Use of computational fluid dynamics (CFD) modeling for design and performance analysis of nasal sprays

A short perspective on nasal spray CFD simulations and use of CFD modeling to design nasal spray devices and analyze spray delivery performance

Arun V. Kolanjiyil, PhD and Worth Longest, PhD
Virginia Commonwealth University

Introduction

Nasal spray pumps are a common device choice to administer locally acting drugs for the treatment of allergic rhinitis, sinusitis and nasal polyposis. Delivering nasally-targeted pharmaceutical formulations using spray pumps has many advantages compared with oral administration including fast onset of action and avoidance of first-pass metabolism. There is also increasing interest in the use of nasal sprays to deliver vaccines, drugs requiring rapid absorption into the systemic circulation, or drugs intended for the central nervous system. Most nasal spray pumps are hand-actuated, which forces the formulation through a spray nozzle and results in atomization of the liquid. These spray products are intended to deliver drugs and other therapeutics primarily to the posterior nasal region (which resides behind the anterior nose and nasal valve) while limiting drug penetration into the lungs. Therefore, nasal spray products are designed to produce relatively large droplets (20-200 μm) that enter the nose with relatively high velocity [1-3]. Due to the large spray droplet size and high spray velocity, these droplets carry significant momentum that can result in enhanced momentum exchange with the gas phase in the droplet-dense region surrounding the spray nozzle [1, 4]. As a result, a cloud motion effect is generated, which remains one of the more challenging problems of multiphase flow physics [5]. The delivery efficiency of nasal spray products to the posterior nasal region depends on many factors including device design, drug formulation properties, patient-related factors such as inhalation conditions and actuation force, and the nasal geometry, which is known to be highly variable [2, 6-13].

Knowledge of drug delivery performance of nasal spray pumps under variable usage conditions is important to facilitate device design improvements and to develop new administration protocols that can enhance posterior delivery efficiency and drug targeting. Furthermore, quantifying the delivered dose and its variability under different usage conditions may be important for assisting in the development of generic products and, in the future, could also be used in the evaluation of those generic products for bioequivalence. Considering nasal spray testing, *in vitro* methods and experimental visualization techniques are available to characterize the spray and/or approximate regional nasal deposition [14, 15]. At the same time, *in silico* studies of spray droplet transport and deposition in nasal airway models using computational fluid dynamics (CFD) simulations can provide detailed and sometimes enhanced information on device performance and nasal deposition [16, 17]. Additionally, CFD simulations validated with *in vitro* experimental measurements can be used as a research tool to analyze the effect of product and usage variability while limiting time and cost associated with extensive *in vitro* testing and/or *in vivo* human subject testing [5, 10, 12, 18].

Computational fluid dynamics (CFD)

CFD is a computational modeling technique widely used to develop, test and improve engineering sys-

tems that include fluid motion [19]. The fluid flow inside an engineering system, which may include complex flow characteristics such as turbulence, compressibility, heat transfer and multiphase regimes, is determined by solving general governing transport equations based on first principles [16]. The use of general governing transport equations makes CFD a versatile research tool with wide portability and usability in many different fields. Of late, CFD has seen increased interest in the field of biomedical engineering, especially for applications related to drug delivery [16, 20]. In the area of respiratory drug delivery, airflow fields, aerosol transport and deposition and even aerosol formation are simulated in realistic three-dimensional (3-D) models of inhalers and respiratory tracts using CFD [21]. Recently, there have been a number of advancements in CFD modeling that have enabled the simulation of complex respiratory drug delivery physics [16, 22-24]. Application of CFD in respiratory drug delivery has resulted in a number of new inhaler devices and designs [25-28]. Furthermore, CFD has been used as a dosimetric tool to quantify delivered dose to specific respiratory tract regions and for providing an understanding of aerosol deposition mechanics [29-32].

