Numerical study of a transient gas and particle flow within a needle-free powdered vaccines delivery system

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Abstract

A unique vaccine delivery system, the Epidermal Particle Injection system (EPI), has been developed. The principle of this system is to accelerate pharmaceuticals in micro-particle form by a supersonic jet flow within a convergent-divergent conical nozzle, so that they can attain sufficient momentum to penetrate the outer layer of human skin and thus achieve a pharmacological effect. In this paper, Computational Fluid Dynamics (CFD) has been utilized to simulate the operation of the delivery system and the simulations have shown a good agreement with experiments. The key features of the gas dynamics and gas-particle interaction are discussed.

1 Introduction

Human skin consists of an epidermis of columnar epithelium and a dermis of fibrous connective tissue. The underlying viable epidermis, with its dense network of antigen-presenting cells (Langerhans cells) and relative lack of sensory nerve endings, has long been recognized as a safe and effective target tissue for vaccination [1]. So far, the most common route for human vaccines injection is intra-muscular vaccine injection. In contrast, skin, a potent immunological induction site, is rarely used for vaccination because of its poor accessibility by needle and its poor permeability to typically applied vaccines.

A unique needle-free Epidermal Particle Injection system (EPI) has been developed [2-6]. This technology can effectively deliver powdered vaccines to the viable epidermis by using a helium powered, needle-free system. The
underlying principle of the EPI system is to accelerate a pre-measured dose of
the vaccine in micro-particle form to appropriate momentum by a high speed gas
flow in order to penetrate the outer layer of the skin to achieve a pharmacological
effect. There are many advantages in terms of effectiveness, cost and health risk.
The EPI system delivers powdered vaccine into a desired epidermis layer of skin
to achieve the optimal effect with a simple administration. Administering
vaccines to the skin is very efficacious. Particle-mediated DNA immunization to
the skin requires 0.4–4% the DNA required for intra-muscular injection [7]. It is
needle-free and has been shown to be painless and applicable to a wide range of
pharmaceuticals.

The gas and particle dynamics of earlier prototypes have been explored
experimentally [3-6]. This has been followed by the development of alternative
systems configured to deliverer particles to the target with a more uniform
velocity distribution [8, 9]. In this paper, we seek to computationally further
investigate the performance of earlier particle delivery systems. We begin with a
brief description of EPI system, followed by a presentation of Computational
Fluid Dynamics (CFD) methodology. The gas flow is then analyzed by solving a
set of differential equations. A drag correlation is employed to explore the gas
and particles interaction. Comparison is made with the published pressure
histories, Schileren photographs [5] and Doppler Global Velocimetry (DGV)
images of the particle velocity. The overall capability of the EPI system to
deliver the particles to human skin with a certain velocity range and spatial
distribution is analyzed though a series of numerical calculations. The primary
emphasis of this study is to achieve new insights into the nozzle starting process,
the over-expanded nozzle flow pattern and interaction between gas and particles.

2 Description of delivery system

A schematic of a commercial EPI system, which is configured for clinical use, is
shown in the Fig. 1, with an actuation pin, a helium micro-cylinder, a powder
vaccine cassette, a converging-divergent nozzle and silencer.

Figure 1: A commercial EPI system.
The medical-grade compressed helium gas is stored in the micro cylinder, typically at 10~60 bar. When the device is activated, the released helium gas ruptures membranes of the vaccine cassette and leads to the formation of a shock wave, which propagates down the nozzle and initiates an unsteady gas flow, as in a classical shock tube theory with consideration of area change [11]. Later, a sustained bulk flow of gas from the cylinder is established. In the course of these processes, particles are entrained in the gas flow and accelerate towards the nozzle exit. As the gas-particle flow impinges on the skin target, gas is deflected away and exhausted through the vented silencer. The particles, with their relatively large inertia, penetrate the stratum corneum and land in the epidermis.

A prototype of EPI system under numerical investigation is illustrated schematically in Fig. 2, the same configuration was studied experimentally (Kendall et al [5]).

![Configuration of prototype EPI system.](image)

In contrast to the clinical EPI system (shown in Fig. 1), a valved gas canister is employed instead of micro-cylinder. The silencer is not considered here. Prior to operation, the gas canister is filled with helium gas to a pressure of about 6 MPa and a polycarbonate diaphragm of 20 µm thickness is loaded with a powdered particle payload of 1.0 mg. The model particles for numerical simulation and experiment studies were 4.7 ± 0.4 µm diameter polystyrene spheres with a density of 1050 kg·m⁻³, supplied by Duke Scientific™.

