Poster number

M1130-05-037

DROPLET EVAPORATION FROM A SOLUTION-BASED METERED DOSE INHALER: A COMPUTATIONAL APPROACH

Ross L. Walenga,[1] Denise S. Conti,[2] Oluwamurewa Oguntimein,[2] Renishkumar R. Delvadia,[2] Alex D. Rygg,[1] Andrew H. Babiskin[1]

[1]Division of Quantitative Methods and Modeling, [2]Division of Therapeutic Performance,

Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

CONTACT INFORMATION: Ross Walenga, Ross.Walenga@fda.hhs.gov.

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

Evaluating a generic locally-acting metered dose inhaler (MDI) with respect to bioequivalence (BE) is challenging because MDIs are complex drug-device combination products (formulation and device impact delivery performance) and currently there are no established methods for directly measuring drug absorption at the sites of action in the lung. The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) has adopted a "weight-of-evidence" approach for BE assessment of MDIs, where published product-specific guidance documents have typically recommended a series of in vitro tests, pharmacokinetic (PK) studies, and either a comparative pharmacodynamic (PD) or a comparative clinical endpoint (CE) BE study, in addition to formulation sameness and device similarity. Though PD/CE BE studies are time-consuming and expensive, these are recommended because there is currently no evidence that the existing in vitro testing or PK data can indicate the same rate and extent of drug delivery to the sites of action in the lung between the reference and test products. Solution-based MDIs have the active pharmaceutical ingredient (API) dissolved in the propellant (e.g., HFA-134a) with the help of a co-solvent, which is typically ethanol. It has been postulated by others that these types of MDIs may render in vitro and PK studies sufficient for BE assessment if it can be shown that inhaled droplets which deposit in the lungs remain in pure solution. To address this issue, this study employed a computational fluid dynamics (CFD) model of the droplet evaporation from a solution-based MDI to predict whether precipitation occurs prior to deposition, and if so, to what extent.

METHOD(S)

Transient droplet evaporation from the commercial product for 0.04 mg per inhalation beclomethasone dipropionate MDI (QVAR® 40, Teva Pharmaceuticals Industries, Ltd.) was predicted using CFD, which was modeled using a combination of commercial code (ANSYS Fluent 19.0, ANSYS Inc., Canonsburg, PA, USA) and user-defined functions. Simulations were performed using a geometric model of a simplified inhaler in combination with a United States Pharmacopeia (USP) induction port. A computational mesh was applied to the model using a hexahedral meshing scheme, where sensitivity of the mesh was tested with two meshes, where the coarser mesh had approximately 11 million hexahedral cells and the finer mesh had approximately 14 million hexahedral cells. Turbulence was predicted with a shear stress transport (SST) two-equation k-ω model. Compressibility effects were considered due to assumed sonic flow at the orifice, where the inlet total temperature was estimated by adjusting the wet bulb temperature of the formulation. An evaporation model was included as a user-defined function based on the models of Longest and Hindle[1] and Chen et al.,[2] where the model considered evaporation of HFA-134a, ethanol, and water. The effect of intermolecular forces on evaporation due to formulation composition was modeled using a Universal Quasichemical (UNIQUAC) Functional-group Activity Coefficients (UNIFAC) model. Droplet trajectories were calculated using a Lagrangian approach, where a representative number of droplets was simulated and the number of particles was increased until results converged. A lognormal particle size distribution was assumed at the inlet, where the mass median aerodynamic diameter (MMAD) was adjusted until the best fit with available experimental data of regional deposition[3] and droplet size distribution at the USP induction port exit[4] was achieved.

RESULT(S)

- Temperature and velocity distribution after actuation (Figure 1 and Figure 2) show a small region immediately downstream of the orifice with very low temperature (~130 K) and very high velocity magnitude (~420 m/s), consistent with shock following a sonic expansion.
- Mesh sensitivity analysis showed a 4.9% decrease in total deposition, a 1.2% increase in actuator deposition, and a 8.8% decrease in USP induction port deposition from the coarse to the fine mesh. The results reported in the figures and tables are from the fine mesh.
- Droplet number convergence was observed for 1,440 droplets in 12 size bins for 17,280 total droplets.
- Regional deposition results (Figure 3) in the actuator were 22.5% and 16.0% in the USP induction port, as compared with average deposition values from Sheth et al.[4] of 22.4% for the actuator and 20.4% for the USP induction port, which were measured from three different measurements from three different lots of the commercial product. These results were obtained by assuming an MMAD of 11 µm for the inlet droplet profile.
- Median volume diameter (Dv50) of the droplet distribution at the exit of the USP induction port was 3.49 µm as compared with 2.70 µm from Haynes et al.[3] for the same product.
- The amount of drug in solution at the exit of the USP induction port (Table 1) was predicted to be 0.12% of the total drug present at the exit.

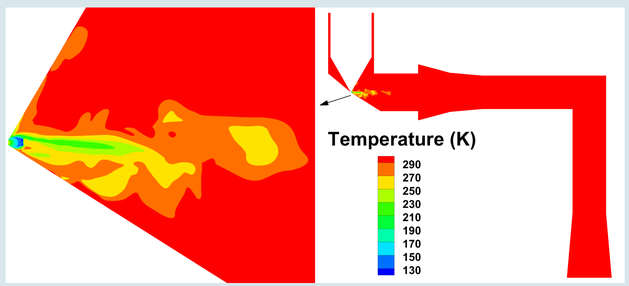

Figure 1. Computational fluid dynamics (CFD) predictions of temperature distribution in cross-sectional plane of 0.04 mg/inhalation beclomethasone dipropionate metered dose inhaler and USP induction port immediately following device actuation.