Pharmaceutical inhaler systems produce millions of multicomponent droplets or particles during the delivery of drug formulations, regardless of whether the formulation is liquid or solid, or changes phase [21]. These discrete elements emitted from aerosol generation devices can also be accompanied with jets or spray momentum arising from the process of aerosol formation and flow through the device. An Euler-Lagrange modeling framework has been shown to be suitable for modeling such aerosol transport systems in many cases of respiratory drug delivery [1]. In the Euler-Lagrange framework, the fluid-carrier phase is considered as a continuum and solved using an Eulerian framework of governing equations, while the particles/droplets are solved as Lagrangian points inside the carrier phase [16, 33]. Instead of modeling all of the millions of individual particles or droplets in a spray system, a parcel-based model is a preferable approach for pharmaceutical aerosol simulations. In the parcel-based approach, each parcel is a representative fraction of the total droplets/particles generated by the device and the trajectory of a parcel is determined by tracking a droplet in the parcel with the specified diameter and mass flow rate.

Within inhaler systems, regions that have relatively low concentrations of particles/droplets compared to the net flow through the region can be considered as having dilute particle physics [21]. In particle dilute regions, effects of the flow on the discrete elements primarily govern the aerosol transport and reverse effects are negligible. Therefore, a "one-way" coupled modeling approach is better suited to simulate the aerosol transport in such regions [16]. When an inhaler system produces a more highly concentrated region of aerosol in comparison to the net flow through the region, then the region can be considered a dense flow-particle system [21]. In these systems, both the effects of flow on discrete elements as well as the effects of the particles or droplets on the flow govern the aerosol transport. Therefore, a "two-way" coupled modeling approach is better suited to simulate flow in these regions [16, 33]. In addition to the drag and gravitational force acting on the aerosol during its transport, collision, breakup, coalescence, agglomeration, deagglomeration and turbulent dispersion forces may also have an influence [16]. Such sub-models may need to be incorporated when applicable, depending on the physics of the real system. For highly accurate simulations of dense multiphase flows, depending on the complexity of the physics involved, advanced computational modeling approaches such as spray-wall interaction models, dense discrete phase models, population balance equation models, discrete element method models and smoothed particle hydrodynamics models may be incorporated into the underlying computational simulation of the flow field, but will significantly increase model complexity and required computational power [1, 20].

While CFD modeling has many advantages, simulation of the inhaler drug delivery systems and aerosol transport in respiratory airways is highly complex due to the underlying physics that must be captured [21]. Therefore, setting up the model and running the simulation requires an understanding of the physics involved and numerical algorithms required to capture such phenomena [16]. There are a number of commercial and open-source software packages available that can solve the CFD governing equations. Considering that highly complex CFD models require many sub-model assumptions, verification of the numerical implementation and validation of the model setup with experimental results are critical steps in developing an effective and scientifically accurate CFD model. The computational modeling aspects of nasal sprays and aerosol droplet deposition in human nasal cavities using CFD, including two-way coupling effects, has recently been developed and validated [1, 4, 5]. The following sections of this article illustrate some recommended modeling practices that could be followed in setting up and running CFD simulations of nasal spray transport and deposition in the nasal airways. Finally, two case studies are provided to illustrate how CFD simulations can potentially be applied for sensitivity/bioequivalence analysis and for design optimization of nasal spray products.

Nasal spray modeling—best CFD modeling practices

Developing and meshing nasal airway geometries

A time-consuming but critical step in the process of building a CFD model is developing and meshing the geometries associated with the system. For nasal spray drug delivery simulations, the nasal airway geometries are typically extracted/reconstructed from computed tomography (CT) or magnetic resonance imaging (MRI) scans by specifying appropriate radio-density thresholds that can delineate the air-tissue boundary [34]. The extracted nasal airway geometries from scanned images are typically exported in stereolithographic (STL) format. These STL-formatted geometries may need further refining to remove surface irregularities from the reconstruction process and to simplify the geometry, for example, by removing the sinus cavities at the narrow ostium inlets. It can be easier to work with a computer-aided design (CAD) accessible geometry format since editing/trimming STL surfaces is usually cumbersome. The STL-formatted surfaces are typically refined and translated into common CAD formats by "skin-overlay" with reasonably large polygonal patches consisting of b-splined surfaces, conforming to the faceted surfaces. This step reduces thousands of STL triangles to approximately 100 CAD-format surfaces and makes it possible to perform CAD processing with any third-party CAD software package [5, 28]. While the spray bottle geometry may not be an important factor for simulating the nasal spray dynamics, it is necessary to account for the presence of the spray pump inside the nasal geometry. This can be achieved by subtracting the volume occupied by the spray pump from the nasal airway volume. This step can realistically capture the partial occlusion of the nostril inlet by the spray pump and its effect on nasal inhalation airflow.