3 Governing equations and numerical procedure

Computational Fluid Dynamics (CFD) has become an integral part of the design and analysis of the particle injection system. In order to better understand the flow physics and explain the experimental observations, CFD is utilized to simulate the complete operation of the prototype EPI, as illustrated in Fig. 2.

3.1 Governing equations for multi-species gas and particles flow

The 2D axisymmetric Reynolds Averaged Navier-Stokes (RANS) equations are

\[
\frac{\partial W}{\partial t} + \frac{\partial F_i}{\partial x_i} = \frac{\partial^2 G_i}{\partial x_i^2} + H
\]

(1)
where \( W = [ \rho, \rho u, \rho v, \rho E]^T \) is the vector of independent variables with variables \( \rho, u, v \) and \( E \) denoting density, velocity components in the \( x \) and \( r \) direction and specific total energy. \( F, G \) and \( H \) are the convective, viscous flux vector and source term, respectively. More details can be found in Ref. [12].

The mass fraction of each species \( m_j \) is predicted through the solution of a convection-diffusion equation for the \( j^{th} \) species

\[
\frac{\partial}{\partial t} (\rho m_j) + \frac{\partial}{\partial x_i} (\rho m_j u_i) = -\frac{\partial}{\partial x_i} (J_{j,i}) + R_j + S_j
\]

(2)

where \( R_j \) is the mass rate of creation or depletion by chemical reaction, and \( S_j \) is the rate of creation by addition from the dispersed phase plus any user defined source. \( J_{j,i} \) is the diffusion flux of the \( j^{th} \) species, which arises due to concentration gradients.

The equation of motion for the particles, which also includes the force of gravity, can be written as

\[
\frac{d\tilde{u}_p}{dt} = \frac{3 \mu}{\rho_p D_p^2} C_D \frac{Re_p}{4} (\tilde{u}_g - \tilde{u}_p) + \frac{g(\rho_p - \rho)}{\rho_p}
\]

(3)

where \( \tilde{u}_g \) and \( \tilde{u}_p \) are the fluid velocity and the particle velocity, respectively; \( \rho_p, D_p \) are the particle density and the particle diameter; \( Re_p \) is the relative particle Reynolds number.

The velocity of the particles is obtained over discrete time steps along the trajectory, with the trajectory itself predicted by

\[
\frac{dx}{dt} = \tilde{u}_p
\]

(4)

### 3.2 Turbulence model

It is well known that no general turbulence model is universally accepted for all classes of problems. For robustness, economy, and reasonable accuracy for a wide range of turbulent flows in industrial and heat transfer simulations, the two-equation turbulence models appear to be the most appropriate model [13].

\[
\rho \frac{Dk}{Dt} = \frac{\partial}{\partial x_i} \left[ (\mu + \frac{\mu_t}{\sigma_k}) \frac{\partial k}{\partial x_i} \right] + G_k + G_b - \rho \frac{e}{k} - Y_M
\]

\[
\rho \frac{De}{Dt} = \frac{\partial}{\partial x_i} \left[ (\mu + \frac{\mu_t}{\sigma_e}) \frac{\partial e}{\partial x_i} \right] + C_{le} \frac{e}{k} (G_k + C_{2e} G_b) - C_{2e} \frac{e^2}{k}
\]

(5)

Given the nature of the current application and the required accuracy, the standard \( k - e \) turbulence model of eqn (5), is considered. The source terms and damping function are introduced in the near wall region.
3.3 Drag correlation

The solution of eqn (3) requires knowledge of the gas flow field as well as the variation of the drag coefficient with relative Reynolds and Mach numbers. The flow field can be obtained by solving the RANS equations. Meanwhile, the drag correlations proposed by Igra and Takayama [14], which consider the unsteady effects and cover a wider range of Reynolds number (200 to 101,000), has been implemented into Fluent (UDF) to evaluate the drag coefficient

\[
\log_{10} C_D = 7.8231 - 5.8137 \log_{10} Re + 1.4129(\log_{10} Re)^2 - 0.1146(\log_{10} Re)^3
\]

3.4 Initial and boundary conditions

Consider the geometry of the experiment (Fig. 2), a diaphragm within the cassette initially separates high-pressure driver gas (mixture of helium and air) and driven gas (air) at atmospheric pressure as shown in Fig. 3. The inlet flow to the canister through an orifice on the driver endwall before diaphragm rupture has been simulated. The driven section is included when the averaged pressure in the canister reaches the diaphragm rupture pressure of approximate 1550 kPa.

