MICRO-ABLATION OF SKIN BY ARC-DISCHARGE JET EJECTION FOR TRANSDERMAL DRUG DELIVERY

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Abstract: This paper presents the design, fabrication and characterization of a jet ejection device that operates on the actuation principle of arc discharge for the purpose of generating micron-scale pores in skin. This thermo-mechanical micro-ablation technique increases skin permeability to drugs, while expected to maintain the patient friendliness of conventional transdermal patches. Laser micromachining and lamination techniques were utilized in fabricating these arc-discharge jet ejection devices. The released jet from the device is characterized in terms of its force, velocity and temperature and is used in skin ablation experiments. The skin is exposed to the jet and the permeability effects are characterized. Skin permeability was increased by approximately three orders of magnitude after jet exposure when compared to non-exposed controls, which is a significant advance for transdermal drug delivery.

Keywords: Transdermal drug delivery, Arc-discharge, jet ejection, Micro-ablation

1. INTRODUCTION

Transdermal drug delivery [1] has gained importance recently as a means of delivering drugs to a patient across the skin. This delivery approach enables convenient delivery of drugs that cannot be taken orally due, e.g., to enzymatic degradation of the drug in the gastrointestinal tract or poor intestinal absorption. Additionally, transdermal delivery offers the possibility of controlling the delivery rate of a drug in a continuous and time-controlled manner from a passive or active patch in contrast to conventional methods, such as hypodermic needle injection, that are more suited for bolus delivery.

Despite these advantages, transdermal delivery methods are highly constrained by the fact that the thin outer layer of skin, a nonviable tissue called *stratum corneum,* is very hard to permeate. If the drug can successfully permeate the *stratum corneum*, the underlying viable epidermis layer, which is 50-100 μm thick containing living cells and nerves, is relatively easy to permeate. For this reason, a variety of chemical and physical techniques have been developed to increase transdermal delivery and have focused on creating nanometer-to-micron-scale disruptions to the *stratum corneum*, thereby increasing skin permeability.

Chemical approaches, involving solvents, surfactants and other compounds, have had varied success, but the permeability enhancement achieved is typically limited to smaller molecules, as opposed to many modern therapies which are protein-based. Physical approaches to permeability increase, such as iontophoresis, electroporation and ultrasound, perturb the *stratum corneum* structure, and are more effective in increasing skin permeability to a wider variety of macromolecules; however, the obtained increase in transdermal transport is still not sufficient for many drugs under clinically relevant conditions. Creating holes of micron-sized dimensions in the *stratum corneum* should permit the delivery of a broad range of compounds, making the skin much more permeable yet maintaining safety and patient compliance. A number of methods to disrupt the *stratum corneum* on the micron scale have been developed, including thermal ablation, jet injection and microneedles.

We present a skin ablation approach that generates micron-scale pores localized to the stratum corneum, and demonstrate an increase in

skin permeability of three orders of magnitude *in-vitro*. This approach involves a combined thermal and mechanical ablation method operating over extremely short time scales. This thermo-mechanical ablation method is carried out by accelerating a microfluidic jet of vapor, and optionally liquids and even solids, from an array of microchambers. This microjet is ejected by an electrically-driven arc across a microjet-formulation precursor ('ejectate formulation') positioned between two electrodes. Typical formulations are FDA-approved and water-based solutions. Impingement of the microjet onto the skin results in ablation of the *stratum corneum* layer and enhanced skin permeability.

2. DESIGN AND FABRICATION

The microjet device utilizes the concept of generating heat rapidly within the device by passing a current through the ejectate formulation. This current generation is most effectively accomplished by generating an arc: applying a high voltage pulse across closely spaced electrodes. This discharge of high currents through the ejectate formulation drives the ejectate in the form of a jet through a constriction at high velocity [2]. This high velocity jet is then used to create micro pores in the exposed skin surface.

In fabricating these microjet ejectors, micromachining approaches were considered with primary emphasis placed on utilizing the simplest fabrication schemes available. Also, as these microjet ejectors are one-time-use devices, fabrication techniques that enable easy batch fabrication (and concomitant ease of high volume manufacturing) were considered. Laser micromachining techniques and lamination of low-cost polymers and metals were used for fabricating different components of the microjet ejector. Fig. 1 shows a schematic of a single arc-discharge jet ejector fabricated by laser micromachining.

The microjet ejector assembly has four basic components: a micro-chamber, two electrodes and a nozzle. The chamber houses fluid to be ejected, typically an aqueous solution containing a drug or a drug model, salt, gelling agent and optional gold particles, while the electrodes were used to create an arc discharge within the chamber.

