

# A Review of CFD Applications to Pulmonary Drug Delivery: Pros, Cons and Gaps

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## Summary

This paper reviews the challenges and opportunities for the application of computational fluid dynamics (CFD) to pulmonary drug delivery. CFD simulations allow the prediction of airflow patterns, particle tracks and deposition in model geometries of inhalation devices and regions of the respiratory tract. However, pharmaceutical companies often complain that CFD data did not bring conclusive answers. CFD is an additional engineering discipline that requires highly skilled, 'dedicated-to-CFD-use' personnel. The inherent complexities of inhalation devices necessitate the continued development of advanced methods. Combinations of numerical tools are likely to provide valuable insight into these complex problems. Recent applications of modern CFD are now showing that this is a tool providing real benefits during the device and product development cycles, especially in a quality by design product development environment.

## Introduction

In the 1960s and early 1970s, the key technical and clinical factors leading to a successful inhalation therapy were poorly understood. However, nebuliser techniques were increasingly widespread and the orally inhaled route for drug delivery was attracting a growing interest in the medical community due to a number of benefits, in particular the avoidance of first pass metabolism in the liver and the ease of use for the patient. At the same time, the automotive and aeronautics industries were realising that new high-technology research and design tools were necessary to accelerate the conception and improve the performance of modern cars and aircrafts. One of these tools was computational fluid dynamics (CFD). Today, whether it is to study the external flow over a vehicle or the internal flow through the engine, CFD has evolved from a mathematical curiosity to become a powerful influence on the way fluid dynamicists and aerodynamicists conduct their investigations. Modern CFD cuts across all disciplines where technical breakthroughs rely on developing deeper insights into fluid phenomena, such is the case in the area of orally inhaled (pulmonary) and nasal drug delivery.

The development of orally inhaled products covers numerous scientific fields such as chemistry, engineering, mathematics or physics and pharmaceuticals. Achieving and reproducing the performance goals are challenging. Indeed the lungs tend to expel "foreign" materials, making it difficult to keep the drug long enough to ensure effective release. Additional issues include design and cost of the delivery device, the deagglomeration and elimination of excipient in the case of dry powder inhalers (DPI), the elimination of propellants in the case of metered-dose inhalers (MDI), the ejection of the drug, dose reproducibility or humidity control to cite only few of them. At the same time, concerns for patient safety and ecological sustainability become increasingly stringent. Further, in a Quality by Design environment using tools that provide knowledge and lead to understanding are critical. Clearly there is room for application of the CFD methodology as a complementary catalyst to other investigation techniques. Nevertheless the industrial biomedical sector remains somehow cautious towards integration of computational procedures into their R&D and design programmes.

## CFD: a valuable design and research tool

The investigation of airflow patterns and particle behaviour applied to pulmonary drug delivery has become a topic of great interest in the academic world. The knowledge of fluid dynamics is essential to understand transport processes, partly because the trajectories of inhaled particles (either solid, gaseous or liquid) depend on the nature of the fluid in which they are entrained. Past CFD studies have shown that the key to an efficient inhalation therapy depend on a subtle combination of critical (quality attributes) parameters ranging from engineering features of the delivery platform, physicochemical properties of the drug particles, operating conditions and morphology of the human respiratory tract to the anatomical variations between subjects. The complexity of the problem is further enhanced if the human factors (i.e. how a patient uses an inhaler) are considered. It is currently difficult to address all these parameters simultaneously but advances are being made. CFD work reported in the scientific literature falls into two categories:

- Understand and engineer 'virtually' the inhalation platform and mechanism,
- Track the drug particles from their release to their deposition.

Table 1 gives a brief overview of these areas of application. The design and operations of inhalation devices are incredibly complex. Small variations can have huge consequences on the performance of the system. CFD has proved to be a valuable tool to achieve a fundamental understanding of what is happening inside the device from the onset of actuation to the release of the drug. This acquired knowledge is aimed at serving as guiding rules for improved designs.

After leaving the delivery device the drug penetrates the respiratory tract. CFD allows tracking the journey of the drug particles over time and predicting their regional deposition. This is a significant step forward in pulmonary delivery: in-vivo measurements are expensive, complex to conduct and show considerable variability between subjects. In-vitro techniques offer a more economic and easier alternative. Initially computational models were constructed based on these physical models. The first simulations used very simplistic representations of the mouth, throat, pharynx, larynx, trachea and the first generations of the lower airways (1, 2). Over the last decades, as computed tomography (CT) and magnetic resonance imaging (MRI) have rapidly advanced, novel and powerful algorithms have been developed for acquisition, analysis, segmentation and reconstruction of the images into three-dimensional computational domains. It is now possible to generate CFD models reproducing very closely the configuration of the human airways. The increasing memory and speed of modern computers also allow to “look deeper down” into the bronchial tree and consider more sophisticated mathematical models.

