In silico Study on the deposition and distribution of particles in a realistic airway model with Handilaher®

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Abstract: Effective pulmonary drug delivery plays an essential role in the treatment of diseases. Drug aerosolization and inhalers play an essential role in the therapeutic effect of pulmonary diseases. The main objective of this paper is to evaluate the effect of inhalers, inhalation flow rates, and particle properties on the transport and deposition of 1-19 μm particles in a realistic airway model. Computational fluid dynamics coupled with the discrete phrase model (CFD-DPM) was performed to predict the transport and deposition of inhaled particles. Good agreement in deposition mechanisms was observed with the *in vivo* published data, which proved the effectiveness of the numerical method in pulmonary drug delivery. Airflow structure as well as deposition pattern showed that differences in turbulence, reverse flow, and vortex formulation between the two different models are determined by the existence of inhaler geometry. Enhancing the air flow rate and particle diameter increases the particle inertial as well as the turbulence level, resulting in an uptrend in deposition fraction (DF) of the mouth-throat (MT) region. In conclusion, this *in silico* method is valuable to help understand the *in vitro* - *in vivo* correlation (IVIVC) of pulmonary drug delivery.

1. Introduction

Pulmonary drug delivery is one of the most important administration routes which can be used locally and systemically to treat diseases. Effective pulmonary drug delivery depends on many factors including inhalation device, anatomical airway structure, inhalation mode, particle properties, etc[1, 2]. The significance of inhalers in the management of pulmonary disease is widely acknowledged and is recognized as important as medication. Dry powder inhalers (DPIs) are the most widely used inhalation devices for drug delivery to manage pulmonary diseases. However, there are still some limitations with this device, such as high deposition fraction (DF) in the upper airway, low dose to the lung, and poor patient compliance[3]. A variety of idealized and realistic airway models, such as the United States Pharmacopoeia (USP) and Alberta throat, have been developed for numerical and experimental studies on particle delivery [2, 4]. However, the mechanisms of deposition in the whole realistic airway model are poorly understood due to the limited detailed structure of the respiratory tract.

The main objective of this study is to investigate the aerosol deposition emitted from a commercial DPI in a realistic airway model. The effect of the inhaler on particle deposition was analyzed based on the comparison between the two models using the CFD-DPM model. Airflow structure and its impaction on deposition pattern have been investigated and discussed at different flow rates and particle properties in the next sections.

2. Methodology

2.1 Inhaler geometry

Handihaler® (tiotropium bromide, Boehringer Ingelheim Pharmaceuticals, Inc. Germany) is a single-dose breath-activated DPI used to control Chronic Obstructive Pulmonary Disease (COPD). It consists of a plastic inhaler body with a capsule chamber that holds a foil blister containing the powder medication. 3D data of the inhaler was obtained by reverse modeling technology. The geometry of the inhaler was reconstructed from the 3D data and optimized in the Computer-Aided Design (CAD) software (Solidworks, Dassault Systèmes, USA), as Figure 1(a) shows, and the inlets and outlet are illustrated.

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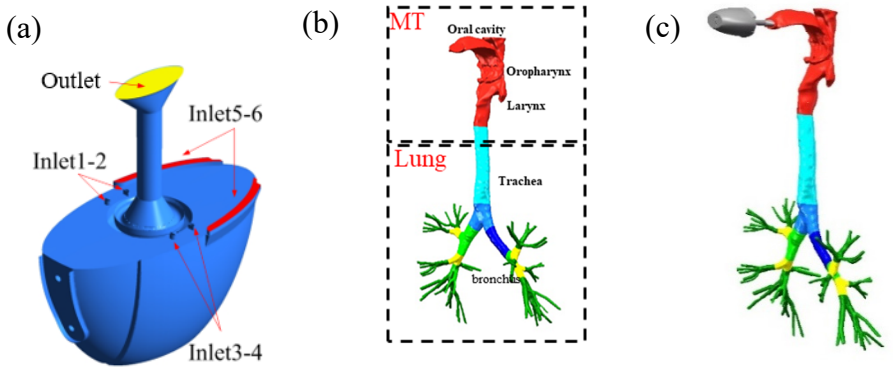


