RDD 2022
Respiratory Drug Delivery

Omni Orlando, ChampionsGate, Florida
In Person May 1-5, 2022
Virtual April 25 - June 30, 2022

RDDONLINE.COM
An In Silico Modeling Framework to Predict Particle Dynamics in Dry Powder Inhalers

Yu Feng,1 Jianan Zhao,1 Ahmadreza Haghnegahdar2 and Rahul Bharadwaj2

1School of Chemical Engineering, Oklahoma State University, Stillwater, OK, USA
2ESSS North America Inc., Woburn, MA, USA

KEYWORDS: dry powder inhaler (DPI), Computational Fluid Dynamics-Discrete Element Method (CFD-DEM), comparability, Spiriva™ Handihaler™ (SH), emitted Aerodynamic Particle Size Distribution (APSD), lung deposition

SUMMARY

The administration of medicines via inhalation is one of the most common treatments for patients with chronic obstructive pulmonary disease (COPD). Capsule-based dry powder inhalers (DPIs) are widely used to deliver active pharmaceutical ingredients (APIs) attached to micron-sized carrier particles into the human respiratory system. To evaluate the drug delivery effectiveness of DPIs, a model has been developed based on computational fluid dynamics (CFD) and the discrete element method (DEM) to simulate the agglomeration/deagglomeration, transport, and deposition of carriers and APIs in the DPI flow channel and human respiratory system. In this study, the CFD-DEM model has been applied to evaluate the comparability of a potential generic DPI (Cipla) and Spiriva™ Handihaler™ (SH) (Boehringer Ingelheim, Germany) based on their (1) device delivery efficiencies, (2) emitted aerodynamic particle size distribution (APSDs), and (3) regional lung depositions. The in silico CFD-DEM model potentially provides a demonstration of how to fully utilize in vitro and clinical data in CFD and DEM simulations to obtain new insights into the transport dynamics of APIs in DPIs and lungs, thereby representing a possible approach to reduce the cost of generic product development.
INTRODUCTION

Documentation of comparability between generic inhaler design and performance and that of the reference listed drug (RLD) product is essential for regulatory approval of the generic product. The capability to accurately predict particle transport, interactions, and deposition in the human respiratory tract using high-fidelity numerical methods are valuable data for regulators to consider during the market authorization of orally inhaled drug products (OIDPs), such as DPIs. Predictive models must accurately predict particle-particle agglomeration/deagglomeration, as well as particle-(airway) wall interactions. To explicitly model the particle-particle and particle-wall interactions, this study developed a CFD and DEM to examine drug delivery efficiency, determine emitted APSDs, and quantify the resultant lung depositions of both lactose carriers and API particles. Numerical parametric studies were also performed with multiple steady, simulated inhalation airflow rates through the DPI, carrier shapes, and DPI designs. Spiriva Handihaler and a potential generic DPI (Cipla) were evaluated in this study. Simulations have been done to unveil the performance of carriers and APIs in the two DPIs in a low-risk, time-saving virtual environment, which can potentially develop innovations faster at a lower cost. Our long-term goal is to use the CFD-DEM model in the early stages of the device development process in advance of, and to complement, in vitro and in vivo studies.

METHODOLOGY

The objective of this study is to develop and test a computational model to predict relationships between DPI design, carrier shape, simulated, steady inhalation airflow rate through the DPI, and the drug delivery efficiency to specific lung regions, i.e., after the 13th airway generation (G13). SH (containing tiotropium bromide) as the RLD and a generic DPI candidate were selected for the comparability assessment case study (see Figures 1(A) and (B)), as both products are single-dose, capsule-based devices, which can cover a broad range of inhalation flow rates [1]. The evaluation of the comparability between the generic DPI and SH has been numerically evaluated by comparing the DPI delivery efficiencies, emitted APSDs, and the resultant lung deposition patterns. An experimentally calibrated and validated CFD-DEM method [2] was employed to predict agglomeration and deagglomeration of carriers and APIs. Utilizing the time-saving and cost-effective CFD-DEM model, simulations were performed at steady inhalation flow rates of 30, 39, 60, and 90 L/min [3]. Simulations were performed on spherical particles and spherocylindrical lactose carriers with an aspect ratio (AR) equal to 5 and 10.

