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Deposition and fine particle production during dynamic flow in a dry powder inhaler: A CFD approach

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ABSTRACT

In this work the dynamic flow as well as the particle motion and deposition in a commercial dry powder inhaler, DPI (i.e., Turbuhaler) is described using computational fluid dynamics, CFD. The dynamic flow model presented here is an extension of a steady flow model previously described in Milenkovic et al. (2013). The model integrates CFD simulations for dynamic flow, an Eulerian-fluid/Lagrangian-particle description of particle motion as well as a particle/wall interaction model providing the sticking efficiency of particles colliding with the DPI walls. The dynamic flow is imposed by a time varying outlet pressure and the particle injections into the DPI are assumed to occur instantaneously and follow a prescribed particle size distribution, PSD. The total particle deposition and the production of fine particles in the DPI are determined for different peak inspiratory flow rates, PIFR, flow increase rates, FIR, and particle injection times. The simulation results for particle deposition are found to agree well with available experimental data for different values of PIFR and FIR. The predicted values of fine particle fraction are in agreement with available experimental results when the mean size of the injected PSD is taken to depend on the PIFR.

1. Introduction

The dry powder inhaler (DPI) is one of the principle means of delivering pharmaceuticals due to its ease of use and cost-effectiveness. DPIs have been used commercially since 1971 and are continuously being improved and updated with new models (Hickey and Hickey, 1996; Islam and Cleary, 2012). The main function of a DPI is to deliver a specific amount of a drug to a target region of the respiratory system by emission of fine particles from the device (Daniher and Zhu, 2008). Airflow and powder dispersion in a DPI are generated by strong inhalation through the device and are complex and highly dynamic processes. The powder is released into the device as particles and aggregates which move through the DPI, colliding with the DPI walls, undergo breakage and/or deposition, and exit into the oral cavity (Ashurst et al., 2000; Newman and Busse, 2002; Tobyn et al., 2004; Islam and Gladki, 2008; Alagusundaram et al., 2010; Islam and Cleary, 2012).

In order to deliver an effective drug dose to a target region of the respiratory system a sufficient dose must be first released by the DPI. The motion of the emitted particles and their deposition in the respiratory tract depends on their velocity, position, and size at the mouthpiece outflow (Matida et al., 2003). The effectiveness of a DPI is often described in terms of two key outflow characteristics, i.e., the total emitted dose as well as the production of fine particles (Alagusundaram *et al.*, 2010). The fine particle fraction (FPF) represents the mass ratio of emitted particles with a diameter less than a critical value, e.g., 4–6 μm, and is a frequently used measure of the effectiveness of powder dispersion in a DPI (Mitchell and Nagel, 2004). Drug losses and low production of fines can result from incomplete breakage of particle aggregates or by internal losses due to deposition.

In order to understand and improve the function of DPI devices, systematic computational studies have been performed and are reviewed in Islam and Cleary (2012) and Milenkovic et al. (2013). Different computational approaches have been employed including computational fluid dynamics (CFD) (Schuler et al., 1999; Ligotke, 2002; Coates et al., 2004, 2005, 2006) and the discrete element method (DEM) (Tong et al., 2010; Calvert et al., 2011). Methods

Abbreviations: CFD, computational fluid dynamics; DEM, discrete element method; DPI, dry powder inhaler; FIR, flow increase rate; FPF, fine particle fraction; HPLC, high performance liquid chromatography; PIFR, peak inspiratory flow rate; PSD, particle size distribution; SST, shear-stress transport; UVS, UV spectrophotometer.

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that track the individual particle constituents of aggregates (e.g., DEM) provide valuable information but are not easily applicable to this problem due to the very large number of constituent particles (e.g., $\sim 10^8$ for 2 μm particles).

From the current state-of-the-art it is clear that the strength of aggregates as well as their interactions with the DPI walls determine the effectiveness of powder dispersion, the emitted dose as well as the particle size distribution (PSD) and the FPF of the DPI outflow (Kroeger et al., 2010; Adi et al., 2011). In Milenkovic et al. (2013) the steady state airflow and the dynamic particle motion were determined in the Turbuhaler DPI employing a particle adhesion model to determine the sticking efficiency with the DPI walls. Recently DEM has been employed to describe the motion and breakup of representative aggregates released during powder dispersion in an inhaler (Tong et al., 2010; Calvert et al., 2011). These approaches underline the importance of both particle adhesion and cohesion forces in the description of powder release and dispersion, aggregate breakage, and deposition.

In general, during a dynamic inhalation through a DPI device the flow rate increases rapidly with time and approaches the peak inspiratory flow rate (PIFR). The flow increase rate (FIR) can be defined as the slope of the flow rate with time at 50% of the PIFR value. Computational efforts to date have focused predominantly on steady state flows in DPIs. However, transient airflow effects can be important and the effects of FIR and PIFR need to be established for dynamic flows. It should be noted that most DPIs function optimally at large values of PIFR (e.g., 60–70 L/min) and FIR (e.g. >5 L/s^2). However, inhalations at reduced values PIFR or FIR can be exhibited by individuals with impaired or limited respiratory function, e.g., children and elderly. Consequently, it is important to understand the characteristics of particle deposition and FPF of emitted particles for a range of PIFR and FIR values encompassing normal and impaired inhalations.

