Computers in Biology and Medicine xx (xxxx) xxxx–xxxx

Contents lists available at ScienceDirect

Computers in Biology and Medicine

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

Computationally efficient analysis of particle transport and deposition in a human whole-lung-airway model. Part II: Dry powder inhaler application

Arun V. Kolanjiyil[a], Clement Kleinstreuer[a,b,*], Ruxana T. Sadikot[c,d]

[a] Department of Mechanical & Aerospace Engineering, North Carolina State University, Raleigh, NC 27695-7910, United States
[b] Joint UNC-NCSU Department of Biomedical Engineering, North Carolina State University, Raleigh, NC 27695-7910, United States
[c] Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Emory University, School of Medicine, United States
[d] Department of Veterans Affairs, Atlanta VAMC, United States

ARTICLE INFO

Keywords:
Lung
Airflow
Whole lung-airway modeling
Computational fluid-particle dynamics (CF-PD)
Particle deposition
Pharmaceutical aerosols
Dry powder inhaler (DPI)
Curcumin

ABSTRACT

Pulmonary drug delivery is becoming a favored route for administering drugs to treat both lung and systemic diseases. Examples of lung diseases include asthma, cystic fibrosis and chronic obstructive pulmonary disease (COPD) as well as respiratory distress syndrome (ARDS) and pulmonary fibrosis. Special respiratory drugs are administered to the lungs, using an appropriate inhaler device. Next to the pressurized metered-dose inhaler (pMDI), the dry powder inhaler (DPI) is a frequently used device because of the good drug stability and a minimal need for patient coordination. Specific DPI-designs and operations greatly affect drug-aerosol formation and hence local lung deposition. Simulating the fluid-particle dynamics after use of a DPI allows for the assessment of drug-aerosol deposition and can also assist in improving the device configuration and operation. In Part I of this study a first-generation whole lung-airway model (WLAM) was introduced and discussed to analyze particle transport and deposition in a human respiratory tract model. In the present Part II the drug-aerosols are assumed to be injected into the lung airways from a DPI mouth-piece, forming the mouth-inlet. The total as well as regional particle depositions in the WLAM, as inhaled from a DPI, were successfully compared with experimental data sets reported in the open literature. The validated modeling methodology was then employed to study the delivery of curcumin aerosols into lung airways using a commercial DPI. Curcumin has been implicated to possess high therapeutic potential as an antioxidant, anti-inflammatory and anti-cancer agent. However, efficacy of curcumin treatment is limited because of the low bioavailability of curcumin when ingested. Hence, alternative drug administration techniques, *e.g.*, using inhalable curcumin-aerosols, are under investigation. Based on the present results, it can be concluded that use of a DPI leads to low lung deposition efficiencies because large amounts of drugs are deposited in the oral cavity. Hence, the output of a modified DPI has been evaluated to achieve improved drug delivery, especially needed when targeting the smaller lung airways. This study is the first to utilize CF-PD methodology to simulate drug-aerosol transport and deposition under actual breathing conditions in a whole lung model, using a commercial dry-powder inhaler for realistic inlet conditions.

1. Introduction

Respiratory drug delivery is becoming an increasingly popular way of administering medicine. It is efficient for treating both pulmonary and systemic pathogenic conditions as discussed in [1–3]. This route of drug delivery has many advantages when compared to other non-invasive administration methods. In cases of pulmonary lung diseases like asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acute respiratory distress syndrome (ARDS), and lung fibrosis, respiratory drugs may be very effective treatment options for several reasons: (i) instantaneous onset of action; (ii) minimal side effects; and (iii) maximal use of drugs at the affected area [4]. Also, the rapid absorption of the inhaled drug-aerosols, especially nanodrugs, through the large surface area of the alveolar lung region into systemic circulation results in rapid bio-distribution when targeting diseased organs [5].

