Computational Fluid Dynamics (CFD) enables a fast and cost-effective evaluation of new drug delivery designs and formulations.

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Interest in more advanced drug delivery systems has increased in line with the acceleration in the discovery and development of novel therapeutic macromolecules for targeted applications. Computational fluid dynamics is a design tool that allows designers of these and other products to evaluate different designs rapidly and cost-effectively.

Computational Fluid Dynamics

The use of Computational Fluid Dynamics (CFD) has seen a big increase in recent years within the pharmaceutical industry. Its application to the development of a new drug offers significant benefits in terms of yielding reduced costs, a faster time to market, an improved understanding of existing or novel innovations, and the knowledge to make informed decisions to help guide and shape the direction of future research efforts. These benefits are of particular significance in the search for an effective delivery system for a new drug – an issue that has become more pertinent in the light of recent moves away from needle and syringe-based injection methods.

Traditionally, animal experimentation has been used to evaluate drug delivery systems but the results are not seen as sufficiently reliable when transposed to humans, whose respiratory physiology, for example, can differ greatly. This often leads to dramatically varying doses being realised from the same initial sample, making useful comparisons problematic. In addition, an obligation exists under law to minimise experimentation on animals, placing restrictions on the level of testing that can be conducted. CFD can help overcome some of these issues, allowing the analysis of various drug delivery designs rapidly and economically, using a three-dimensional model of human physiology (Figure 1).

Computational Fluid Dynamics works by using numerical methods to solve the equations that govern fluid flow. A domain to be analysed is first determined and split into thousands of small 3-D cells known as a computational mesh (Figure 1). For each cell within the mesh, the fundamental equations (Navier-Stokes) for fluid flow are solved automatically to arrive at an overall solution.

Figure 1. Section of the pulmonary artery, imaged using a computational mesh.
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The major leap forward that this gives the user is the ability to reduce significantly the amount of physical experimentation required by conducting a series of virtual analyses. Multiple designs, variations of similar designs and numerous process parameters can be tested to achieve maximum efficiency and consistency of dose deposition. A multifaceted examination of an unlimited number of locations in the area of study can be performed concurrently, without being constrained by the number of time-points or regions of analysis – as are more established, practical experimental methods. Also, specific phenomena or condition scenarios can be easily isolated and subjected to further study. This allows the clear identification of potential final designs for further testing, requiring fewer prototypes to be constructed.

Clearly, the value of the resulting reduction in man-hours spent on testing, and the ability to concentrate development efforts on only those designs with serious potential, means a product can reach the market significantly faster than would otherwise be the case – a goal that is achievable at a greatly reduced investment in cost and time.

Once the final design and parametric data (such as dose concentration and variation) have been obtained, the results can then be displayed in a variety of formats to ensure clarity of the data-set. An example of this could include displaying the results of a simulation as a 3-D visualisation, with regions of temperature, pressure and fluid flow represented in colour code. Such tools are useful for clearly presenting the results of a study to all participants involved in a drug delivery project.

In order to use CFD software accurately and effectively, it is important that a fully trained user is deployed to conduct the analyses. Depending on the level of usage required, an in-house capability can be developed and the appropriate licence(s) purchased. Alternatively, expert CFD consultancy can be employed, giving the flexibility of using as much or as little as required, and removing the need to buy the software.

Applications

Some of the current and possible applications of CFD in the development of drug delivery systems are reviewed below.

**Inhaler design** Inhalation technology is extensively used for treating lung diseases such as asthma, cystic fibrosis and emphysema. This method enables the rapid and easy administration of drugs, and offers the ability to administer lower dosages. Most drug absorption in the lung occurs across the alveolar epithelium (Figure 2). The rate of drug deposition depends on the particle size and rate of inspiration (2). Dry powder inhalers (DPIs) and metered dose inhalers (MDIs) are two commonly available inhalers, and MDIs containing chlorofluorocarbon (CFC) gases have been the most prescribed type of inhalation system for the past few years. However, MDIs have two main weaknesses: actuation of the aerosol and the low concentration of dose (typically 10% of the normal dose). Pharmaceutical companies started researching inhaler design to improve factors such as ease of use, efficiency of drug deposition (currently 30–35%, 3) and reproducibility of drug dosage. The research was accelerated because of the global drive towards reducing the level of CFC gas emissions.

Drug delivery systems normally involve the transportation of additional-phase material to the area being treated. These materials may be medicated particulate, liquid drops, a gaseous species or a mixture of these. A variety of established modelling methodologies is available to the CFD practitioner to scrutinise design variations. This allows the characterisation of an effective device for the delivery of a specified dose concentration, dose variation and particle dispersion. Equally, any cause of particle loss can be identified, and subsequent design modifications can be tested to ensure the problem is successfully addressed.

The magnitude of velocity in a DPI is illustrated in Figure 3. The simulation results were used to identify regions of high velocities, shear forces and circulation loops, particle residence times for larger...
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**Drug absorption and dissolution** Drugs can be administered via various different routes, for example subcutaneously, rectally, orally, nasally and so on. CFD provides the ability to model such routes to predict dissolution and absorption of a drug in particular circumstances.

For example, drugs intended for delivery via the respiratory tract are frequently micronised to create microparticles sufficiently small to be inhaled and targeted at a specific area of the lung (Figure 2), or absorbed through the alveolar epithelium and into the capillaries (1). These particles have a high surface area and high charges, forming an unstable cohesive system. This means the particles could adhere to any surface on the way to the targeted region of the respiratory system (2). CFD can be used to trace the trajectories of a medication particle through the nasal passage (Figures 4) to its final deposition in the lung in order to ensure the necessary dosage is achieved.

**Conclusion**

CFD can be used for a range of applications including the design of drug delivery systems and the analysis of drug absorption. The accuracy of CFD simulations will depend largely on the geometry, the physical models employed and the boundary conditions used in the simulation. Although CFD does not entirely eliminate the necessity for experimental work, it does provide quick and cost-effective evaluations of new designs and formulations, the drug delivery process, and the performance sensitivity of delivery systems to changes in parameters.

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Further information about Computation Fluid Dynamics can be obtained from the Fluent company website: www.fluent.com

**References**