The resultant depositions of API and carriers in a 3D human respiratory system (see Figure 2) were simulated using the validated Euler-Lagrange-based CFD model [4–13]. We considered API deposition after the G13 to be an important feature of DPI efficiency, because particles that escape from G13 outlets are considered deposited in the small airways with diameters less than 2 mm [14, 15]. Such airways are the target of many OIDPs. Therefore, this study provides an in silico prediction of fundamental carrier-API interactions in DPIs, and the effect of carrier shape and DPI flow channel designs on the drug delivery efficiency from DPIs and deposition patterns in the human respiratory system.
Figure 1. Computational DPI geometries and the hybrid polyhedral meshes, including the flow channels, grids, and capsules for DPI simulations modeling actuation airflow as steady-state inhalation at multiple flow rates: (A) SH, and (B) the generic DPI.

Figure 2. Geometry and polyhedral mesh with near-wall prism layers of the human respiratory system.
RESULTS AND DISCUSSION

Emitted APSDs

To evaluate the similarity between the two DPIs, Figures 3 and 4 compare the airflow velocity fields and emitted APSDs from the innovator and generic DPI with different inhalation flow rates, $Q_{in}$. By comparing the APSDs predicted at $30 \text{ L/min} \leq Q_{in} \leq 90 \text{ L/min}$, two observations can be made. (1) In general, similar APSDs are generated using both DPIs for $Q_{in}$ values from $30 \text{ L/min}$ to $90 \text{ L/min}$, which indicates that the generic DPI has a high potential to show comparability. (2) The generic DPI, however, predicts slightly higher particle number fractions (NFs) for small particles (i.e., API), and lower NFs for large particles (i.e., carrier).

![Figure 3](image1.png) Airflow patterns at midplane $z=0$ in the flow channels of the two DPIs at different actuation flow rates ($Q_{in} = 30, 39, 60, \text{ and } 90 \text{ L/min}$): (A) SH, and (B) the generic DPI.

![Figure 4](image2.png) Emitted APSDs from the DPIs flow channels: (A) SH, and (B) the generic DPI.
Lung deposition

The similarity between the generic and SH DPIs in airway depositions is evaluated by comparing the carrier and API deposition distribution and their regional deposition fractions (DFs) in the 3D human respiratory system model colored by localized deposited mass [2] as shown in Figures 5(A) and (B). The API lung deposition predicted for the generic DPI agrees well with the results predicted for the SH across a range of airflow rates. Between the generic and the SH cases, the differences in regional lung DF API for all three airway regions are within 2.0% at 30 L/min ≤ Q_{in} ≤ 90 L/min.

Figure 5. Predicted sample API deposition patterns and regional deposition fractions in the human respiratory system with different carrier shapes (ARs, defined in the text) and inhalation flow rates using (A) SH DPI, and (B) the generic DPI (AR = 1).

Overall DPI-airway drug delivery efficiency

To model the delivery efficiency to deeper airways representative of sites targeted by COPD and/or asthma treatments, overall DPI-airway drug delivery efficiency $\psi$ is calculated (as defined in Table 1). The $\psi$ values with different $Q_{in}$ and carrier ARs are listed in Table 1. The results demonstrate
that low $Q_{in}$ (i.e., 30 L/min) is favored to achieve a higher overall drug delivery efficiency using the SH DPI, and $Q_{in}$ is the dominant factor influencing the regional API DF after G13, with the particle shape of carriers having less effect. Furthermore, the $\psi$ comparisons between SH and the generic DPI using spherical carriers (AR = 1) demonstrate that $\psi$ generated from the generic DPI has good agreement with the SH at inhalation flow rates from 30 to 90 L/min. Specifically, at $39 \text{ L/min} \leq Q_{in} \leq 90 \text{ L/min}$, the difference in $\psi$ between generic and SH cases is less than 1.5% for carriers with isotropic shape. Only at the low actuation flow rate (i.e., 30 L/min), is there a slightly higher difference in $\psi$ between two cases (5.7%) due to the relatively lower delivery efficiency of the generic DPI at $Q_{in} = 90 \text{ L/min}$. Therefore, we concluded that the generic DPI shows satisfactory agreement with the SH DPI in terms of the general DPI-airway drug delivery efficiency.

