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Penetration and delivery characteristics of repetitive microjet injection into the skin

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ABSTRACT

Drugs can be delivered transdermally using jet injectors, which can be an advantageous route compared to oral administration. However, these devices inject large volumes deep into the skin or tissues underneath the skin often causing bruising and pain. This may be prevented by injecting smaller volumes at lower depth in a repetitive way using a microjet injection device. Such a device could be used to apply drugs in a controllable and sustainable manner. However, the efficacy of microjet injection has been rarely examined. In this study, the penetration and delivery capacity was examined of a repetitive microjet injection device. Various experiments were performed on epidermal and full-thickness ex vivo human as well as ex vivo porcine skin samples. Results revealed that microjets with a velocity exceeding 90 m/s penetrated an epidermal skin sample with a delivery efficiency of approximately 96%. In full-thickness human skin, the delivery efficiency drastically decreased to a value of approximately 12%. Experiments on full-thickness skin revealed that the microjets penetrated to a depth corresponding to the transition between the papillary and reticular dermis. This depth did not further increase with increasing number of microjets. In vivo studies on rats indicated that intact insulin was absorbed into the systemic circulation. Hence, the microjet injection device was able to deliver medication into the skin, although the drug delivery efficiency should be increased.

1. Introduction

Jet injectors have been used to deliver various drugs, such as vaccines, insulin and growth hormones, into the skin or into tissues underneath the skin [7]. This route of administration has several advantages over oral administration of drugs that are digested before entering the circulation. Moreover, it obviates the need for hypodermic needles to achieve intramuscular or subcutaneous injection, with its association with needle phobia. However, current available jet injectors may cause pain and bruising of the skin, which are assumed to be caused by its relative deep penetration and large injection volumes [7]. Particularly in the case of chronic diseases, such as diabetes and Alzheimer's, where medication has to be frequently applied, patient acceptability and compliance needs to be improved. Skin damage and irritation should be minimized and the delivery precisely controlled. A microjet injector that is able to repetitively inject smaller volumes of medication superficially is thought to overcome the disadvantages of the current jet injector [1]. These microjet injectors are potential wearable transdermal drug delivery devices that allow for a precisely, continuously controlled and sustainable delivery of drugs for patients with chronic diseases.

In both jet and microjet injectors, a drug solution is ejected through a nozzle with a diameter ranging from 30 to 560 μm at a velocity of approximately 100 m/s [7]. Various techniques have been used to generate this high velocity jet, such as spring-driven devices [6,9,12], piezo actuation [1,14], compressed gas [9,13], Lorentz force actuation [17] and laser-induced jet generation [5,18]. Most jet injectors eject volumes of 10 to 500 μl. However, the injection depth has been shown to be correlated to the injection volume [2]. Therefore, for superficial injection the injected volume should be reduced, resulting in a microjet, which is designed to inject volumes in the nanolitre range [1,5,15].

For the jet injection devices the penetration characteristics have been examined. In addition to the injected volume, it has been reported that jet velocity, nozzle diameter, and stiffness of the penetrated material influence the penetration depth [2,11,12]. Contrary, there is a paucity of data on the penetration process and efficiency of microjet injectors. Nevertheless, it has been demonstrated that a microjet injector is feasible to penetrate the epidermis and deliver fluid into the skin [1,14].

There are still unanswered questions about microjet penetration. Specifically, what proportion of the ejected dose is delivered into the skin? And further, what makes the microjet penetrate to a specific

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depth? What kind of damage is induced in the skin? Is the delivered drug still intact? These questions provide motivation for the current study to assess the feasibility of a microjet drug delivery device for controlled and sustained drug delivery. Various aspects of the penetration process of microjets into the skin were examined using ex vivo porcine and human skin. A threshold value for the microjet velocity and the amount of microjets to penetrate the epidermis were determined. Moreover, the penetration depth and damage were assessed with histology and confocal microscopy. The delivery efficiency was examined using a radioactive tracer. In addition, the ability of the microjet injection device to deliver medication that is taken up in vivo was assessed by measuring the effect on blood glucose levels in a rat model after administration of insulin.

2. Materials and methods

2.1. Microjet drug delivery system

A microjet drug delivery device was developed at Philips Research (Eindhoven, the Netherlands), which was able to repetitively eject small volumes of a solution at high velocity, with the aim of delivering a drug into the superficial layers of the skin.