The CFD simulations resolve the flow field within millions of representative micro-to-millimeter scale discrete volumes (i.e., control volumes) inside the geometry and predict aerosol transport as the flow progresses through these volumes. In order to successfully resolve flow within an airway geometry, a computational mesh (or grid) needs to be created with sufficiently small control volumes (or elements) in regions of high flow gradients to minimize computational errors [21]. Accurate spray simulations in nasal airways have been shown to require ~2 million polyhedral elements per nasal cavity, excluding the nasopharyngeal region, together with near-wall prism elements and a refined mesh in the vicinity of the spray nozzle tip. Additionally, to capture the near-wall flow dynamics, near-wall regions require approximately ~5 near-wall prism layer mesh elements with a first prism layer thickness resulting in an average wall y^+ of approximately one [5] (where wall y^+ is a non-dimensional distance parameter that is controlled for accurate modeling of near-wall turbulence characteristics in wall-bounded flows).

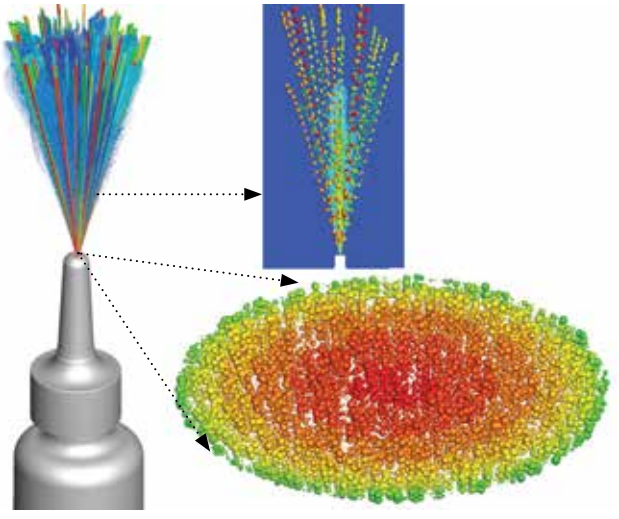
Setting up a CFD nasal spray simulation

Nasal sprays have a characteristic spatio-temporal variation from a dense spray droplet regime adjacent to the spray nozzle to a dilute regime further away from the spray nozzle. Spray simulations reveal that spray droplets injected into the nasal airway cavity impart significant momentum to the fluid phase, which induces a cloud-based gas velocity and significant coupling between the phases (Figure 1). The cloud-based gas velocity as a whole imparts significant momentum on the smaller droplets and transports them further into the flow field, as fully captured in a two-way coupled simulation [1, 5]. Based on the validated nasal spray model, nasal spray transport with two-way coupled momentum exchange and the related impact on the dispersed phase transport is realistically captured by CFD simulations using an Euler-Lagrange framework [1, 5].

To simulate a nasal spray product, the CFD model requires initial and boundary conditions, and ideally benchmark validation data. CFD nasal spray models typically require input parameters such as polydisperse spray droplet size distribution, spray cone angle and plume shape, spray mass flow rate, spray velocity and formulation density. These metrics are typically first evaluated in an *in vitro* setting to characterize the nasal spray using bench-top experimental setups [14]. In a two-way coupled simulation, spray droplets must be injected with a predetermined mass flow rate so that the net mass of the liquid droplets injected is equal to

Figure 1

CFD nasal spray model with spray droplets injected from the spray nozzle orifice with a solid conical injection shape and a turbulent velocity profile. The momentum-jet due to the momentum exchange from the spray droplets is shown in the sub-figure.



