Development of Novel Arrayed Microjet Devices for Transdermal Drug Administration


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ABSTRACT SUMMARY

The micro-arrayed needle-free injector technology being developed for trans-dermal vaccine administration is based on PARC’s work on ballistic aerosol transport. The underlying idea is to use high speed air jets (at sonic to supersonic speeds) in order to accelerate entrained particles at sufficiently high speeds such that their kinetic energy would be sufficient to cause penetration or interaction with a substrate. This multi-year effort resulted in the development of a number of devices capable of producing high-speed air jets using microchannel-based arrayed venturi structures that were shown to successfully create print images using toner particles (typically in the size range of 4 to 8 µm). Recently, we have also successfully used such approach to deliver liquid jets. In this paper we describe a project to leverage this technology and PARC’s significant know-how in this area to develop novel drug delivery devices for transdermal administration of encapsulated powder vaccines.

INTRODUCTION

The limitations of traditional approaches such as needle-based injections for vaccine delivery have stimulated the development of needle-free jet injectors over the past decades. While several jet-based transdermal drug delivery technologies have been used for administering a variety of vaccines and protein drugs, needle-free jet injectors face significant challenges, such as frequent bruising and pain, contamination and low bioavailability per dose. The resulting minimal acceptance of these technologies has been disappointing.

Leveraging decades of micro-jetter research for toner manipulation and ink-jet printing, PARC is developing a supersonic micro-jet device to transdermally administer vaccines in a safe and cost effective manner while maximizing therapeutic efficacy.

The basic principle behind the device operation is illustrated in Figure 1. Pressurized air (50 to 75 psi) is provided at the inlet of microchannels with nominal cross-sectional dimensions ~100 µm to 600 µm. A venturi structure inside the channels causes rapid acceleration of the flowing air post-constriction, where the drug (vaccine) particles are entrained by the mild suction caused by a brief drop in the air pressure. The entrained particles rapidly accelerate to the speed of the air jet prior to exiting the channel (on the right side in Figure 1). We have shown experimentally as well as through detailed modeling work that the jets stay well-collimated and maintain their high speeds for up to a few millimeters from the exit. The particle jets will thus create the desired impingement and penetration into the skin in order to elicit the appropriate immune response.

EXPERIMENTAL METHODS

Figure 2 below shows some views of actual test devices fabricated at PARC. The devices consist of parallel arrays of a large number of delivery channels similar to those shown above in Figure 1, thus allowing for selection of an appropriate number of active microchannels depending on the desired dosage. Real-time switching of the desired number of channels can enable in-situ dosage selection based on individual patient requirements as well as compensation for variations in local skin conditions based on real-time measurements of characteristics such as skin thickness and elasticity (modulus), and the expected bounce-back/scatter related losses. The fabrication of the devices involves standard micro-electromechanical system (MEMS) processing techniques including photolithography for patterning the channels and venturi structures, followed by deep-reactive ion etching (DRIE) for creating the desired structures in silicon and anodic bonding for attaching a cover glass to create the sealed flow paths. Inlet ports for air are created in the cover glass by drilling (Figure 2 [a]), followed by interfacing to controlled pressurized air (Figure 3 below). Back-side etched holes in the silicon serve as the post-venturi drug particle inlet ports (holes seen in Figure 2[c]).

Test cells used for device testing and performance characterization are shown in Figure 3. For continuous operation (as opposed to one-shot application that will be used in the final device), a fluidized zone of the particles is created under the drug inlet ports using piezo actuation and low pressure air (Figure 3 [a]).
This sustained ‘cloud’ of particles in the test chamber and the continuous air jet created using the high pressure air enables continuous operation of the device for testing and characterization under various actuation pressures and corresponding particle speeds and throughputs.

RESULTS AND DISCUSSION

A high-speed recording (12930 fps) of a magnified view of the channel exit during testing is shown in Figure 4. The particles can be seen approaching the field of view (FOV) in Frame 1. It is important to note that even at this high frame rate and short exposure (76 µs) per frame, the particles in motion appear to be significantly blurred compared to the static particles shown in Frames 1 and 2 at the top portion of the channel near the exit. Frame 3 shows the single dose of particles completely covering the FOV and the remaining frames 4 – 6 show the single-shot dose finishing up and clearing out of the channel. The transfer of the entire dose of packed particles (about 150 µg) took 1 millisecond in this case.

The delivery technology will be based on 1) a reusable hand-held applicator designed to reproducibly interface with the skin and controllably trigger the input carrier gas used for therapeutic delivery and 2) a disposable drug cartridge containing the sealed therapeutic agents which, upon triggering, releases the agents into a supersonic (> 340 m/s) micro-jet perpendicular to the skin. The ballistics of the particles will be designed to maximize delivery across the stratum corneum into the adjacent cell layers below (granular and spinous) while minimizing penetration deeper into the dermis and the associated pain (Figure 5). Test injections with a prototype device onto 20% polyacrylamide gel (simulates skin Young’s modulus) suggests a penetration of up to 40 µm by optical microscopy, which will be further analyzed and confirmed by microtome.

CONCLUSION

At the current phase of the development of the micro-arrayed venturi structures, focus is placed on repeatability of jetting, the trajectory and the speed. A high speed camera (DiCam Pro, PCO-Tech), a high power flash lamp and a long working distance microscope (Infinity K2) system have been acquired and will be used to measure supersonic speeds (Figure 6). It is well-known that the thickness of the stratum corneum is fairly variable, based on a number of factors including the subject, the body location and many others. In a study of Japanese adults, the average thickness is 20-30 µm on the forearms or back of hands. Fine-tuning the penetration depth using pig skin from 20-120µm will be performed in the next phase prior to using human skin. After vaccine particle administration with the supersonic micro-jet device, the skin will be snap frozen immediately in a tissue freezing medium. A cryo-microtome (Leica CM-1950, Figure 7) has been used to successfully section frozen steak in 10 µm thickness which can be customized to the eventual vaccine particle size, so that localization (depth of penetration) of the embedded particles and the morphology of their surrounding tissues are preserved. In vitro and in vivo vaccine efficacy tests will also follow.

REFERENCES