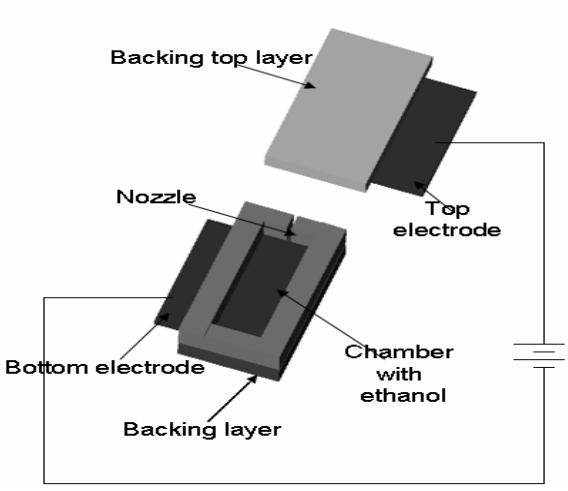

Fig. 1 Schematic of a single jet ejector system.

The chamber and the substrate layers are patterned in a mylar layer, which is a low cost polymer, using a CO_2 laser that has a spatial micromachining resolution of 100 μm. The thickness of the chamber layer is 250 μm. The electrodes were made by patterning an inexpensive thin metal film such as brass or nickel using an IR laser. Feature sizes as small as 60 μm can be machined by the IR laser. The thickness of the metal used is approximately 25-50 μm. Conical or cylindrical nozzles are fabricated either by integrating these along the chamber in the same layer or are fabricated as a separate layer. These layers are then adhered together and laminated to the substrate layer in a hydraulic press between aluminum molds.

The lamination sequence consists of the following steps: 1) Laminate the bottom electrode onto the base substrate. The base substrate helps provide the mechanical strength to the electrode layer, thus reducing any deformations caused due to mechanical or thermal effects during operation. 2) The chamber and nozzle layers are then laminated on top of the bottom electrode and the chamber is filled with the desired solution. 3) The filled chambers are sealed by laminating with a top electrode and a supporting backing layer.

Both individual devices as well as arrays were fabricated. As the creation of arc discharge depends strongly on the distance between the electrodes, optimum chamber thickness is chosen based on this distance. Nozzles with diameter ranging from 50 to 400 μm and chambers with volume ranging from 1-8 mm^3 with distance

between electrodes of 250 μm were considered. The device was actuated by applying a charged capacitor to the device electrodes through a MOSFET switch and, upon triggering of the switch, discharging the capacitor through the ejectate formulation via the electrodes. Capacitances varying between 100-600 μF and minimum voltages of 150 V were supplied for a time span of 0.1-5 ms.

To further localize the exposed area and to control the size of skin ablation in a rapid and highly targeted manner, the microdevice surface is covered with a PDMS mask of rectangular holes aligned with the micronozzles. Corresponding to a mask size of 100 μm x 100 μm, the holes generated in the skin measured approximately 100 μm in size. The size of these holes could be changed by simply changing the size of the masking holes on the microdevice.

3. DEVICE CHARACTERIZATION

The characterization process involves the activation of the device while imaging it using high speed microscopic photography, and in some cases simultaneously measuring the reaction force produced by the jet. Fig. 2 shows an image of the jet emitted from the microdevice upon activation.

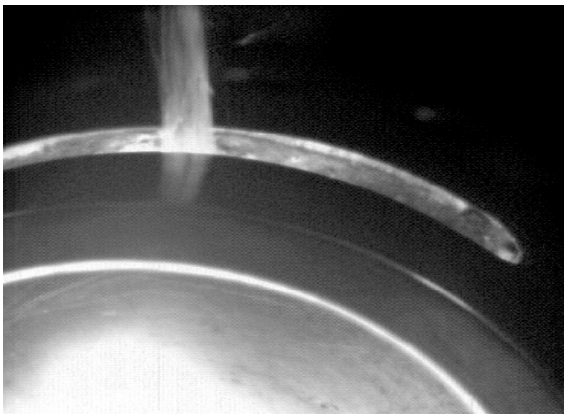

Fig. 2 Jet released from the nozzle.

The device is then placed in contact with human cadaver skin, actuated, and the skin is imaged and assessed with respect to its permeability to a fluorescent drug analog, calcein. Histological examination of skin showed highly selective removal of *stratum corneum* without visible damage to the viable epidermis, as shown in Fig. 3.

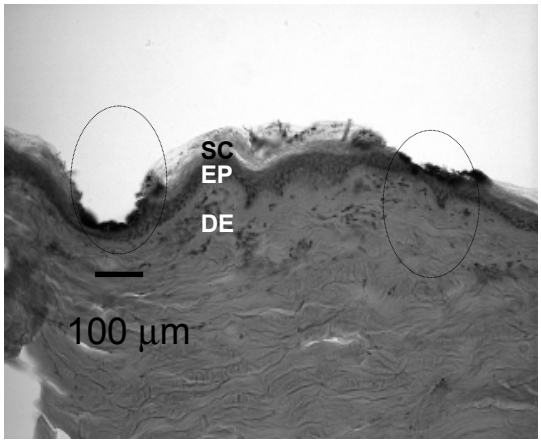

Fig. 3 Exposed skin: Outer layer of stratum corneum is removed.