Area of investigation	CFD investigations	Areas in development
<b>Delivery platform</b>	<ul style="list-style-type: none"> <li>- Influence of the device's design <ul style="list-style-type: none"> <li>▪ Air inlets (3)</li> <li>▪ Mouthpiece (4, 5)</li> <li>▪ Presence of a grid (4)</li> <li>▪ Presence of a capsule (6)</li> </ul> </li> <li>- Influence of the particles' size and distribution (7)</li> <li>- Influence of the inhaled airflow (6)</li> <li>- Effect of humidity (1, 8)</li> <li>- Human factors i.e. patients' handling skills (9), breathing profiles (9)</li> </ul>	<ul style="list-style-type: none"> <li>- Powder deagglomeration (15, 16, 17)</li> </ul>
<b>Human respiratory tract</b>	<ul style="list-style-type: none"> <li>- Flow visualisation</li> <li>- Particle tracking vs size and air flow rate</li> <li>- Inter-subject variations</li> <li>- Influence of anatomical abnormalities / diseases</li> </ul>	
Mouth-throat region	<ul style="list-style-type: none"> <li>- Influence of the tongue (10)</li> <li>- Intra-subject variations (10)</li> </ul>	
Larynx	<ul style="list-style-type: none"> <li>- Effect of the anatomy on the flow (7)</li> <li>- Laryngeal jet and turbulence generation (11)</li> </ul>	
Trachea and bronchial tree	<ul style="list-style-type: none"> <li>- Impingement jet (11)</li> <li>- Airflow profile and particle impaction in the bronchi and bifurcations, up to the 17<sup>th</sup> generation (12)</li> <li>- Influence of turbulence models on the prediction of airflow patterns and particle deposition (13)</li> <li>- Effect of gravity, orientation, particle size, airflow rate and generation number on drug deposition at the alveolar level (14)</li> </ul>	

**Table 1: Areas of CFD application in pulmonary drug delivery**

CFD has demonstrated several complementary advantages over the in-vivo and in-vitro techniques:

- It has been a decisive research tool to successfully identify inertial impaction as the governing mechanism of deposition in the mouth-throat region,(1)
- It represents a non-invasive, faster and more economic way to visualise the complex flow occurring in the respiratory tract and draw a map of the regional drug deposition,
- Parametric studies are quicker to conduct.

It is obvious that CFD exhibits potential for the development of therapeutic trials and shorten the road to market of novel drugs and delivery platforms.

### CFD: a tool to use with discretion

The attitude on how to approach the problem at hand is crucial. CFD represents another research and design approach and should be considered as an equal partner with theory and experiment in the analysis and solution of fluid problems. The success of an R&D project depends upon a proper balance of all three approaches, each helping to interpret and understand the others.

Producing accurate and reliable CFD predictions depends on some major prerequisites:

- **Specialised knowledge in fluid dynamics, mathematics and numerical techniques.** The governing principles of the problem have to be understood beforehand in order to appreciate the difficulty of the modelling exercise. CFD involves mathematics, even so the CFD solution is an acceptable ‘approximation’ of the exact solution of the problem. Getting to that ‘approximation’ solution requires the manipulation of discretisation schemes, convergence criteria, mathematical models and iterative algorithms in such a way that the final solution should be independent to all numerical criteria. Nowadays it is easy to underestimate the diligence of the task: commercial CFD packages compete with user-friendly interfaces and provide the user with a large range of pre-built, pre-installed mathematical models covering many fields of scientific / industrial applications.