Table 1. The overall DPI-airway drug delivery efficiencies ($\psi$) vs. AR and $Q_{in}$.

<table>
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<tr>
<th></th>
<th>AR 1</th>
<th>AR 5</th>
<th>AR 10</th>
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<tbody>
<tr>
<td>30 L/min</td>
<td>65.0%</td>
<td>60.7%</td>
<td>64.7%</td>
</tr>
<tr>
<td>39 L/min</td>
<td>54.8%</td>
<td>56.0%</td>
<td>56.3%</td>
</tr>
<tr>
<td>60 L/min</td>
<td>32.9%</td>
<td>32.9%</td>
<td>33.7%</td>
</tr>
<tr>
<td>90 L/min</td>
<td>28.6%</td>
<td>29.4%</td>
<td>30.0%</td>
</tr>
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Generic DPI

<table>
<thead>
<tr>
<th></th>
<th>AR 1</th>
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<tr>
<td>30 L/min</td>
<td>59.3%</td>
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<tr>
<td>39 L/min</td>
<td>55.2%</td>
</tr>
<tr>
<td>60 L/min</td>
<td>34.1%</td>
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<tr>
<td>90 L/min</td>
<td>28.0%</td>
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$\psi = \frac{(\text{Deposited API after G13})}{(\text{Total amount of API injected into the DPI})} \times 100\% = (1 - D_{F(API-DPI)}) DF_{(API-after G13)}$

CONCLUSIONS

In this study, a numerical approach has been developed based on the CFD-DEM and CFPD models and employed to predict the transport, interaction, and deposition of API and carrier particles with different shapes from the flow channels of two DPIs into a 3D human respiratory system model. DPI delivery efficiencies, emitted APSDs, and lung deposition data were obtained and compared between the two DPIs. The ‘all-in-one’ modeling framework developed in this study has the potential to numerically generate in vitro-lung deposition correlations, reduce the cost of generic product innovations, and possibly accelerate generic product review and approval.

The CFD-DEM based model in this study is a first effort at the development of an in silico modeling framework to understand OIDP transport dynamics in both DPIs and the human respiratory system. Although valuable insights have been gained, further work is necessary to develop a more realistic modeling strategy which considers particle transport dynamics. Specifically, the following mechanisms will be considered in the next version of this CFD-DEM modeling effort (see Figure 6):

- Particle size change dynamics due to hygroscopic growth/evaporation effects [6, 10, 16, 17] in the human respiratory tract.
- Comparability of DPIs using anisotropic shaped carriers will be further evaluated as an extension of the this study, which only evaluated the equivalence using isotropic shaped carriers (AR = 1).
• Instead of constant inhalation flow rates and static lung geometries, patient-specific and disease-specific breathing waveforms for drug inhalation will be employed, and the physiologically realistic airway deformation kinematics will be simulated simultaneously with the particle transport from mouth/nose to alveoli [18].

• The effect of excessive secretion and/or stagnation of mucus on airflow and particle deposition in airways [19, 20] via Volume of Fluid (VOF) plus DPM [21].

• Pharmacokinetic (PK) and pharmacodynamics (PD) equivalence will be assessed by employing a CFPD-PBPK/PD modeling frameworks [9, 10, 22].

ACKNOWLEDGEMENTS

The research was made possible by funding through the award for project number HR19-106, from the Oklahoma Center for the Advancement of Science and Technology and the award provided by Cipla Inc. (Mumbai, India). The use of Rocky DEM (ESSS, Woburn, MA) and Ansys software (Ansys Inc., Canonsburg, PA) as part of the ESSS-CBBL and Ansys-CBBL academic partnerships coordinated by Dr. Thierry Marchal are gratefully acknowledged.

REFERENCES


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