplets in the liquid aerosol could grow due to condensation or shrink due to evaporation. If it would be possible to tell whether, and if so, how much the aerodynamic diameter of inhaled particles is changed while traversing the respiratory tract, it could aid in optimizing formulations for inhalation. By taking into account growth and/or shrinkage of the particles, the deposition location in the respiratory tract could be further tailored for each treatment.

Indeed, a lot of effort has gone into modeling the condensational growth of solid submicron particles during inhalation to allow targeted deposition in the respiratory tract, mainly by Longest et al. (Ferron, 1977; Golshahi et al., 2013; Hindle & Longest, 2010; Longest & Hindle, 2010, 2011, 2012; Longest, McLeskey & Hindle, 2010; Longest, Tian & Hindle, 2011; Longest, Tian, Li, Son & Hindle, 2012; Tian, Longest, Li & Hindle, 2013; Tian, Longest, Su & Hindle, 2011; Worth Longest et al., 2012) but others as well (Broday & Georgopoulos, 2001; Kleinstreuer & Zhang, 2010). In addition, a lot is known about the conditions to which inhaled particles and droplets are subjected when inhaled (Ferron, 1977; Olson, Sudlow, Horsfield & Filley, 1973; Tian, Longest, Su & Hindle, 2011). Most of these studies revolve around the use of computational fluid dynamics (CFD), which is an excellent method to accurately model the complex flow profiles that exist inside the airways. However, such models lack openness and accessibility for researchers who are not directly involved in such fields. The same can be said for more analytical models that use pre-formulated sets of equations that describe, for example, the evaporation rate from a droplet. Furthermore, the complete models are not readily available online. Although simpler models using standard heat and mass balances usually result in less detailed results, their use often allows more openly accessible models to be developed that can be used and adapted by others. In addition, given enough effort, the complexity of the model can be increased to obtain more accurate results. Furthermore, we believe that understanding the basic mechanics underlying such a model can also greatly increase the understanding of the system under consideration.

Therefore, the aim of this study is to investigate the behavior, i.e. growth and shrinkage, of inhaled particles in the respiratory tract with a theoretical model based on standard heat and mass balances. This will be done by primarily focusing on aqueous particles. Although dissolved components such as drugs and excipients will be left out of the model to prevent it from becoming overly complex, the model will be constructed such that it can be expanded by anyone who wishes to do so. Therefore, the model will be developed in an open source platform called GNU Octave and be made available freely. Consequently, a model will be obtained that can form a basis for further expansion and development to create a more complex but also more complete model of dry particle and droplet behavior in the respiratory tract without resolving to CFD. Finally, the clinical relevance of the results of this study towards inhalation practices will also be discussed.

2. Materials and methods

2.1. Open source software

The model was developed entirely in GNU Octave, which is freely available (Eaton & Community, 2014). Furthermore, the developed model itself is available online as Supplementary data.

2.2. Model input parameters

The basis for the input of the models was obtained from the Respimat® soft mist inhaler (Boehringer Ingelheim, Ingelheim, Germany). The inhaled jet that is ejected from the inhaler contains about 15 mg of water and lasts for about 1.2 s. Furthermore, the starting droplet diameter is 4.5 μm (Dalby, Eicher & Zierenberg, 2011). For the simulations, an inhalation flow of 40 L/min was chosen, although for comparison, a fast inhalation with an inhalation flow of 100 L/min will also be considered (Brand, Hederer, Austen, Dewberry & Meyer, 2008). Finally, a room temperature of either 293 K or 303 K, and a relative humidity of either 35, 50 or 70% will be used. Note that all of these parameters can be easily customized in the developed model, if desired.