the shot weight of the spray. Furthermore, for capturing an approximate spray droplet injection condition and near-nozzle spray momentum conditions, spray droplets can be injected from the nozzle orifice with a conical injection and a turbulent velocity profile with an average velocity matching the experimentally measured spray velocity at 3 cm from the spray tip, as shown in Figure 1 [1, 5]. This approach of incorporating the *in vitro* measured spray parameters is a time and resource efficient computational spray modeling framework that can accurately predict spray transport in nasal airways and nasal deposition upon initial wall contact, while avoiding the need to simulate the highly complex spray atomization process [1, 5]. The CFD spray modeling framework can be further simplified by added assumptions on the quasi steady nature of the momentum exchange ("quasi two-way coupled" approach), while still maintaining reliability and accuracy [5]. Simulations may also be performed in conjunction with a nasal inhalation flow to study the influence of the subject's inhalation on spray droplet transport [5]. Furthermore, in simplified CFD models of nasal spray droplet transport and deposition, a deposit-on-touch boundary condition can be employed. However, depending on spray pump administration conditions and insertion angles, nasal sprays may interact with the nasal surface/mucus layer in a way that creates complex droplet-wall interactions followed by significant liquid motion after initial wall contact [35]. In order to model these phenomena, additional physics based sub-models need to be added to the CFD modeling framework [35].

Use of CFD for spray metric sensitivity analysis/bioequivalence evaluation

In vitro spray metrics, such as spray plume geometrical features, are currently used to characterize nasal sprays. Most commercial nasal sprays are hand-actuated; therefore, a change in spray usage conditions or any change in formulation characteristics and/or actuation conditions could result in changes in spray metrics, which could lead to variability in the amount of drug delivered. Currently, there is only limited information on the sensitivity of nasal deposition to changes in a specific spray metric. When comparing generic nasal inhalation drug products to reference listed product performance, it may be advantageous to know how variability in an *in vitro* test metric of a specific product impacts nasal delivery in comparison to the reference product. This section of the article illustrates the applicability of CFD simulations in determining the sensitivity of nasal spray drug delivery to a given spray metric. Specifically, the simulations show the effect of changes in cone angle on spray transport and its impact on posterior nasal deposition in a human nasal airway model [5]. The model estimates spray droplet deposition with the assumption that the droplet deposition location is the initial point of wall contact.

For the nasal spray pump chosen for this study, the baseline spray metrics that are required for setting up the initial and boundary conditions of the CFD model were measured using in-house *in vitro* spray experiments [14]. Mean values of the measurements were used as the baseline case spray simulation parameters for the specific spray, which consisted of an average spray injection velocity = 14.4 m/s, average cone angle = 35^0, ovality ~1, shot weight = 56.3 mg, formulation density = 960 kg/m^3, spray duration = 50 ms and polydisperse droplet size distribution. To calculate the relative efficiency of nasal spray delivery to the intended site of action, which is the posterior nasal region, the nasal model was split into anterior and posterior regions based on the nasal valve location [36]. To investigate the effects of changes in spray cone angle, simulations were conducted while varying the cone angle metric by ~30% from the baseline value and simulated the spray deposition in the anterior and posterior nasal regions while holding all other parameters (including the insertion conditions) at baseline. A new relative deposition parameter, relative difference in the posterior delivery (RD_PD) with respect to the baseline case, was introduced to compare the sensitivity of drug delivery to change in a spray metric value (e.g., change in cone angle or spray velocity). The use of a relative parameter helped to avoid the need to simulate spray deposition for a large number of spray metric values while enabling extrapolation to wider ranges of spray metric values [6].

Figure 2

CFD simulation results showing the impact of spray cone angle on nasal delivery (image modified from Kolanjiyil, et al. [6] with permission from Respiratory Drug Delivery 2021, RDD Online).