Respiratory drugs are administered to the lungs with the inhaled air using an inhaler device, as discussed in [6–9]. The dosage of administered drugs to different regions of the lungs depends on the drug formulation and inhaler-device characteristics. The dry powder inhaler (DPI) is a frequently used device because of the greater drug stability and minimally required patient coordination, as pointed out

* Corresponding author at: Department of Mechanical & Aerospace Engineering, North Carolina State University, Raleigh, NC 27695-7910, United States.
E-mail address: ck@ncsu.edu (C. Kleinstreuer).

http://dx.doi.org/10.1016/j.compbiomed.2016.10.025
Received 23 May 2016; Received in revised form 4 October 2016; Accepted 31 October 2016
Available online xxxx
0010-4825/

by [10,11]. In a DPI, the aerosols are generated by de-agglomeration of the powdered drug particles *via* the shear forces generated by the inhaled airflow [8,12]. Hence, the amount of drug delivered to lung regions from a DPI inhaler depends on the patient's inspiratory capacity [13]. Currently, there are more than 30 different DPIs on the market. Among the different DPIs available, the Novolizer from Meda Pharmaceuticals (Somerset, NJ) is a multidose breath-actuated DPI, approved for delivery of budesonide and salbutamol [14]. In this DPI, the drug is stored as a powder blended with lactose-carrying particles. The patient's inspiratory flow actuates the Novolizer valve, and when the inspiratory flow is above a threshold value (usually peak inspiratory flowrate (PIFR) of 30–50 LPM), a predetermined drug dose is released into the inhalation chamber [15,16]. The design of the flow channel, mouth piece and the cyclone-base help in generating aerosols of clinically effective fine particle fractions [14]. The inspiratory air with the drug aerosols exit the mouth piece through a 6 mm-diameter opening, forming a fluid-particle jet at the mouth-inlet.

Scientific measurements to predict the lung dosage and device function are required for new inhaler devices. New or generic drugs have to be bio-equivalent before approval for clinical application. The most common way of measuring the amount of drugs deposited in the lung airways are *in vitro* tests using idealized oral cavity models and assuming that the particles exiting the oral cavity deposit in the lung airways [16–18]. Clearly, these measurements cannot provide detailed total and regional lung deposition/dosage measurements. Alternatively, *in vivo* experiments using radio-nuclide imaging (*via* gamma scintigraphy and positron emission tomography) and/or pharmacokinetic studies were used [13,19,20]. For radio-nuclide imaging the active therapeutic agents are labelled with a radionuclide before inhalation by the subject. After administration of the radio-labelled drug formulation using the device, the different views of the lung are captured using a gamma camera [13,21,22]. In pharmacokinetic measurements, the amount of drugs deposited in the lungs is estimated based on the amount of drugs measured in blood and urinary samples, collected from the subjects after administration of the drugs [19,23,24]. There are many limitations for these two measurement techniques; both techniques need human subjects and these techniques involve either inhalation of radioactive materials or requiring blood and urinary samples during intervals of time. The radio-nuclide image measurement method is further complicated due to the limited ability to radiolabel drug formulations without varying the aerodynamic properties. However, the gamma scintigraphy image can provide direct image visualization and an approximate whole-lung and regional deposition measurements [2,20,25,26]. In case of the pharmacokinetic measurement method, only an approximate estimate of total lung deposition is possible; thus, without any information regarding the deposition sites. Recently, there has been an effort to combine single-photon-emission-computed-tomography (SPECT) image of deposited radio-labelled drugs with high resolution computed-tomography (CT) scan images of the same subject to accurately estimate the deposition sites [27–29]. However, due to the limited resolution of airway imaging *via* CT and SPECT, associated with long processing times, detailed lung anatomical mapping is not possible except for few upper bronchial airways. Considering all these limitations of the experimental and *in vivo* measurement methods, computational analysis has significant advantages as it is safe as well as time and cost efficient [15,30–35]. Once validated, computer simulations can provide detailed total and regional particle-deposition results which are of interest to toxicologists, health-care providers and inhaler-manufacturers alike [36–38].