![Figure 3: Schematic diagram of computational domain and boundary condition.](image)

The atmospheric pressure is given across the section of outlet boundary, the total temperature needed only for the reverse flow condition. The device wall temperature is assumed to remain at constant temperature during operation, with non-slip wall condition. The non-reflected boundary condition is set for the far-field boundary, with free-stream Mach number and static conditions being specified. Figure 3 shows a schematic diagram of computational domain, with boundary condition marked.

3.5 Computational grid

The flow fields under consideration have circular cross sections and the flows are assumed to be axisymmetric. The computational domain (shown in Fig. 3) has been extended to be 40D x 20D (D, diameter of the nozzle throat). The CFD calculations with the different combination of grids, physical models and the particle drag correlations are conducted for the purpose of grid independency and drag law for the micro particle in the transient supersonic flow studies. The grid has 22140 cells with 250 points along the axis direction and 61 points in the radial direction inside the nozzle. The mesh is concentrated near the...
wall and well placed in the region of interest, with the first adjacent cells being 10.6 \( \mu m \) away from the wall.

### 3.6 Numerical procedure

The transient gas flow and its interaction with particles are modeled simultaneously and interactively. The solution of multi-species gas phase is obtained by numerically solving the RANS equations (1), together with turbulence model (5), and species transport equation (2). The particle trajectory equations (3) and (4), aided by the drag correlation, are advanced in time with gas flow simulation. The inter-phase exchange of momentum and heat is considered in each time step. An overall second order accuracy is required both spatially and temporally.

For the solution, Fluent, commercial CFD software [12], is chosen to numerically simulate the gas and particles flow within the prototype of the EPI system. A coupled explicit solver is selected in order to capture the main features of the unsteady motion of the shock wave process. The convective flux is discretized by an upwind Roe’s FDS (Flux Difference Splitter) method [17]. The quantities at cell faces are computed using a multidimensional linear reconstruction approach, in which higher-order accuracy can be achieved at cell faces through a Taylor series expansion of the cell-centered solution about the cell centroid. The viscous term is evaluated by the central difference. Time integration has been explicitly performed. A multi-stage (Runge-Kutta), time stepping algorithm is employed to achieve a desired temporal accuracy.

The numerical approach used here has been validated with studies of a number of similar shock tube based particle injection systems [9, 10], particularly in which different drag correlations of Igra & Takayama [14], Henderson [15] and Kurian & Das [16] have respectively been assessed. The results presented in this paper are obtained with the turbulence calculation and with drag correlation of Igra & Takayama, which shows the best agreements with experimental measurements in those applications.

### 4 Results and discussion

#### 4.1 Gas flow

The transient calculation for the nozzle flow is started when the pre-simulated averaged pressure in the rupture chamber (\( P_2 \), with the location marked in Fig. 2) reaches approximate 1550\( kPa \) of diaphragm rupture pressure.

The measured canister pressure history (\( P_1 \), in Fig. 2), in conjunction with the assumed choked flow condition, is imposed as the inlet pressure boundary condition. An ideal diaphragm rupture is also assumed. The calculated pressure history in the rupture chamber, compared with pressure transducer measurement (Kendall, [5]), is shown in Fig. 4a, with time zero from diaphragm rupture. In general, the solution shows good agreement with the experimental data.
Fig. 4 also respectively shows the pressure traces at nozzle location P3, P8 and P10, which illustrate a typical starting process for a supersonic nozzle. The flow is initiated by a primary shock (indicated by the sudden pressure rise), which opens a transient starting process, followed by a quasi-steady flow region. The quasi-steady region is then terminated by the upstream oblique shock wave, which originates at the nozzle exit wall due to over-expanded condition. Here, the starting process is well modeled in terms of shock strength and termination time.

Fig. 5 presents the simulated contour plots of strain rate at two different stages compared with corresponding Schlieren photograph, in which primary, contact surface and oblique shocks (secondary shocks) are respectively marked (Fig. 5a). The strain rate, which is represented by velocity gradient along axis and radial direction, indicates the degree of flow distortion (compression/expansion waves, shocks and separations, etc.) defined as $s = \partial_x v + \partial_r u$ [18]. Thus, the strain rate is one of the important parameters that illustrate the flow structure characteristic.