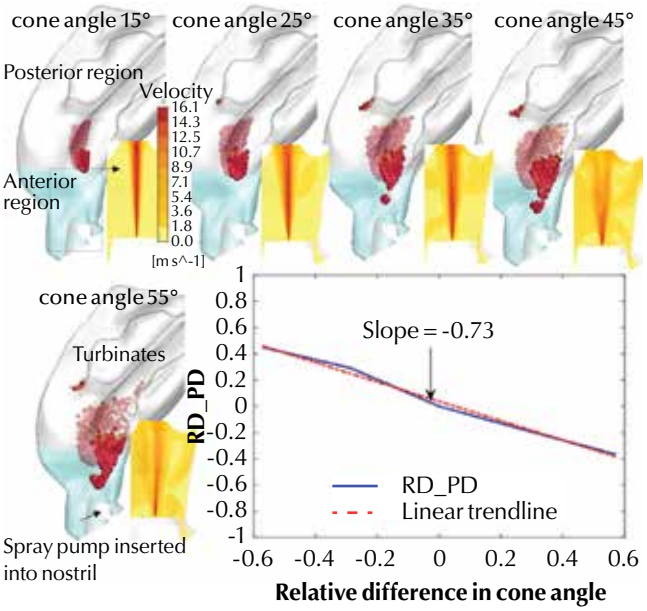


Figure 2 shows the locations of the deposited spray droplets for each spray cone angle. It was observed that with an increase in cone angle, the spray coverage increased and resulted in greater dispersed deposition along the direction of the spray projection. The momentum-jet developed due to the momentum transfer from the spray droplets to the air molecules (two-way coupling) is also plotted as sub-figure panels. The results indicate that with an increase in cone angle, the anterior deposition increases, while the posterior deposition decreases. Figure 2 also shows the parameter RD_PD plotted against the relative change in cone angle with respect to the baseline case and captures the influence of variability in spray cone angle on posterior deposition. The gradient of the RD_PD trend line indicates that small changes in spray cone angle will influence the nasal drug delivery profile. This procedure could also be used to compare the delivery efficiency of a generic spray to a reference spray by comparing the slope of the RD_PD trend line. The trend line provides a way to map differences in the *in vitro* metric to differences in expected posterior nasal drug delivery. For example, the generic sprayer may have a 30% relative difference in the spray cone angle compared with the reference listed product, which would result in a 30% x 0.73 = 21.9% relative difference in posterior nasal deposition.

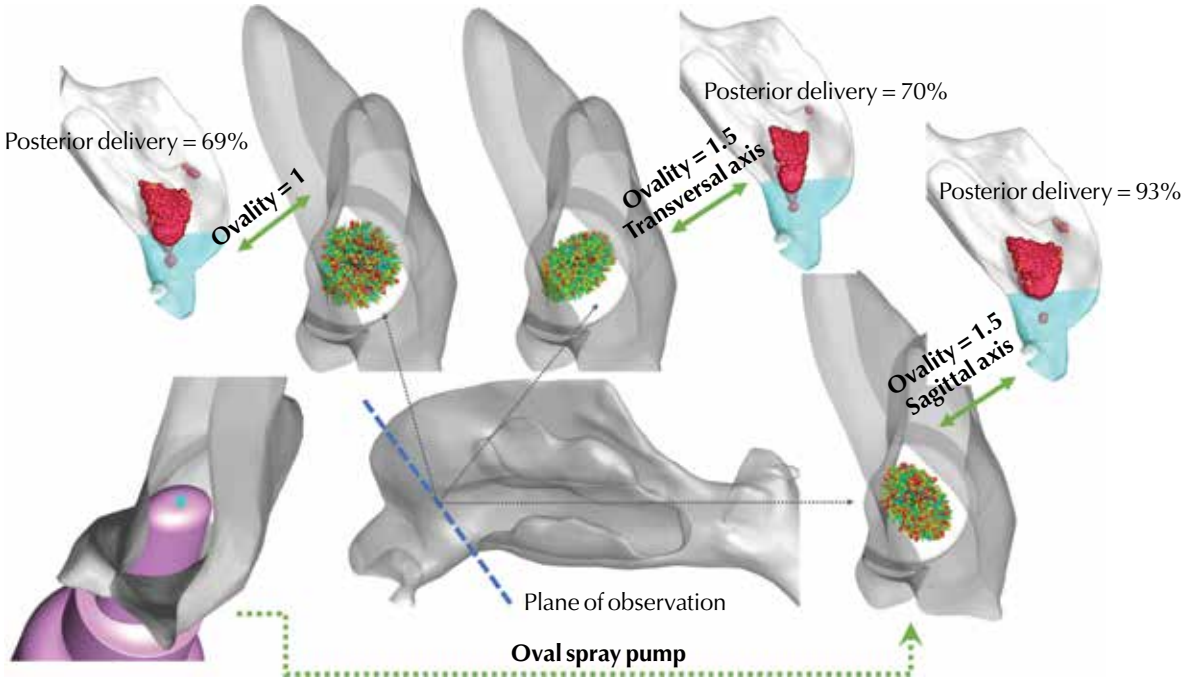
Use of CFD for improving nasal spray designs and optimizing drug delivery