Figure 1. Schematic diagram of geometries: (a) Handihaler®, (b)RTM, (c) RTM+Inhaler

2.2 Airway model

The realistic respiratory tract model was acquired from computed tomography (CT) images of a healthy, 25 years old, Asian female. The geometry includes mouth-throat (oral cavity, ora-pharynx, and larynx), trachea, and tracheobronchial tree (also the lung region) up to 9 generations. The 2D image data was calculated in an image processing software (Mimics, Materialise NV, Belgian) to create a 3D surface model. The 3D model was then modified for segmentation and optimization in 3Matic (Materialise) and Solidworks, respectively. As shown in Figure 1(b), one can clearly see the whole respiratory tract model (RTM) with sufficient details of anatomy. Figure 1(c) shows the airway model coupled with inhaler geometry, which is used to study the effect of the inhalation device on particle deposition in the airway.

2.3 Numerical model and conditions

The drug particle delivery process was considered as a two-phrase (particle-fluid) flow in this work. The discrete particles and the continuous airflow were solved by discrete DPM and CFD. The airflow was considered as a steady state and the built-in transition SST model in ANSYS Fluent was utilized to solve the Reynolds stress term. The one-way Lagrangian particle tracking approach was used to study particle transport and deposition. As the particle phase is dilute, the effect of the particle on airflow, particle-particle interaction, pressure gradient force, and the lift force was ignored. Only the drag force from the air to the particle and the gravity were considered in this work. The discrete random walk model was employed to include the turbulent velocity fluctuations in the simulation. Tetrahedral meshes were generated and mesh independence was validated in this paper. The wall of the airway model was set as a trap without particle rebound. This numerical model has been demonstrated to be able to get a better correlation between the *in silico* particle deposition and *in vivo* results[5]. A summary of physical parameters and model setting for simulation is given in Table 1.

Table1 Physical parameters and model settings for simulation.

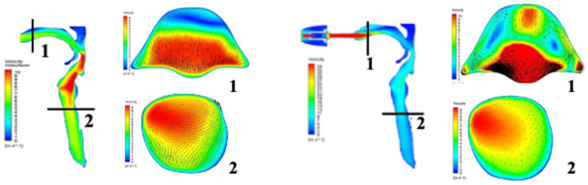
Parameters	Values
Air density (25 °C) (kg/m3)	1.1845
Air dynamic viscosity (25 °C) (kg/m·s)	1.84E-05
Particle density (kg/m3)	1000
Aerodynamic diameter of particles (*da*)(μm)	1-19
Airflow rate on inlet (L/min)	30
Mesh number (cells) - Tetrahedral meshes	RTM-7522508; RTM+Inhaler-11256142

3. Results and discussion

3.1 Flow pattern

Velocity contours alongside vectors in different cross sections at 30 L/min were utilized to analyze the airflow structure in these two models. Figure 2 shows the contours and vectors of velocity at sagittal and two axial cross-sections. A more complex airflow pattern is observed in the RTM+Inhaler compared to that of the RTM model. The mean velocity of the RTM+Inhaler model is much higher, especially in the oral cavity. Most of the airflow passed from the middle of the oral cavity in the RTM model, while the flow passed from the bottom half near the tongue in the RTM+Inhaler model, leading to more vortex formation at the upper half of the oral cavity. Vortices are one of the major characteristics of turbulent flow created by fluid motion[6]. The velocity vectors of section 1 in figure 2 (b) illustrate that reverse flow in the oral cavity results in deflected streamlines and formulation of vortices in the MT region, which leads to increased probability of particle collision with the wall and high DF. The jet emitted from inhaler results in higher air velocity magnitude, corresponding to higher turbulence level and streamlines change dramatically. The distribution of the flow field in section 2 shows that the magnitude and distribution of the velocity tend to be consistent in the trachea region. It therefore appears that the effect of the device on particle depositions mainly concentrated in the oral cavity region. With the increase in the number of tracheal branches, the fluid velocity decreased rapidly as the total transverse section area increased. The dominant deposition mechanisms in these regions are sedimentation and diffusion[7]. The effect of the inhaler on particle deposition was reduced gradually in downstream regions. Overall, the results show that the inhaler brings obvious differences in the flow pattern in

