Investigations of gas and particle dynamics in first generation needle-free drug delivery devices

N.J. Quinlan1,∗, M.A.F. Kendall1, B.J. Bellhouse1, R.W. Ainsworth2

1 PowderJect Centre for Gene and Drug Delivery Research, University of Oxford, Oxford OX2 6PE, UK
2 Department of Engineering Science, University of Oxford, Oxford OX1 3PJ, UK

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Abstract. Transdermal powdered drug delivery involves the propulsion of solid drug particles into the skin by means of high-speed gas-particle flow. The fluid dynamics of this technology have been investigated in devices consisting of a convergent-divergent nozzle located downstream of a bursting membrane, which serves both to initiate gas flow (functioning as the diaphragm of a shock tube) and to retain the drug particles before actuation. Pressure surveys of flow in devices with contoured nozzles of relatively low exit-to-throat area ratio and a conical nozzle of higher area ratio have indicated a starting process of approximately 200 µs typical duration, followed by a quasi-steady supersonic flow. The velocity of drug particles exiting the contoured nozzles was measured at up to 1050 m/s, indicating that particle acceleration took place primarily in the quasi-steady flow. In the conical nozzle, which had larger exit area ratio, the quasi-steady nozzle flow was found to be overexpanded, resulting in a shock system within the nozzle. Particles were typically delivered by these nozzles at 400 m/s, suggesting that the starting process and the quasi-steady shock processed flow are both responsible for acceleration of the particle payload. The larger exit area of the conical nozzle tested enables drug delivery over a larger target disc, which may be advantageous.

Key words: Needle-free drug delivery, Transdermal powdered drug delivery, Powder injection, Biolistics, Supersonic nozzle, Shock tube, Doppler global velocimetry

1 Introduction

Over the past five years, a new technology for the needle-free injection of drugs into the skin has emerged. The underlying principle is to accelerate powdered drug particles to an appropriate velocity in a gas jet, directed towards the skin, such that they can pass through the outer skin and lodge in deeper layers of tissue without causing injury or pain. This technology, known generically as transdermal powdered drug delivery, was first patented by Bellhouse et al. (1994) and is being developed commercially as the PowderJect system. It has been shown to be a viable alternative to injection by needle and syringe for many applications (Burkoth et al. 1999). Moreover, it can enhance the potential of a variety of drugs and vaccines which is limited by available delivery methods.

Transdermal powder drug delivery has many advantages over other techniques. Most obviously, it is painless and causes no injury, unlike liquid jet injectors and the conventional needle and syringe. It does not leave dangerous sharps for disposal, create a contamination hazard, or require a skilled operator. It shares some of the advantages of the needle and syringe in offering rapid action and localised delivery, when required. The direct use of drugs in powder (rather than liquid) form is attractive in itself, since drugs are often manufactured and distributed as powder for compact storage and improved chemical stability, and must be constituted as a liquid prior to use in a needle and syringe. In addition to these logistical advantages, this drug delivery technique can enhance the power of certain new and existing treatments. DNA vaccines, for example, as well as some conventional vaccines and anti-viral drugs, benefit from delivery to particular layers within the skin, which is difficult to achieve accurately with conventional technology. The PowderJect system offers the potential to target these specific layers through control of drug particle kinetic energy (and hence, penetration depth), or at least to achieve blanket delivery into the shallow regions of the skin. Drugs which require self-administration, or local delivery to sensitive sites, can be made more attractive and accessible for the patient with this technology.

Successful implementation of this simple concept is not trivial. In order to achieve an optimal biological response, it is desirable to deliver the drug particle payload
with uniform velocity and particle number density over the largest possible area. This capability must be available in an economical, compact (hand-held), robust and acoustically quiet system. Future applications of the technology may call for devices with adjustable performance in order to accommodate a variety of drugs and doses. These criteria demand a thorough fundamental understanding of physical and biological processes underlying transdermal powdered drug particle delivery. A substantial multidisciplinary programme of research has been directed towards this goal.

An integrated review of the medical, pharmacological and engineering aspects of the technology has been given by Burkoth et al. (1999). The paper includes descriptions of clinical trials in which efficacious delivery was achieved for lidocaine, a local anaesthetic, and encouraging results were obtained for alprostadil, which is used in the treatment of male erectile dysfunction. Recently, Kendall et al. (2000) have described fundamental investigations of the biomechanics of powder injection, using a calibrated piston-based test system to propel particles into excised skin at known velocities up to 260 m/s. It was demonstrated in these experiments that particles can penetrate the stratum corneum (the tough outermost layer of the skin) to reach underlying tissue, and the dependence of penetration depth on particle velocity, size and density was characterised.

This interaction between high-velocity drug particles and biological tissue is one essential facet of the complete powder injection system. The means of imparting momentum to the powdered drug dose is equally important. In the practical drug delivery devices to be discussed here, particles are accelerated by entrainment in a high-speed gas flow. Particular aspects of the fluid dynamics of certain devices have been discussed by Bellhouse et al. (1997) and Quinlan et al. (1997). The present paper is an integrated account of research into the fluid dynamics of early generations of prototype practical dermal PowderJect devices in which gas-particle flows are exploited to realise the concept of high-velocity particle injection.

The overall objective of this research is to arrive at an understanding of the mechanisms which determine the distribution and velocities of drug particles accelerated through these prototype drug delivery devices. Particle velocity and distribution (along with the mechanical properties of particles and skin) are fundamentally important characteristics which determine the efficacy of drug delivery. In order to explore the fluid dynamics which underlie these aspects of device performance, prototype devices were characterised experimentally by pressure surveys and field measurements of time-integrated particle velocity. Analytical modelling of bulk gas flows in the devices has also been carried out. This research has been concerned with three prototype device nozzles, which will be discussed in detail below.

## 2 Prototype devices tested

The configuration of a clinical device for transdermal powdered drug delivery is shown in Fig. 1. The key components of the device are a gas reservoir, in which compressed helium is stored, typically at a pressure of tens of atmospheres; a drug cassette, in which the powdered drug is retained between a pair of bursting membranes; and a convergent-divergent nozzle. Basic compressible flow theory provides a qualitative description of this system’s expected mode of operation. When gas is released from the reservoir, a large pressure difference builds up across the drug cassette. The membranes rupture, leading to the formation of a shock wave, which propagates down the nozzle and initiates an unsteady high-speed gas flow, as in a classical shock tube. Later, a sustained bulk flow of gas from the cylinder is established, and under certain conditions, the device’s convergent-divergent nozzle functions as a supersonic nozzle. In the course of these processes, particles are entrained in the gas flow and accelerate towards the nozzle exit. As the particle-laden flow impinges on the skin, gas is deflected away to the side and vents to the atmosphere through a silencer. The particles, with their relatively large inertia, maintain a high axial velocity and penetrate the tough outer layer of dead cells (the stratum corneum), coming to rest in deeper layers of the skin. There, the drug either acts locally, or diffuses into the bloodstream for systemic effect.

The configuration of the prototype devices tested here is illustrated in Fig. 2. In contrast with the production design shown in Fig. 1, these prototypes feature an annular valve at the downstream end of the cylindrical reservoir, connecting the reservoir to the rupture chamber. The prototypes were tested without a silencer for the purposes of this investigation. Devices were tested with two contoured nozzles, which differed in their nominal exit Mach numbers, and a conical nozzle, with a substantially larger exit area.

A geometric description of each nozzle is given in Table 1. Some nozzle flow parameters, calculated for steady quasi-one-dimensional isentropic flow, are also included to