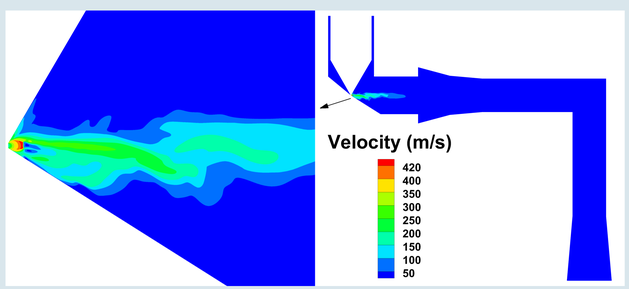

Figure 2. Computational fluid dynamics (CFD) predictions of velocity magnitude distribution in cross-sectional plane of 0.04 mg/inhalation beclomethasone dipropionate metered dose inhaler and USP induction port immediately following device actuation.

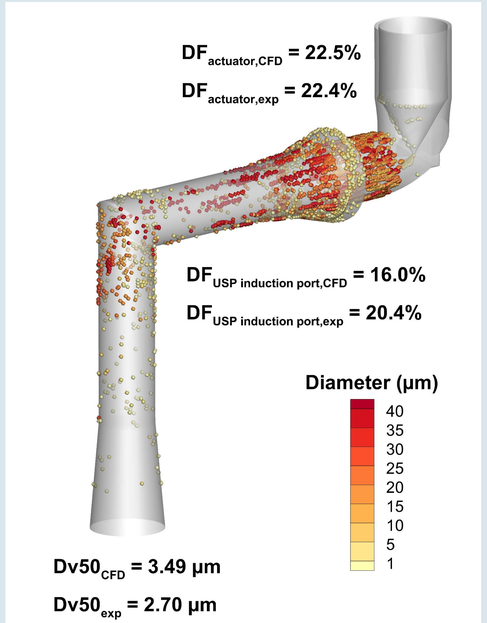

Figure 3. Computational fluid dynamics (CFD) predictions for 0.04 mg/inhalation beclomethasone dipropionate metered dose inhaler of exit median volume diameter (Dv50) and regional deposition fraction (DF), with corresponding experimental data from Haynes et al.[3] and Sheth et al.,[4] respectively.

Table 1. Amount of drug available initially at the orifice, at the exit of the USP induction port, and dissolved at the exit of the USP induction port. The droplet sizes correspond to simulation particle size bins.

Initial Droplet Size (µm)	Initial Mass (µg)	Exit Mass (µg)	Exit Mass Dissolved (µg)
1.1	0.11	0.090	0.000024
1.6	0.36	0.298	0.000078
2.5	1.54	1.301	0.000342
4.0	4.65	3.967	0.001044
8.0	15.05	12.293	0.003236
12.0	11.00	8.385	0.002207
15.0	5.40	2.057	0.000542
18.0	3.71	1.485	0.000393
21.0	2.56	0.477	0.000255
25.0	2.27	0.241	0.017590
32.0	2.19	0.029	0.010102
40.0	1.17	0.000	0.000000
Total	50.0	30.62	0.03582

CONCLUSION(S)

- Computational fluid dynamics (CFD) modeling was used to predict regional deposition values after actuation of 0.04 mg/inhalation beclomethasone dipropionate metered dose inhaler (MDI) into a USP induction port.
- Predicted values of regional deposition and exit volume median diameter (Dv50) agreed reasonably well with available experimental data.
- The predicted amount of drug in solution at the exit of the USP induction port was 0.12% of the predicted drug available.
- Altogether, the CFD modeling results suggest that precipitation occurs prior to entering the lung, and that the aerosols depositing in the lung at the sites of action are most likely particles rather than droplets.
- CFD modeling is a powerful tool that can help, together with in vitro and other modeling/simulation approaches, in the process of evaluating BE.

REFERENCES

1. Longest PW, Hindle M. Numerical model to characterize the size increase of combination drug and hygroscopic excipient nanoparticle aerosols. Aerosol Sci Tech. 2011;45(7):884-899.
2. Chen X, Feng Y, Zhong W, Kleinstreuer C. Numerical investigation of the interaction, transport and deposition of multicomponent droplets in a simple mouth-throat model. Journal of Aerosol Science. 2017;105(1):108-127.
3. Haynes A, Shaik MS, Krarup H, Singh M. Evaluation of the Malvern Spraytec® with inhalation cell for the measurement of particle size distribution from metered dose inhalers. J Pharm Sci. 2004;93(2):349-363.
4. Sheth P, Sandell D, Conti DS, Holt JT, Hickey AJ, Saluja B. Influence of formulation factors on the aerosol performance of suspension and solution metered dose inhalers: A systematic approach. AAPS J. 2017;19(5):1396-1410.

ACKNOWLEDGEMENTS/DISCLAIMER

Poonam Sheth, Dennis Sandell, Jay Holt, Anthony Hickey, and Bhawana Saluja are gratefully acknowledged for providing experimental regional deposition data as part of Grant #1U01FD004943 funded by the Generic Drug User Fee Amendment (GDUFA) regulatory science program at the FDA. Drs. Walenga and Rygg were supported in part by an appointment to the Oak Ridge Institute for Science and Education (ORISE) Research Participation Program at the Center for Drug Evaluation and Research administered by the ORISE through an agreement between the U. S. Department of Energy and CDER. Views expressed in this poster do not necessarily reflect the official policies of the U.S. Food and Drug Administration, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

FDA U.S. FOOD & DRUG ADMINISTRATION