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Pharmaceutical aerosols deposition patterns from a Dry Powder Inhaler: Euler Lagrangian prediction and validation

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ABSTRACT

This study uses Computational Fluid Dynamics (CFD) to predict, analyze and validate the deposition patterns in a human lung for a Budesonide drug delivered from the Novolizer Dry Powder Inhaler device. We used a test case of known deposition patterns to validate our computational Euler Lagrangian-based deposition predictions. Two different lung models are used: (i) a basic ring-less trachea model and (ii) an advanced Human Zygote5 model. Unlike earlier attempts, the current simulations do not include the device in the computational domain. This greatly reduces the computational effort. To mimic the device, we model the inlet particle jet stream from the device as a spray entering the mouth in a conical fashion. Deposition studies in the various lung regions were performed. We were able to computationally predict and then demonstrate the enhanced deposition in the tracheal and first generation rings/ridges. The enhanced vorticity creation due to the ring structure and the geometrical design contributes to larger deposition in the Zygote5 model. These are in accord with existing data, unlike the ring-less model. Our validated results indicate the need to (i) introduce the ridges in the experimental casts and the CFD surface meshes to be anatomically consistent and obtain physiologically consistent depositions; (ii) introduce a factor to account for the recirculating lighter particles in empirical models.

1. Introduction

Pulmonary drug delivery using Orally Inhaled Drug Products (OIDPs) is increasingly used for both treatment of lung diseases and in delivering drugs to the systemic circulation [1–3]. In order to reach the desired effectiveness and safety of OIDPs, appropriate disposition on targeted regions is essential. However, the bioavailability of the OIDPs is determined by complex factors, such as physical characteristics of particles, spray characteristics, inhaler type/design, anatomical parameters of airways, inhalation profiles and respiratory conditions of subjects [4,5].

Currently, the deposition in the human airway tract can be estimated using "quasi" experiments [6,7], empirical approaches [8–10], computational approaches [11–14] or a mix of the above [15–18]. The "quasi" experiments are performed on respiratory tract casts/models. The flowrates are controlled by pumps whose flowrates do not replicate breathing profiles.

Empirical models like the Typical Path Lung [9] (TPL) and the National Commission on Radiological Protection (NCRP) models [10] assume constant flowrates. The deposition of the particles is computed from a single breathing cycle. These methods cannot account for the spray spread at the mouth inlet, differential particle velocities, the turbulence effects downstream, the geometrical influence on the deposition, the effect of Cartilaginous rings or the effects of the recirculation.

The computational approaches use Computational Fluid Dynamics (CFD) to solve the flow transport and Euler Lagrangian formulations to track the transport and the deposition of the particles. The computational mesh is generally truncated after 6-8 airway generations to reduce the overall Degrees Of Freedom (DOF) and simplify the mesh generation effort. This truncated mesh is reasonable to study the deposition in the upper airways for OIDPs [19,20]. In general, the CFD simulations can account for the complicated features like local turbulence creation, enhanced deposition in the ridges, non-symmetric deposition in the bifurcations and recirculation physics.

Recently, Kannan and his collaborators came up with a robust, fast running and easily adaptable computational approach called the Quasi-3D (Q3D) approach for simulating the air flow in human lungs [36]. A high fidelity surface CFD type lung airway mesh was contracted to a structure of connected wires, with well-defined radii. The conservation equations are then solved in each of these

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wires. The resulting simulations are extremely fast (compared to using CFD simulations) due to the Quasi-3D nature of the wire mesh, with the Q3D approach being 3000–25,000 times faster than the CFD simulations. The Q3D simulations also converge more easily, since there are no badly skewed cells or highly stretched cells, thereby requiring fewer steady/unsteady sweeps during a steady/transient simulation. This Q3D approach cannot capture the detailed flow phenomena, like the ones mentioned in the earlier paragraph. Hence, they cannot be used to accurately predict the drug depositions. However, the above is unnecessary when the objective is just to obtain the pressures or the increased resistance (as in calibration of diseased lungs using parameter inversion methods).