The calculated strain rate contours give a very clear flow pattern, which are quite similar to the experimental Schlieren photographs. The CFD predicted inclination of the oblique shocks is higher than that seen in the Schlieren photographs at a time of 354 µs after diaphragm rupture (Fig. 5b). This discrepancy is attributed to the experimental work using circular-to-square section of the nozzle (Kendall, [5]).
In general, key flow features, such as formation and propagation of the primary and secondary shock, separation zone, unsteady expansion/compression waves and the oblique shock, are clearly shown.

Figure 5: Visualization of the nozzle flowfield after diaphragm ruptures (Up: Schlieren photograph, Down: contour of strain rate).

Figure 6: Calculated and experimental axial Mach number profiles.

These visualizations, together with pressure histories in Fig. 5, demonstrate that the transient nozzle starting process has been reasonably predicted by the numerical method employed in this paper.

A comparison between the simulated and experimentally derived axial flow Mach number, obtained from Pitot probe and static pressure transducer measurements by using Rayleigh Pitot tube formula, is shown in Fig. 6. The error bar is marked in the exit plane. The experimental results shown are averaged Mach numbers, since the diameter of the Pitot probe is about 2 mm in contrast with 10 mm of the exit nozzle plane diameter. The pressure histories show a strong oscillation due to the transient shock waves and the resultant flow separation. In fact, the simulated Mach number distribution along the nozzle axis accurately captures the effect of the oblique shocks.

Further insights are obtained through examination of the gas flow field near the nozzle exit as shown in Fig. 7, when the oblique shock terminates the nozzle
starting process, identified in Fig. 5 to be 354 μs after diaphragm rupture. The structure of oblique shocks and their reflections can be identified in Fig. 7a, which is clearly observed in pressure contours expressed on logarithmic scale. The oblique shock interacts with the boundary layer and flow is separated from the nozzle wall. The oblique shock structure and resultant separation, shown in Fig. 7b and Fig. 7c, would seriously deteriorate the flow aerodynamics. This oblique shock wave system and resulting flow separation has a significant effect on the performance of a transient nozzle in a vaccine delivery device, since the vaccine particles will be delivered by a separated jet.

![Contour plot of static pressure (logarithmic scale).](image)

(a) Contour plot of static pressure (logarithmic scale).

![Velocity vector and contour plot of Mach number.](image)

(b) Velocity vector and contour plot of Mach number.

![Contour plot of density.](image)

(c) Contour plot of density.

Figure 7: Flowfield of the nozzle at time of 354 μs after diaphragm ruptures.

4.2 Particle flow

The particle dynamics are calculated by introducing eqn (4) to the generated transient gas flow field. In the calculation, the particles are assumed to be initially arranged in a matrix representing all the different possible positions within the vaccine cassette (shown in Fig. 3).

A comparison between the calculated particle velocity and trajectories, obtained with the transient gas-particle simulation, and measurements of the DGV by Quinlan [4] has been made. The simulated particle distributions, measured velocity images at the time of 67 μs and 177 μs after diaphragm rupture are shown in Fig. 8. In general, the simulated results show good agreement with the DGV images in terms of the particle velocity magnitude and locations.
5 Conclusions

Transient gas and particles dynamics within a prototype Epidermal Particle Injection system (EPI) have been investigated numerically. A CFD methodology has been implemented in order to gain new insights into the behavior of the convergent-divergent supersonic nozzle used to accelerate micro particles to impact the outer layer of human skin.

Simulated pressure histories and Mach number distributions agree well with the corresponding reported static and Pitot pressure measurements. Comparison with Schlieren photographs and pressure histories indicate that the shock waves are accurately captured with a numerical approach. These calculations have been used to further explore the gas flow field, with an emphasis on the nozzle starting process.

The action of the gas flow accelerating the particles was calculated by implementing drag correlation within a turbulent modeled flow field. Furthermore, the calculations and DGV images both show that pressure losses and large area ratio have resulted in over-expanded nozzle operation. This has led to gas and particle flow non-uniformities generated by an oblique shock wave system along with associated flow separation within the starting process and the subsequent quasi-steady supersonic flow. Recently, research has been directed towards providing new EPI systems based upon shock tubes. They can deliver particles with a narrow and more controllable velocity and spatial distribution [8].

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References