The efficiency of respiratory drug administration is highly dependent on the type of delivery device [7]. Most of the currently used inhalers have low lung deposition efficiencies because high amounts of drugs are deposited in the oral cavity [39]. Efficient delivery of drugs to the deeper lung regions requires proper coordination between modified inhaler-device, its actuation, and breathing pattern [1]. Hence, direct drug-delivery to the required lung sites, *e.g.*, optimal lung-tumor targeting, has become an active research area. For example, Kleinstreuer et al. [4] introduced and validated a new methodology to achieve direct drug-particle delivery from the injection point to the desired lung site, using an optimal particle-release map to generate a unique air-particle stream. The optimal particle-release positions can be predicted on a subject-specific basis with computer simulations of drug-aerosol transport and deposition [1].

In recent years, there have been several medical applications of curcumin for treating critical organ diseases, as discussed in [40–44]. Curcumin is a polyphenol compound present in *Curcuma longa* plant (commonly known as turmeric) which is largely cultivated in sub-tropical Asian countries. Recent investigations have shown that curcumin possess high therapeutic potential as an antioxidant, anti-inflammatory and anti-cancer agent [44,45]. More recent studies have reported that curcumin has the therapeutic potential to inhibit lung inflammatory reactions and additionally, curcumin has shown to possess potential to reverse steroid resistance in patients with asthma and COPD [45–47]. Corticosteroid resistance is a major barrier to adequate disease control for asthma and COPD patients and curcumin may be an alternative medicine to these pathological conditions [46,48]. However, efficacy of treatments with curcumin is limited because of the low bioavailability of curcumin when ingested [49]. Hence, delivering curcumin *via* inhalation to specific lung sites has been suggested. However, this type of treatment is limited because of the unstable nature of the colloidal formulation, *e.g.*, particle-aggregation may occur. Further investigations are required to improve both drug formulation and delivery to lung airways using inhaler devices.

In Part II the WLAM is employed to analyze particle transport and deposition in a human respiratory tract model when a drug-aerosol is inhaled *via* a commercial DPI. The DPI assumed for the current study is the powder inhaler Novolizer (Meda Pharmaceuticals, Somerset NJ) which has shown reproducible dosing capabilities. Additionally, to validate the current computational modeling methodology, accurate *in vivo* lung deposition measurements for the Novolizer DPI were used [13]. With our validated model much needed information has been obtained concerning the efficacy of delivering curcumin dry powders to lung airways, when using a DPI.

2. Theory

The background information for the development of the first-generation WLAM, *i.e.*, the 3-D plus 1-D model geometries (see Fig. 1), governing equations plus boundary conditions for the fluid-particle dynamics analysis, and the numerical solution method are described in Part I. Inhalation waveforms emanating from the DPI are discussed next.

The Novolizer DPI uses the patient's inspiratory airflow to generate drug aerosols by de-agglomeration of the powdered drug particles. When the inspiratory flow is above a critical threshold, *i.e.*, the peak inspiratory flowrate (PIFR) of 50–100 LPM), a predetermined drug dose is released into the inhalation chamber. Hence, the inhaler is inherently breath actuated. Depending on the inhaler type, appropriate

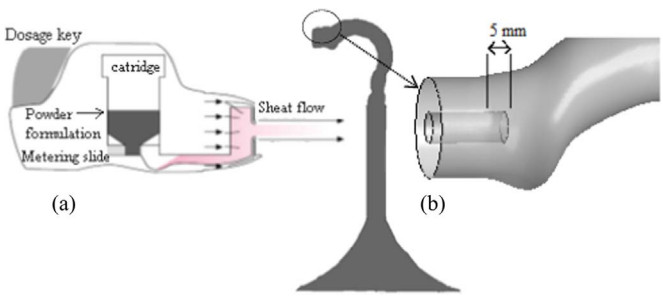

Fig. 1. (a) Novolizer DPI (adapted from [14] with permission of Springer); and (b) WLAM with attached dry powder inhaler mouthpiece.