the airway. The effect of the inhaler on the deposition pattern will be discussed in detail in the next section.



(a) (b)

Figure 2. Contour and vector of velocity magnitude in the central sagittal plane and at various cross-sections at 30 L/min.(a) RTM, (b) RTM+Inhaler.

3.2 Effect of inhaler on DF in the airway model

Deposition fraction (DF) is an important parameter utilized to quantize the inhaled particle deposition, and it can give us a good insight into the deposition patterns of inhaled pharmaceutical particles[8]. It was determined based on deposited particles of inhaled particles in different regions of the airway model. Particle deposition of two models at 30 L/min are presented in figure 3. The results illustrate that DF of lung region decreases with increasing particle diameter. Due to the filtering function of MT, most large particles were deposited in the extrathoracic region, and more fine particles reached the lung region.

Figure 3(a) shows the deposition pattern of the 1-19 um particles in the two models at the airflow rate of 30 L/min. The different deposited regions of particles with size distribution can be clearly observed between the two models. For the RMT+Inhaler model, particles emitted from the inhaler delivered with high momentum, even small particles (1-10 μm) tended to deposit in the oral cavity due to impaction. While for the RTM model, most fine particles can penetrate the oral cavity and enter the lower regions along with the steady airflow, and most of the particles deposited in the oral cavity are larger than 10 μm. Overall, the deposition pattern was consistent with the airflow pattern, which means that high-velocity magnitude enhanced the particle deposition in the upper airway.

The noticeable difference in DF of lung between RTM and RTM+Inhaler is illustrated in figure 3(b). Within the size range of inhaled particles, the DF of the RTM model is obviously higher than that of RTM+Inhaler, especially for the range of 1-10 μm. While for the RMT+Inhaler model, the DF of lung region fell much more slowly as the particle diameter increased, which was consistent with the data plotted in figure 4. The phenomenon can refer to the airflow structure in the oral cavity where higher turbulence level is generated by the inhaler. The initial condition of airflow entering the mouth region directly determined the flow pattern in the airway. Compared with the soft airflow in the RMT model, the jet stream from the inhaler corresponded to higher velocity magnitude, more vortex, and strong turbulence in the oral cavity, resulting in more impaction and deposition in this region.

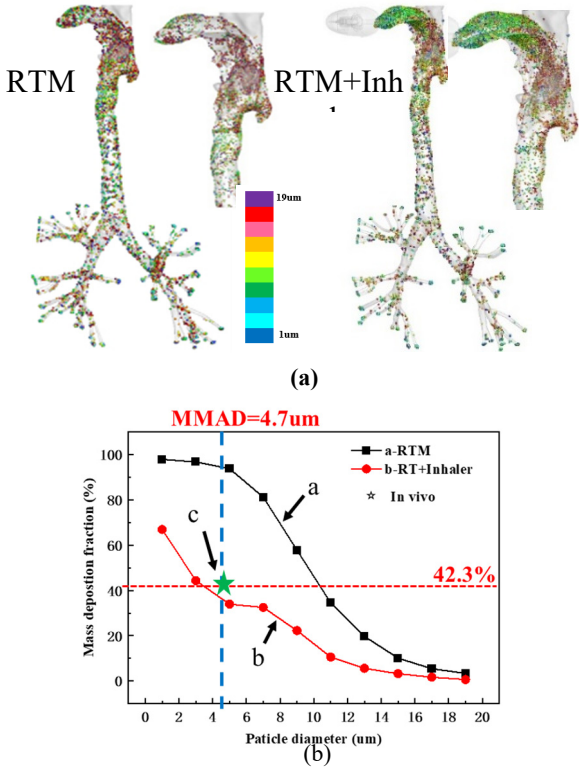
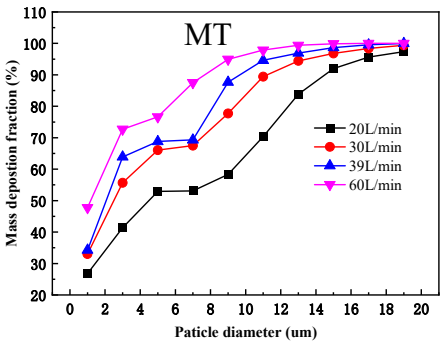