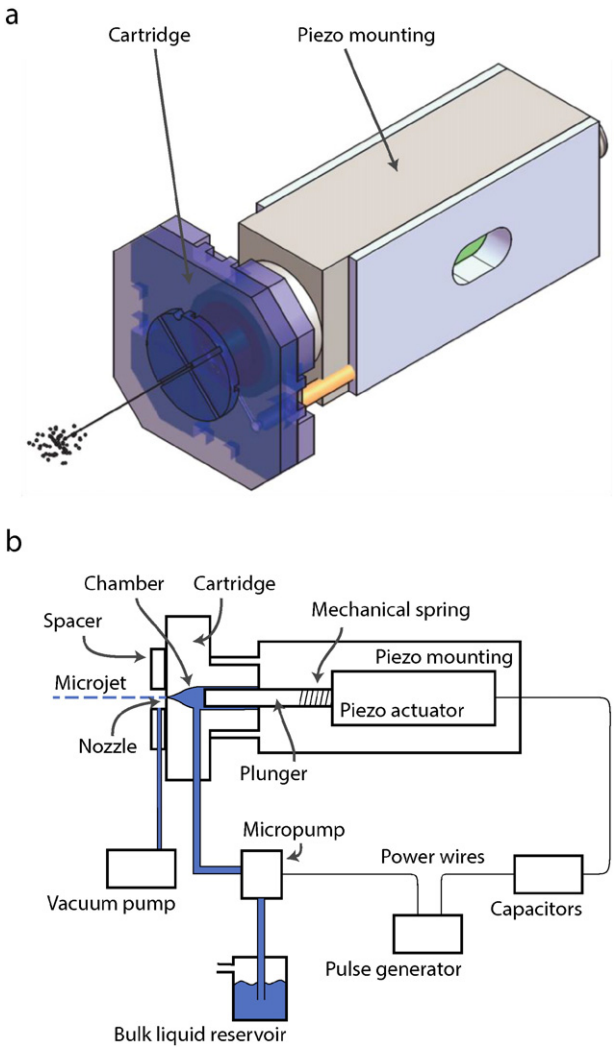

Fig. 1. Schematic pictures of the microjet drug delivery system. A piezo actuator displaced a plunger, compressing a solution in the chamber of the replaceable cartridge. Subsequently, a microjet was ejected through the nozzle into the skin. The cartridge was refilled using a micropump. Excess fluid at the nozzle was removed using a vacuum pump.

The system consists of a piezoelectric actuator that is attached to a plunger (Fig. 1). When a voltage is applied to the piezoelectric actuator with a pulse generator, the plunger will be displaced and quickly compresses a solution in the chamber of the replaceable cartridge. This almost instantaneous expansion allows a high pressure build up in the chamber. The high pressure results in the ejection of a high velocity microjet through a nozzle with a diameter of 50 μm. Without any actuation, capillary forces prevent the liquid from leaking out of the chamber. After extension, the piezoelectric actuator and plunger are placed back to their original position by a mechanical spring and the chamber in the cartridge is refilled with a micropump via the refill channel. Excess fluid from the refilling process was removed using a vacuum pump (Fig. 1b). A spacer of 1 mm thickness prevented the nozzle to come in direct contact with the skin. This microjet injector produces repetitive microjets with a volume of 7 to 30 nl as determined with a radioactive tracer (Section 2.5). In this study, all repetitions within one series of experiments were performed with the same cartridge.

2.2. Preparation of skin samples

Fresh porcine ears were obtained from a local abattoir. These ears were removed from the cadaver before it was exposed to the high temperature cleaning procedure to maintain their integrity. After transfer to the laboratory, the porcine ears were washed and hairs were trimmed. Subsequently, skin slices with a thickness of approximately 800 μm were obtained using a dermatome (Humeca, Enschede, the Netherlands). The epidermis was separated from the dermis using enzymatic separation with dispase II [4,16]. The samples were then wrapped in plastic and aluminium foil and stored at −80 °C until further processing.

Human skin of patients who had undergone abdominoplasty was obtained from the Catharina Hospital in Eindhoven, the Netherlands, with approval of the Medical Ethics Committee of the same hospital. Human skin samples with a thickness of approximately 0.2 and 1.2 mm were prepared in a similar manner as porcine samples using a dermatome. In addition, samples containing only the epidermis were prepared using enzymatic separation. All samples were stored at −80 °C wrapped in plastic and aluminium foil.

2.3. Penetration of porcine and human skin

To assess the ability of the microjet injector to penetrate the skin, single microjets were injected into porcine epidermal samples at jet velocities ranging from 45 to 130 m/s. Before injection, these samples were thawed and subsequently placed on top of a 0.4% agarose gel to support the tissue and to prevent it from dehydration. Deionized water was used as injection liquid. The penetration depth of a single microjet penetrating the epidermal layer into the agarose gel was measured to determine the minimal velocity of the microjet necessary to penetrate the epidermal layer. The velocity was determined by recording the microjet with a high speed camera mounted perpendicularly to the direction of the microjet. Using the distance travelled between successive frames and the known frame rate, the microjet velocity was calculated. The velocity could be controlled by varying the voltage applied to the piezoelectric actuator.

Based on the results on porcine skin, the ability of the microjet to fully penetrate human skin samples was assessed using a microjet velocity of 105 to 125 m/s. Since the single microjet did not always fully penetrate the human skin, multiple microjets were injected at the same location at a frequency of 0.25 to 1 Hz. Injections were performed on both human epidermal samples and skin samples with a thickness of approximately 200 μm, which included a part of the human dermis. All human samples were also placed on top of a 0.4% agarose gel.