The observed efficient removal of stratum corneum is expected to increase skin permeability. Fig. 4 shows permeability measurements made for delivery of calcein across human cadaver skin. For untreated skin, this permeability is just 10^{-5} cm/h, because calcein is a relatively large (623 Da), hydrophilic compound. After arc ablation of the skin with water, the permeability is increased by 1000 fold to a value of 10^{-2} cm/h. This large increase in skin permeability is highly significant for drug delivery applications.

As the extent of skin ablation depends on the properties of the jet discharge, ablation could be controlled by the properties of the ejectate formulation. Electrical, chemical, and physical properties of the filling material affect the jet properties and ultimately the skin ablation characteristics. Hence, several ejectate formulations were tested and skin permeability was compared.

Arc ablation with an ethanol-saline formulation leads to increased skin permeability, but to a lesser extent than water without ethanol. Arc ablation with an empty (i.e., air-filled) micro-chamber also causes increased skin permeability, but only by a factor of 10. Arc ablation with water ejected from the microchamber is probably more effective because it more efficiently transfers heat and momentum to the tissue as compared to air.

As the temperature to which the skin is exposed is highly significant, efforts were made to measure the temperature at the surface of the skin using a liquid crystal temperature indicator paper. The temperature indicator paper was placed beneath a

50 µm thick polymer film in order to protect it from damage caused by the jet. Using this technique, the temperature below the polymer film at the site of the liquid crystal paper was determined to be between 60 and 100 ˚C. However, further studies are needed to determine the surface temperature more accurately.

To determine the duration of arcing and resulting microjet ejection, the electrical current in the capacitive discharge circuit is monitored across the MOSFET switch. Simultaneously, the recoil force of the microdevice during jet ejection is measured. The apparatus shown in Fig. 5 was utilized to measure the recoil force of the jet. A piezoelectric force sensor is incorporated into the apparatus to yield time-resolved force data during the discharge.

Both current and force measurements indicated that the arc discharge and microjet ejection occurred on a timescale of 100 µs. The force generated from the ejected jet (Fig. 5) is measured to be approximately 1-10 N. The force generated from the jet is then correlated to the skin permeability (Fig. 6).

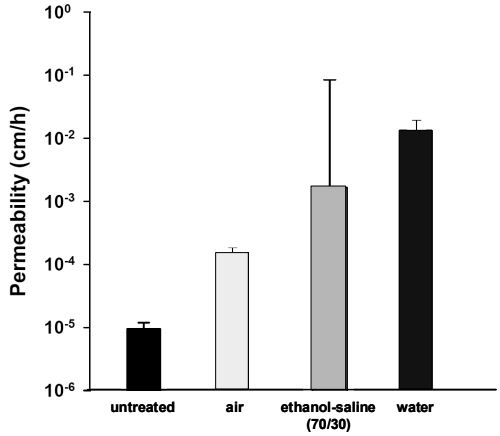

Fig. 4 Permeability of human cadaver skin after arc-generated jet impingement.

4. CONCLUSIONS

A microjet arc-discharge ejector device is successfully fabricated and tested for skin ablation. Using this device, it was observed that the skin permeability to calcein has increased by three orders of magnitude compared to non-treated skin. Microscopic studies have shown that this increase in skin permeability was correlated with the selective removal of the *stratum corneum* layer of skin. We can conclude that arc-based microjet ablation has promise as an effective means to increase skin permeability for transdermal drug delivery.

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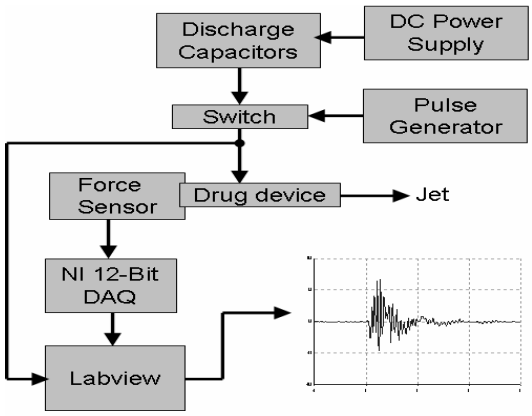

Fig. 5 Force sensing setup.

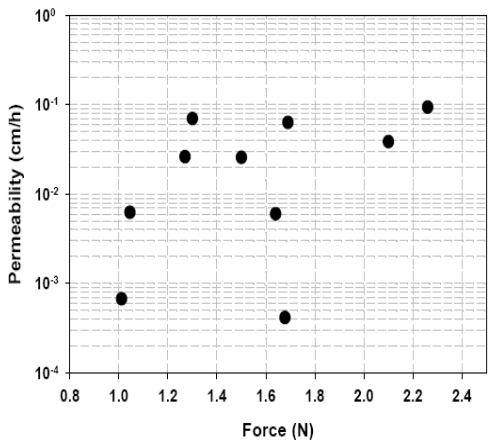

Fig. 6 Comparing skin permeability with force generated from the jet device.

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