The Turbuhaler (AstraZeneca) is a multidose dry powder inhaler that is widely used to deliver a number of drugs (typically for asthma), e.g., budesonide (as Pulmicort), to the upper respiratory tract (Wetterlin, 1988; Tsima et al., 1994). Experimental investigations have provided detailed information on particle capture as well as the FPF and size distribution of particles in the outlet flow (de Koning et al., 2001; Hoe et al., 2009; Abdelrahim, 2010). Recently CFD simulations have detailed the particle deposition behaviour in the Turbuhaler assuming steady flow (Milenkovic et al., 2013).

In this work a multi-scale computational model of the Turbuhaler DPI is employed in which the dynamic airflow is determined by CFD simulations, dynamic particle motion is determined by Eulerian/Lagrangian simulations, and particle/wall interactions are described by a collision/adhesion model. In what follows the DPI geometry, the discretization procedure, the CFD simulations, and the particle model are summarized and the aspects of the dynamic flow simulations are described in detail. Next the results for dynamic airflow are presented followed by the results for particle deposition and fine particle production. Finally, the computational results are compared to available experimental data.

2. Computational model

2.1. CFD model

The Turbuhaler DPI geometry was constructed in a CAD/CAM environment (i.e., CATIA v5 R19) (Fig. 1a) and the individual components of the DPI were then assembled to obtain the DPI device (Fig. 1b). Subsequently, the geometry of the airflow domain was extracted and then imported into GAMBIT (v2.1) where several computational grids were constructed (Fig. 1c). It should be noted that a mouthpiece extension was added onto the DPI geometry to facilitate numerical convergence. A computational grid consisting of 1.7×10^6 tetrahedral cells was found to provide sufficiently grid independent solutions in steady flow simulations (in Milenkovic et al., 2013) and was employed in all the dynamic flow simulations of this work.

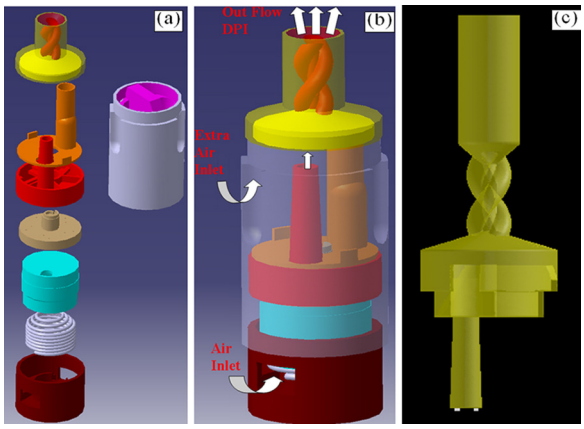

Fig. 1. Turbuhaler DPI: (a) component geometry, (b) assembled device, and (c) airflow domain of DPI.

A previous CFD model for steady flow in the DPI (Milenkovic et al., 2013) was extended for dynamic flow. The Navier–Stokes equations are solved using the commercial CFD software FLUENT (v6.3). The PISO scheme was employed to describe pressure–velocity coupling. Second order discretization was used for pressure and third order MUSCL for momentum and turbulent variables. Zero gauge pressure boundary conditions were employed at all the inflows, i.e., two powder loaded cylinders (see bottom of Fig. 1b) and four extra air inlets in the DPI circulation chamber (see Fig. 1a). Different dynamic airflows in the DPI were simulated by imposing dynamic outlet pressures which produced an initial rapid increase in flow which then gradually converged to a steady flow rate, i.e., the PIFR.

In this work the instantaneous volumetric outflow rate, Q, is assumed to obey the following equation:

$$Q = \mathrm{PIFR}(1 - e^{-\alpha t}) \quad (1)$$

where t is inhalation time and a is a constant that depends on the values of PIFR and FIR according to:

$$\alpha = 2.31 FIR/PIFR \quad (2)$$

The instantaneous outflow gauge pressure, P, is given by:

$$P = -1.7856 Q^2 \quad (3)$$

established in Milenkovic et al. (2013) for steady flow simulations.

The dynamic simulations were performed from an initial quiescent state which was perturbed by the application of a dynamic outflow pressure (Eq. (2)). A very small initial time step of 10^{-6} s was necessary to obtain stable results and to maintain the solution residuals (i.e., of continuity, momentum, k, and ω) less than 10^{-4} during the iterations with time. As the flow rate increased with time the numerical solution became more stable and the solution step size was gradually increased up to a maximum value of 5×10^{-3} s.

2.2. Particle model

The motion of particles in the DPI was determined by Eulerian-fluid/Lagrangian-particle simulations of particles encompassing the size ranges of typical pharmaceutical powders employed in the Turbuhaler. Particle simulations were conducted in the dilute limit, i.e., without considering any effects of particles on flow, as the solids volume ratio in the DPI device was less than 10^{-2}. For the particles