- **Software and hardware.** Commercial CFD packages are expensive: a licence fee is around £12-15K and is negotiated annually. An alternative is to develop an in-house CFD code but this is time, effort and hence cost consuming. CFD models are large, complex and require significant computing resources. Simulation runtimes can be reduced by performing parallel computations on multiple processors. Although the computer power rises while the prices decrease, such platforms still represent a fair amount of money and skilled maintenance.
- **The objectives.** Prior to begin the simulations, the R&D team has to decide:
  - *What are the objectives of the simulations? Which data are of major practical interest for the progress of the R&D project? What can be modelled?* The use of CFD beyond its capabilities leads to inaccurate results. The faithfulness of the computational model with the delivery device or the respiratory tract is critical for accurate CFD predictions. Digital models of the lower airways derived from a CT scan exhibit differences in the texture / roughness and number of the branches included in the simulation (18). It is likely that these differences may result in different and maybe inaccurate predicted deposition.
  - *What is the best way to numerically describe the problem?* Commercial CFD codes offer a broad variety of mathematical models, ranging from the simplest to a more sophisticated description of the physical process (turbulence (19), particle tracking for examples). Some models are better at predicting some types of flow patterns than others. The choice of the boundary conditions is another issue that must be considered carefully. It is possible to measure the breathing profile of patients but it is more challenging to evaluate the airflow profile at the entrance of, say, the trachea.
  - *Which level of accuracy has to be achieved?* If the intent of the simulation is to model the gross behaviour of the particles and their carrier, then the set-up of the CFD model does not have to be as stringent as it should be when details of the flow are of prime interest. In particular the computational grid can potentially affect the quality, and even the physical interpretation, of the solution. There are five mesh styles (structured hexahedral, unstructured tetrahedral, flow adaptive tetrahedral, hybrid and polyhedral grids). Depending on the alignment of the cells with the predominate direction of the flow, the style of the grid can have a major impact on the run times, the size of the model, the grid convergence and the numerical diffusion, hence detailed flow features can be better (or poorly) captured and particle deposition match more closely (or differ from) the empirical, in-vivo or in-vitro results (20). The selection of the mesh style depends on the time and computational resources available, as well as the desired accuracy of the results.
- **Validation and interpretation of the results.** It is important to demonstrate that the preliminary CFD results are in agreement with the experimental data but also to prove that this agreement is not fortuitous i.e. resulting from compensating numerical errors (18). Accuracy of the computational domain compared with the inhaler or the respiratory tract is a critical issue, since small differences may result in larger discrepancies. Only in-depth comparisons can help fortuitous agreements to be eliminated. However, sometimes it is impossible to compare the CFD data due to the lack of experimental measurements; for example particle deposition has rarely been validated at the sub-branch level. The interpretation of the results requires a sound expertise in fluid mechanics, knowledge of the past findings, as well as a good understanding of the CFD code.

CFD is a powerful tool if used with the right level of planning and knowledge. However, the literature tends to limit the use of the CFD tool to well established modes of applications. CFD does have its own limitations but perhaps a constructive way forward is not to concentrate on *what has been done* but rather on *what should be done*.

## CFD: a potential tool to broaden the horizon

CFD has potential to deliver more value than it currently has done and hence becomes a more powerful research and design catalyst. Currently CFD capabilities are not challenged enough; progress needs to be made to:

- Push the limits of what a 'code' can be made actually do,
- Use the code in an even more complementary way, e.g. coupling the CFD simulations with models coming from different length scales,
- Integrate the CFD methodology in the various phases of a product development programme, rather than focusing to the concept and early design development phase.

An effort to increase the accuracy of the CFD simulations has already been initiated in the area of near-wall turbulence modelling. For example, DPI devices use turbulence to deagglomerate the powder through swirls, grids or impinging jets. Further, the laryngeal jet tends to enhance the turbulence of the inhaled airflow. As the air decelerates whilst travelling down the bronchial tree, the turbulence gradually dies and the flow becomes laminar. Turbulent flows are characterised by eddies with a wide range of length and time scales. The powder particles interact with these eddies which therefore influence the deposition. Particle deposition on the walls (of the device or the respiratory tract) is a key parameter when assessing the performance of a delivery system, as it is linked to aerosol losses. Standard turbulence models do not properly predict the structure of the eddies, requiring modifications to the eddy-particle interaction models. Commercial CFD packages account for these latter interactions using two methods: mean flow tracking (i.e. there is no turbulence-particle interaction) or the stochastic eddy interaction model (EIM) (which assumes the isotropy of the turbulence throughout the flow). Matida et al (13) demonstrated that these models cause inaccuracies in predicting particle behaviour near the

walls, especially when small particles are considered. The highly sophisticated Large Eddy Simulation (LES) turbulence model can largely improve the predictions but at the expense of significantly increased computational times and computer memory requirements (21). The solution is to modify the EIM in order to take into account the anisotropy of the turbulence near the wall. Near-wall corrections recognise that the fluctuating velocity component normal to the walls play a major role for particle deposition.