In addition to the use of CFD to assess existing and generic nasal spray products, CFD can also be used as a tool to optimize nasal spray delivery and develop new devices with improved targeting. In this study, simulations show the effect of changes in spray nozzle design on the spray transport and its impact on drug deposition in the posterior nasal region. For nasal sprays, there is considerable delivery to the anterior part of the nasal cavity, which increases with spray cone angle and, consequently, the posterior delivery decreases. Because the intended site of action for most nasal sprays is the posterior region, it would be beneficial to have maximum delivery to this region and also have a wider distribution of drug on the posterior nasal surface for maximum absorption. With the objective of optimizing nasal spray delivery and considering that plume geometry has a pronounced impact on nasal delivery, different spray nozzle designs that produce sprays with different plume ovality were tested using CFD. While CFD could be used to simulate different spray nozzle designs and their effect on liquid atomization and droplet formation, for brevity, this study focused on envisioned outcomes of nozzle designs by simulating droplets injected from the designed nozzle surface.

Two nozzle designs were considered that produced sprays with plume ovality ratios of either 1.0 or 1.5 (Figure 3). Since the spray pump insertion axis with respect to the nasal valve was also found to affect the posterior nasal delivery, two pump insertion axes (the transverse and sagittal axes, shown in Figure 3) were considered in the study. Simulation results indicated that when the plume had the major axis in the transverse direction with the plume width decreased in the sagittal direction, the posterior delivery was similar to the circular spray nozzle, but with reduced drug

Figure 3

Spray nozzle designs and the related impact on nasal drug delivery. Also shown is an oval nozzle design for improved posterior delivery.



distribution on the nasal surface. However, when the plume had the major axis in the sagittal direction with the width decreased in the transverse direction, there was marked improvement in the drug delivery to the posterior region, while maintaining high drug distribution on the nasal surface. Therefore, an oval spray nozzle with the major plume axis aligned with the sagittal axis provided improved delivery to the posterior nasal region. To physically produce this device, a spray pump manufactured with an oval actuator body could ensure that spray pump insertion lines up with the nostril opening, while an oval spray nozzle orthogonal to the actuator body would ensure an oval spray plume with alignment in the sagittal axis direction (Figure 3).

The quantitative relationships identified here may be impacted by different insertion conditions including depth and angle; however, it is expected that the qualitative trends identified will remain unchanged under normal use conditions. Further analysis using different nasal airway models with different insertion conditions are required to complement the findings of this study.

Conclusion

This article provides a short perspective on CFD simulations of nasal spray transport and use of CFD modeling to design nasal spray devices and analyze spray delivery performance. Overall, as illustrated in this article, *in silico* testing using CFD, guided with *in vitro* measurements, is a potentially valuable approach that can reduce the time and cost associated with evaluating nasal spray delivery performance under variable usage conditions in realistic nasal airway models.

Funding and disclaimer

Funding was provided by Contract HHSF2232 01810144C from the Department of Health and Human Services, US Food and Drug Administration. Views expressed in this manuscript do not necessarily reflect the official policies of the US Food and Drug Administration, nor does any mention of trade names, commercial practices or organizations imply endorsement by the United States Government.

References

1. Kolanjiyil AV, Hosseini S, Alfaifi A, Hindle M, Golshahi L and Longest PW: Importance of cloud motion and two-way momentum coupling in the transport of pharmaceutical nasal sprays. Journal of Aerosol Science 2021,156.

2. Kundoor V and Dalby R: Effect of formulation- and administration-related variables on deposition pattern of nasal spray pumps evaluated using a nasal cast. Pharmaceutical Research 2011,28:1895-1904.

