

# Getting with the Flow

CFD flow simulation technology looks to revolutionise the development of needle-free epidermal vaccinations, reports Yi Liu at the University of Oxford.



Dr Liu graduated from Xi'an Jiaotong University, China, with a PhD in 1996 and commenced work primarily as a Postdoctoral Research Fellow at Seoul National University in South Korea and subsequently at the University of Surrey in the UK as a Research Fellow in fluid dynamics and thermodynamics. He joined the PowderJect Centre at Oxford University in January 2001 to work on numerical simulations of complex powder injection system, including the resolution of transient transonic/supersonic gas flow initiated by complex shockwave structures, interactions between those shocks and boundary layers, and performance analysis of the particle dynamics. He has published over 100 papers and is a senior member of CSME, AIAA.

In recent years, there has been a definite move to search for an effective alternative method for drug injections to that offered by needle-based delivery. This is because traditional needle and syringe administration has several drawbacks, including:

- ◆ Complexity of dose preparation
- ◆ Patient compliance
- ◆ Patient reaction to the reconstituted form of the drug
- ◆ Safety concerns related to the handling and disposal of used syringes

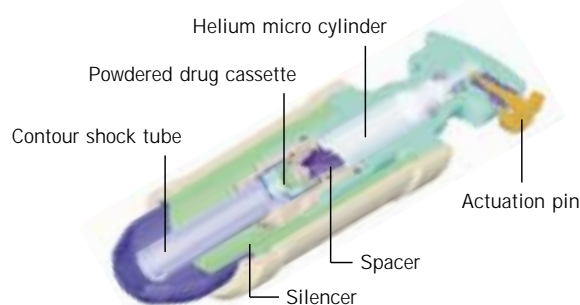
Several alternative drug delivery systems have been investigated, such as powder injection, together with techniques for the sustained release of drugs formulations, and the evaluation of new formulations for oral and injectable drug administration.

Traditional, needle-based delivery introduces a drug either intravenously or, more commonly, intra-muscularly for the delivery of vaccines (making use of the capillary network for distribution). Research in recent years has shown the human skin to be a safe and effective potential target tissue for vaccination, and it is now widely recognised as such. In particular, the underlying viable epidermis is of interest with its dense network of antigen-presenting cells (Langerhans cells) and relative lack of sensor cells. However, until recently, skin – a potent immunological induction site – has rarely been considered as a target organ for vaccination because of its limited accessibility by needle and its poor permeability to topically applied vaccines.

Using CFD flow simulation techniques, it has been possible to work towards the development of a unique needle-free device that overcomes these issues (see Figure 1). The device makes use of biolistics technology, where tiny particles are injected through cell walls by a high-powered gun. Configured to effectively deliver powdered vaccines in micro-particle form, it works through the skin into the viable epidermal layer where Langerhans cells reside.

The principle is to accelerate a measured dose of vaccine in micro-particle form by gas flow to an appropriate momentum in order to penetrate the outer layer of the skin, achieving a

Figure 1: Schematic of a Prototype Biolistics System, Configured for Clinical Use

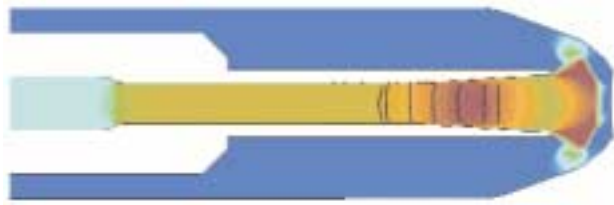


pharmacological effect. By targeting these cells, an optimal immune response can be elicited, potentially decreasing both the risk of disease and cost of protection. A key advantage is enhanced effectiveness with minimum health risk. For instance, particle-mediated DNA immunisation to the skin requires 0.4-4 per cent of the DNA required for intra-muscular injection. In addition, the approach is needle-free, pain-free and applicable to a wide range of pharmaceuticals. There are a number of applications for epidermal vaccination, some of which are in Phase I or II clinical trials, a few examples are:

- ◆ Influenza (Flu) vaccine
- ◆ Chronic Hepatitis B
- ◆ Lung Cancer
- ◆ AIDS (HIV)

Studies have employed CFD simulation software to gain the level of mechanism understanding required. The use of CFD as an analysis tool is increasingly common in the pharmaceutical, biotechnology and medical device industries, where its ability to predict fluid flow, chemical reactions and heat transfer, and display the results in formats including datasets and three-dimensional visualisations, makes it very useful in providing critical design insight. CFD is employed particularly for its comprehensive capabilities in modelling the biolistics system, from the transient gas and particle dynamics to interactions with the skin target. CFD works by using numerical methods to solve

Figure 2: Instantaneous Contour Plot of the Gas Velocity and Particle Trajectories for a Silenced Configuration, Taken 120µs After Diaphragm Rupture



the equations that govern fluid flow. A domain to be analysed is first determined and split into thousands of small three-dimensional cells known as a computational mesh. For each cell within the mesh, the fundamental equations (Navier-Stokes) for fluid flow are solved automatically to arrive at an overall solution.

CFD software tools can be used to improve the performance of the biolistics-driven needle-free device. This allows not only gaseous and liquid flows to be simulated, but the transport of micro-particles within these flows to be modelled (known as species transport). The unsteady motion and shock wave produced can all be accurately simulated using a CFD software tool. Using CFD, a variety of design changes can be quickly and efficiently analysed, with the drug particle transportation and distribution within the epidermis able to be predicted for each. Key parameters can also be evaluated.

The primary emphasis of these studies is to achieve new insights into the nozzle starting process and the interaction between gas and particles. These and other aspects of the needle-free vaccine delivery system have been explored numerically, using CFD flow simulation. Initial studies of gas and particle dynamics of prototype devices were explored experimentally and analytically. The results demonstrated that micro-particles were delivered within the range of velocities of 200-800m/s, and also with non-uniform spatial distribution (1,2).

However, for the powder injection concept to be optimised for a range of applications in vaccine delivery, systems should preferably deliver particles to the skin with a narrow and controllable velocity range and uniform spatial distribution. Subsequently, work using CFD has guided the development of alternative systems, configured to deliver particles to the target at a more uniform velocity and spatial distribution. These systems have been used in studies aimed at exploring the mechanism of ballistic mechanics of particles with tissue, with the spatial and velocity distribution of particles impacting the target being calculated (see Figure 2).

Simulations of the whole prototype biolistics system, as well as of the key components, have shown an excellent agreement with the static pressure measurements, Pitot probe survey, and images made using Doppler global velocimetry (DGV) and particle image velocimetry (PIV) (3,4). A space/time diagram that shows different gas flow regimes and particle cloud trajectories can be used to illustrate the performance of the prototype. The diagram demonstrates that the particles are accelerated to the nozzle exit, avoiding the starting process and the reflected expansion wave, and thereby remaining in the quasi-steady supersonic flow regime, as desired (see Figure 3). These results have allowed considerable progress in the development of an effective needle-free epidermal vaccine delivery system. ♦

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Figure 3: The Key Gas Flow Regimes and Particle Cloud Trajectories of the Prototype Biolistics System are Shown Together in the Calculated Space-Time (x-t) Diagram