CFD is usually used to model airflows and particle trajectories within a DPI device after the blister, the capsule or the powder reservoir has been emptied. The “evacuation” of the powder bulk from its containment or reservoir, the deagglomeration and dispersion are still poorly understood, although they are all of major interest in the design of a DPI. These processes are extremely challenging to model: CFD is able to track the motion of single particles and monitor the influence of flow turbulence but it needs to be coupled with additional techniques, such as the Discrete Element Method (DEM) to investigate the particle-particle interactions and study the break-up of agglomerates by wall-impaction mechanisms. Two distinct mechanisms of powder bed break-up, erosion and fracture, have been observed (16). Erosion entrains non-cohesive individual particles in the airflow and does not promote agglomeration. In contrast, fracture concerns carrier particles: the powder bed tends to break-up along lines of weakness (or cracks). The detachment of the active drug particles from their carrier and their dispersion within the DPI involve complex separation mechanisms. Particle-airflow and particle-wall effects are known to overcome particle-particle separation forces and cause the particle detachment but they have not been fully investigated. As a result, CFD coupled with additional models can potentially become a powerful tool for understanding the dispersion mechanisms in inhalers and bring significant value for formulation and device design. Nichols et al. (17) introduced the notion of “torque” as a measure of ease of separation of an active particle from its carrier. “Separation torque” (derived from measurements) the maximum torque that the active drug/carrier attachment can withstand before detachment. The authors developed a coupled CFD-DEM model aimed at calculating the torque arising from the particle motion in the inhaled airflow as it travels through the device (fluid-based torque) and the forces generated by particle-inhaler wall collisions (impact-based torque). The study showed that although both events should be considered during inhaler design, impact-based events have the greater effect on particle detachment than fluid-based events. Comparison between the values of the numerically predicted torque and the measured separation torque predicts the onset of dispersion. The work also demonstrated that the size of the active particles influences more the torque than the size of the carrier particles. DEM and CFD coupled simulations provide a means of tackling challenging problems when designing and optimising DPIs for specific drugs in order to achieve the required level of performance of the device.

Application of CFD to human airways should also incorporate their pulsation and motion due to both cardiac rhythms and breathing manoeuvres. Also the lungs are coated with a mucus layer which provides a highly efficient defence barrier to chemical damages. Inhaled particles stick to the mucus layer rather than penetrate it, before being rapidly removed from the lung region by a clearance mechanism. While prolonged and sustained drug delivery (via mucoadhesive particles) can benefit the presence of the mucus layer, the latter may also adversely affect the absorption of drugs administered orally (22). Also diseases can have major effects on the properties of this layer. Therefore the interactions between mucus, drugs and delivery systems are important considerations. CFD, coupled with chemical and diffusion models, can be of great help in assessing the influence of the airways surfaces and thermal conditions on the drug dissolution or absorption to the lung tissues.

Finally, for the successful application, development and commercialisation of an inhalation device, the pharmaceutical company has to demonstrate a thorough understanding of how the product “works”. Currently CFD is recognised as a valuable tool to enable significant returns by reducing time-to-market and creating better utilisation of engineering resources throughout the design process. However, it is a long journey from concept phase to product registration dossier before market launch. CFD can potentially fill that gap by being used as an ‘analytical’ tool to trouble-shoot operational problems and provide fundamental proof-of-concept.

## Conclusions

Consistent ‘desired’ inhaled product performance is the critical quality attribute that must be built in from every design stage from prototype to marketed product. To achieve this increasingly, the delivery device features and the drug physicochemical properties are going to be more tightly coupled. It is important to recognise that each category of inhaler delivers a product with different aerosol characteristics and that these together with the anatomy and physiology of the lungs determine the site of deposition and the mechanism of clearance. In order to compete in this arena, companies will have to demonstrate the higher ‘patient’ value that their combination of drugs and delivery devices bring to the market. To do so, they will have to implement a broad portfolio of advanced engineering R&D technologies that will be used in synergy.

This paper reviewed the challenges and opportunities for the applications of CFD to pulmonary drug delivery. CFD is a complex tool; unskilled and inexperienced people may not use effectively. Yet despite this, much has been achieved by the research community to enhance our fundamental aerosol knowledge. This biomedical field has offered many challenges to the mathematical modeller, in particular in relation to problem identification, parameter estimation and validation. However, limitations in existing CFD methods are driving the development of a range of integrated advances.