3. Liu X, Doub WH and Guo C: Evaluation of droplet velocity and size from nasal spray devices using phase Doppler anemometry (PDA). International Journal of Pharmaceutics 2010,388:82-87.

4. Kolanjiyil A, Hosseini S, Manniello M, Alfaifi A, Farkas D, Hindle M, Golshahi L and Longest PW: Effect of spray momentum on nasal spray droplet transport and deposition. Respiratory Drug Delivery 2020,3:691-696.

5. Kolanjiyil AV, Hosseini S, Ali A, Farkas DR, Walenga R, Babiskin A, Hindle M, Golshahi L and Longest PW: Validating CFD predictions of nasal spray deposition: Inclusion of cloud motion effects for two spray pump designs. Aerosol Science and Technology 2022,56:304-322.

6. Kolanjiyil AV, Hosseini S, Alfaifi A, Farkas D, Hindle M, Golshahi L and Longest PW: How spray metric variability impacts the initial deposition of nasal sprays. Respiratory Drug Delivery 2021,1:349-354.

7. Gao M, Shen X and Mao S: Factors influencing drug deposition in the nasal cavity upon delivery via nasal sprays. Journal of Pharmaceutical Investigation 2020,50:251-259.

8. Guo C, Stine KJ, Kauffman JF and Doub WH: Assessment of the influence factors on *in vitro* testing of nasal sprays using Box-Behnken experimental design. European Journal of Pharmaceutical Sciences 2008,35:417-426.

9. Dayal P, Shaik MS and Singh M: Evaluation of different parameters that affect droplet-size distribution from nasal sprays using the Malvern Spraytec®. Journal of Pharmaceutical Sciences 2004,93:1725-1742.

10. Kimbell JS, Segal RA, Asgharian B, Wong BA, Schroeter JD, Southall JP, Dickens CJ, Brace G and Miller FJ: Characterization of deposition from nasal spray devices using a computational fluid dynamics model of the human nasal passages. Journal Of Aerosol Medicine 2007,20:59-74.

11. Warnken ZN, Smyth HD, Davis DA, Weitman S, Kuhn JG and Williams III RO: Personalized medicine in nasal delivery: The use of patient-specific administration parameters to improve nasal drug targeting using 3D-printed nasal replica casts. Molecular Pharmaceutics 2018,15:1392-1402.

12. Inthavong K, Ge Q, Se CM, Yang W and Tu J: Simulation of sprayed particle deposition in a human nasal cavity including a nasal spray device. Journal of Aerosol Science 2011,42:100-113.

13. Chen JZ, Kiaee M, Martin A and Finlay WH: *In vitro* assessment of an idealized nose for nasal spray testing: Comparison with regional deposition in realistic nasal replicas. International Journal of Pharmaceutics 2020:119341.

14. Manniello MD, Hosseini S, Ali A, Esmaeili AR, Kolanjiyil AV, Walenga R, Babiskin A, Sandell D, Mohammadi R, Schuman T, Hindle M and Golshahi L: *In vitro* evaluation of regional nasal drug delivery using multiple anatomical nasal replicas of

adult human subjects and two nasal sprays. International Journal of Pharmaceutics 2021,593: 120103.

15. Newman SP, Pitcairn GR and Dalby RN: Drug delivery to the nasal cavity: *In vitro* and *in vivo* assessment. Critical Reviews™ in Therapeutic Drug Carrier Systems 2004,21:21-66.

16. Longest PW, Bass K, Dutta R, Rani V, Thomas ML, El-Achwah A and Hindle M: Use of computational fluid dynamics deposition modeling in respiratory drug delivery. Expert Opinion on Drug Delivery 2019,16:7-26.

17. Walenga RL, Babiskin AH and Zhao L: *In silico* methods for development of generic drug–device combination orally inhaled drug products. CPT: Pharmacometrics & Systems Pharmacology 2019,8:359-370.

18. Kiaee M, Wachtel H, Noga ML, Martin AR and Finlay W: An idealized geometry that mimics average nasal spray deposition in adults: A computational study. Computers in Biology and Medicine 2019,107:206-217.

19. Versteeg HK and Malalasekera W. An introduction to computational fluid dynamics: The finite volume method, Prentice Hall, New York, 2007.