In this study, we have validated the regional CFD predictions of pharmaceutical aerosol deposition in the human lungs by comparing them to multiple datasets. In particular, the data sets collected for comparison with these Euler Lagrangian-based depositions included measurements and simulations for the Budesonide based Novolizer DPI. The datasets include the 2D gamma scintigraphy for the Budesonide Novolizer DPI (Meda Pharmaceuticals) by Newman et al. [21] and the simulation results of Tian et al. [22]. The salient features of this research include:

(i) Excluding the device/mouthpiece (MP) from the computational domain. Instead, we have developed a conical spray formulation for injecting the particles. The apex of the cone is located outside the mouth and the actual distance is the length of the MP. The length of the MP and the particle entry velocities were obtained from the literature [22–24].
(ii) Using two lung models to study the effect of the cartilaginous rings on the drug deposition patterns. The first model is a basic ring-less trachea model (PNNL Laboratory) and the second is the more advanced Human Zygote5 model. Qualitative comparisons of the deposition patterns in the tracheal regions and the first generation regions (wherein the cartilaginous rings are present) were made. The enhanced deposition in the location of the cartilaginous rings is predicted using CFD analyses and later validated using a particle transport formulation.
(iii) Presence of a recirculating ring for lighter particles is predicted using CFD and later validated using the particle transport formulation.

Quantitative regional deposition comparisons were made between the current CFD predictions and the existing in vivo and simulation datasets. The data obtained using the advanced Zygote5 model simulations is in good agreement with the available results. The deposition fractions in the ring-less trachea model were considerably lower due to (a) its geometrical design and (b) insufficient vorticity creation. These are discussed in the subsequent sections.

2. Materials and methods

2.1. The lung models

Two lung models are analyzed in this study: a basic ring-less trachea model and an advanced Zygote5 model. Fig. 1 shows the ring-less trachea model and some of its specific attributes, such as:

(i) No rings in the trachea;
(ii) No rings in the first bifurcation region;
(iii) Nonsymmetrical bifurcations;
(iv) One-to-many splits in the airways;
(v) Non-circular cross-sections in trachea and other airways;
(vi) Out of plane rotations for the bifurcations.

Table 1
Diameters bounds for each airway generation in the Zygote5 lung model. Results compared with the data provided by Hoffmann et al. [25].

Airway Number	D-Hoffmann (cm)	D-Zygote5-min (cm)	D-Zygote5-max (cm)
0 (trachea)	2.01	1.9526	2.022
1	1.56	1.348	1.3928
2	1.13	0.754	1.007
3	0.827	0.715	0.744
4	0.651	0.5222	0.545
5	0.574	0.3166	0.4138
6	0.435	0.2546	0.3362
7	0.373	0.216	0.266

In contrast, the model C [19] had features like (i) cartilaginous rings in the trachea; (ii) a D-shaped tracheal cross section; (iii) asymmetrical bifurcations; and (iii) out-of-plane rotation of the bifurcations. Features that were not included in model C include non-circular cross-sections beyond the trachea and non-ideal bifurcation shapes [19]. Hence, although most model C features are observed in the ring-less trachea lung model, the absence of rings is a noticeable omission.

Fig. 2 shows the snapshots of the Zygote5 model and its attributes, such as:

(i) A strong ring structure present in the trachea;
(ii) Noticeable ring structure in the first bifurcation region;
(iii) Non-symmetrical bifurcations;
(iv) One-to-many splits in the airways;
(v) Non-circular cross-sections in trachea and other airways;
(vi) Out of plane rotations for the bifurcations.

The Zygote5 model is structurally very similar to the model C, except that the former has rings in its first bifurcation region. A snapshot of model C is shown in Fig. 3. Table 1 shows the bounds for the diameters for each airway generation in the Zygote5 model. They are close to the reported data[25]. The latter airways (generation number > 2) in the ring-less model have noticeably smaller diameters than the Zygote5 model. It must be noted that the reported data [25] was based on lung casts, which tend to over-predict these dimensions because the material tends to swell [19].

2.2. The CFD simulations

The flow solver in the Computational Biology (CoBi) suite (CFDRC's numerical suite) uses a second order accurate pressure-based (SIMPLE algorithm) finite volume method. The turbulent stresses were modeled by the use of a turbulent viscosity, computed using the Smagorinsky closure formulation. More details on the CoBi numerical suite can be obtained from the literature [20,26,27]. Fig. 4 shows the flowrates in the Novolizer DPI [22].

The fine mesh for the ring-less lung model had around 1.5 million DOF and the fine mesh for the Zygote5 model had around 2.12 million DOF. The second order simulations, coupled with the omnitree structure makes the fine mesh highly resolved and mesh independent. This aspect is well discussed and analyzed in our previous research study [20]. The y component of the velocity for the coarse and fine meshes are provided at $t = 1.2$ s in Fig. 5. The difference is marginal: the maximum difference is around 0.3 m/s. Fig. 6 shows the steady state (flowrate = 60 L/min) yplus readings using the Zygote5 fine mesh. Most of the values are less than one, thus enabling our fine mesh to capture all the detailed wall effects.

The fine meshes described above were used for all the simulations and analyses in this study. Fig. 7 shows the Y component of

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