## References:

1. Zhang, Y., Chia, T.L. and Finlay, W.H. "Experimental measurement and numerical study of particle deposition in highly idealized mouth-throat models", *Aerosol Science and Technology* 2006, No. 40, pp 361-372.
2. Luo, H.Y. and Liu, Y. "Modeling the bifurcating flow in a CT-scanned human lung airway", *Journal of Biomechanics* 2008, No. 41, pp 2681-2688
3. Coates M.S., Chan, H-K., Fletcher, D.F. and Raper, J.A. "Effect of design on the performance of a dry powder inhaler using computational fluid dynamics. Part 2: Air inlet size", *Journal of Pharmaceutical Sciences* 2006, Vol. 95, No. 6, pp 1382-1392.
4. Coates M.S., Fletcher, D.F, Chan, H-K. and Raper, J.A "Effect of design on the performance of a dry powder inhaler using computational fluid dynamics. Part 1: Grid structure and mouthpiece length", *Journal of Pharmaceutical Sciences* 2004, Vol. 93, No. 11, pp 2863-2876.
5. Coates M.S., Chan, H-K., Fletcher, D.F, and Chiou, H. "Influence of mouthpiece geometry on the aerosol delivery performance of a dry powder inhaler", *Pharmaceutical Research* 2007, Vol. 24, No. 8, pp 1450-1456.
6. Coates M.S., Fletcher, D.F, Chan, H-K. and Raper, J.A. "The role of capsule on the performance of a dry powder inhaler using computational and experimental analyses", *Pharmaceutical Research* 2005, Vol. 22, No. 6, pp 923-932.
7. Cebral, J.R. and Summers, R.M. "Tracheal and central bronchial aerodynamics using virtual bronchoscopy and computational fluid dynamics", *IEEE Transactions on Medical Imaging* 2004, Vol. 23, No. 8, pp 1021-1033.
8. Rau, J.L. "Practical problems with aerosol therapy in COPD", *Respiratory Care* 2006, Vol. 51, No.2, pp 158-172.
9. Underwood, R., Davies, G., Dufour, F., Simpson, I., Pocock, A., Cuney, S., Oakley, J. and Gupta, A. "Using computational modelling to improve dry powder inhaler performance", *Drug Delivery to the Lungs* 2006.
10. Heenan, A.F., Finlay, W.H., Grgic, B., Pollard, A. and Burnell, P.K.P. "An investigation of the relationship between the flow field and regional deposition in realistic extra-thoracic airways", *Aerosol Science and Technology* 2004, No. 35, pp 1013-1023.
11. Takano H., Nishida, N., Itoh, M., Hyo, N. and Majima, Y. "Inhaled particle deposition in unsteady-state respiratory flow at a numerically constructed model of the human larynx", *Journal of Aerosol Medicine* 2006, Vol. 19, No. 3, pp 314-328.
12. Gemci, T., Ponyavin, V., Chen, Y., Chen, H. and Collins, R. "CFD simulation of airflow in a 17-generation digital reference model of the human bronchial tree", *Series on Biomechanics* 2007, Vol. 23, No. 1, pp 5-18.
13. Matida, E.A., DeHaan, W.H., Finlay, W.H. and Lange, C.F. "Simulation of particle deposition in an idealized mouth with different small diameter inlets", *Aerosol Science and Technology* 2003, No. 37, pp 924-932.
14. Harrington, L., Prisk, G.K. and Darquenne, C. "Importance of the bifurcation zone and branch orientation in simulated aerosol deposition in the alveolar zone of the human lung", *Journal of Aerosol Science* 2006, No. 37, pp 37-62.
15. Chan, H-K "Dry powder aerosol delivery systems: current and future research directions", *Journal of Aerosol Medicine* 2006, Vol. 19, No. 1, pp 21-27.
16. Shrimpton, J.S. and Tuley, R. "Modelling device emptying and dispersion mechanisms in dry powder inhalers", *Respiratory Drug Delivery* 2007, pp 207-213.
17. Nichols, S. and Wynn, E. "New approaches to optimizing dispersion in dry powder inhalers – Dispersion force mapping and adhesion measurements", *Respiratory Drug Delivery* 2008, Vol. 1, pp 175-184.
18. Oldham, M.J. "Challenges in validating CFD-derived inhaled aerosol deposition predictions", *Inhalation Toxicology* 2006, No. 18, pp 781-786.
19. Luo, X.Y., Hinton, J.S., Liew, T.T. and Tan, K.K. "LES modeling of flow in a simple airway model", *Medical Engineering & Physics* 2004, No. 26, pp 403-413.
20. Longest, P.W. and Vinchurkar, S. "Effects of mesh style and grid convergence on particle deposition in bifurcating airway models with comparisons to experimental data", *Medical Engineering & Physics* 2007, no. 29, pp 350-366.
21. Finlay, W.H. and Martin, A.R. "Modeling of aerosol deposition with interface devices", *Journal of Aerosol Medicine* 2007, Vol. 20, Supplement 1, pp S19-S28.
22. Khanvilkar, K., Donovan, M.D. and Flanagan, D.R. "Drug transfer through mucus", *Advanced Drug Delivery Reviews* 2001, No. 48, pp 173-193.