20. Tu J, Inthavong K and Ahmadi G. Computational fluid and particle dynamics in the human respiratory system, Springer, New York, 2012.

21. Longest PW and Holbrook LT: *In silico* models of aerosol delivery to the respiratory tract - Development and applications. Advanced Drug Delivery Reviews 2012,64:296-311.

22. Wong W, Fletcher DF, Traini D, Chan HK and Young PM: The use of computational approaches in inhaler development. Advanced Drug Delivery Reviews 2012,64:312-322.

23. Feng Y, Hayati H, Bates AJ, Walter K, Matthias L, Odo B, Ramiro O and Gerda K. Clinical CFD applications 2. Clinical and biomedical engineering in the human nose, Springer, New York, 2021.

24. Tong Z, Zhong W, Yu A, Chan H-K and Yang R: CFD–DEM investigation of the effect of agglomerate–agglomerate collision on dry powder aerosolisation. Journal of Aerosol Science 2016,92:109-121.

25. Saikat B, Holbrook LT, Kathryn K, Olulade F, Wu J, Burke A, Langworthy BW, Zainab F, Mamdani M and Bennett WD: Numerical evaluation of spray position for improved nasal drug delivery. Scientific Reports (Nature Publisher Group) 2020,10.

26. Xi J, Wang Z, Nevorski D, White T and Zhou Y: Nasal and olfactory deposition with normal and bidirectional intranasal delivery techniques: *In vitro* tests and numerical simulations. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2017,30:118-131.

27. Bass K, Farkas D, Hassan A, Bonasera S, Hindle M and Longest PW: High-efficiency dry powder aerosol delivery to children: Review and application of new technologies. Journal of Aerosol Science 2021,153:105692.

28. Bass K, Boc S, Hindle M, Dodson K and Longest W: High-efficiency nose-to-lung aerosol delivery in an infant: Development of a validated computational fluid dynamics method. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2019,32:132-148.

29. Kimbell JS and Subramaniam RP: Use of computational fluid dynamics models for dosimetry of inhaled gases in the nasal passages. Inhalation Toxicology 2001,13:325-334.

30. Walenga RL and Longest PW: Current inhalers deliver very small doses to the lower tracheobronchial airways: Assessment of healthy and constricted lungs. Journal of Pharmaceutical Sciences 2016,105:147-159.

31. Longest PW, Tian G, Khajeh-Hosseini-Dalasm N and Hindle M: Validating whole-lung CFD predictions of DPI aerosol deposition at multiple flow rates. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2016,29:461-481.

32. Kolanjiyil AV and Kleinstreuer C: Computational analysis of aerosol-dynamics in a human whole-lung airway model. Journal of Aerosol Science 2017,114:301-316.

33. Mahian O, Kolsi L, Amani M, Estellé P, Ahmadi G, Kleinstreuer C, Marshall JS, Siavashi M, Taylor RA, Niazmand H, Wongwises S, Hayat T, Kolanjiyil A, Kasaeian A and Pop I: Recent advances in modeling and simulation of nanofluid flows-Part I: Fundamentals and theory. Physics Reports 2019,790:1-48.

34. Cherobin GB, Voegels RL, Gebrim EM and Garcia GJ: Sensitivity of nasal airflow variables computed via computational fluid dynamics to the computed tomography segmentation threshold. PLOS One 2018,13:e0207178.

35. Kolanjiyil AV, Alfaifi A, Aladwani G, Golshahi L and Longest, W: Importance of spray–wall interaction and post-deposition liquid motion in the transport and delivery of pharmaceutical nasal sprays. Pharmaceutics 2022,14(5):956.

36. Hosseini S, Schuman TA, Walenga R, Wilkins Jr JV, Babiskin A and Golshahi L: Use of anatomically-accurate 3-dimensional nasal airway models of adult human subjects in a novel methodology to identify and evaluate the internal nasal valve. Computers in Biology and Medicine 2020,123:103896.

Arun V. Kolanjiyil, PhD, is a postdoctoral research associate and Worth Longest, PhD, is a Professor in the Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, Virginia, US, pwlongest@vcu.edu, www.sites.google.com/vcu.edu/longest-lab/home.