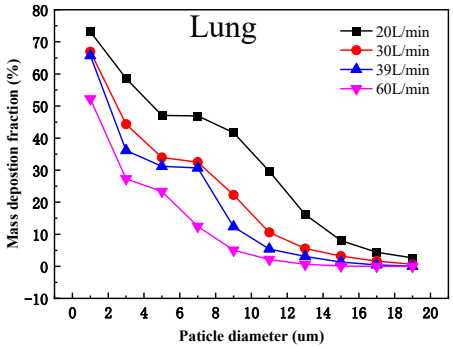
Figure 3. Deposition pattern in two models at 30L/min. (a) Particle distribution, (b) DF of lung.

3.3 Effect of flow rate and particle size on the DF

Impaction, sedimentation, and diffusion are the dominant deposition mechanisms in pulmonary drug delivery[9]. Regional deposition at four constant inhalation flow rates (20, 30, 39, 60 L/min) of RTM+Inhaler is presented in figure 4. The DF of MT improved with the increase in inhalation flow rate and particle diameter, which was expected due to the increasing turbulence and particle momentum. This uptrend is consistent with the conclusion that impaction is the main deposition mechanism reported by several researchers[10]. The trend of DF in the lung region was opposite to the MT.



(a)



(b)

Figure 4. Regional deposition in the RTM+Inhaler model. (a) mouth-throat (MT), (b) lung region.

3.4 Comparison of DF between our data and in vivo data

To verify the numerical results, the results were directly compared with the previously reported *in vivo* data published by Brand et. al (2007)[11]. Lung deposition of radiolabeled tiotropium administered via the DPI Handihaler® was investigated in a group of 5 healthy subjects using γ scintigraphy. Their study showed that mean DF of lung was 42.3%. The aerodynamic median particle of Handihaler® at a constant flow rate of 30 L/min with 4 L volume air tested by Next Generation Impactor (NGI) is 4.7 um. Figure 3(b) shows a comparison of DF of lung between the two models. DF of Lung in the RTM+Inhaler model is 33.94% at 4.7 um which is quite different from 93.86% in the RTM model. It can be clearly observed that DF of lung in RTM+Inhaler was much closer to the *in vivo* data. The results demonstrated that numerical simulation considering inhaler geometry agreed well with *in vivo* data.

4. Conclusion and Shortcomings

In this paper, a realistic airway model based on CT images and inhaler geometry were developed to study the effect of the inhalation device, flow rate, and particle diameter on pulmonary drug delivery. A validated CFD-DPM model was utilized to investigate the particle transportation and deposition in the airway models. In conclusion, airflow structure as well as deposition pattern analysis illustrated that differences in turbulence, reverse flow and vortex formulation between RTM and RTM+Inhaler models were determined by the existence of inhaler. Particle deposition distribution of different size particles were also affected by the inhaler. This *in silico* method can be valuable to help understand the IVIVC of pulmonary drug delivery.

The shortcomings of this study include a lack of representativeness and limited operating conditions. To achieve more accurate and comprehensive results, it is necessary to consider multiple airway models and take into account the effect of other factors like humidity and static electricity on drug delivery.

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