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Characterization of needle-assisted jet injections

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ABSTRACT

Hypodermic injections have been the standard for transcutaneous drug delivery for many years. However, needle phobia, pain, and risks of needle-stick injuries have manifested in poor patient compliance. Needle-free jet injections (NFJI) have been developed to address these drawbacks but the reliability of dose and depth of delivery have been limited by a lack of control over jet parameters, and by variability in the skin's mechanical properties among individuals. Moreover, the device size and cost have been restrained by the high pressure (>20 MPa) required to penetrate the skin. Needle-assisted jet injections have been proposed to improve delivery reliability of conventional jet injectors by penetrating the skin with a short needle (<5 mm) and thereby allowing jet delivery to a desired injection depth at a reduced pressure.

This study characterized needle-assisted jet injections performed after first penetrating the skin with a 1.5 mm needle, examining the effect of needle size on jet parameters, and evaluating injection performance in porcine skin. A voice-coil actuated jet injector was modified to incorporate needles of 30 G, 31 G and 32 G. A series of pulse tests was performed to compare jet velocity and injection volume across the needle sizes, where it was found that the jet velocity and injection volume achieved with 32 G needles were 13% and 16% lower, respectively, than with 30 G. In contrast, there was no significant difference in jet velocity and injection volume between 30 G and 31 G needles, suggesting that a reduction of 10 μm in the mean inner diameter of the 31 G needle has minimal impact on jet velocity and injection volume.

Injection studies performed in porcine skin revealed that injections driven by fluid pressures ranging between 0.8 MPa and 1.4 MPa were able to achieve substantial injectate penetration (~10 mm) and delivery (~100 μL) into subcutaneous fat regardless of needle size, in a period of 40 ms. The required pressures are an order of magnitude lower than those used in NFJI, yet still maintain the high-speed nature of jet injection by achieving a delivery rate of 2.25 mL/s. The lower pressures required in needle-assisted drug delivery can lead to reduced device size and cost, as well as reduced shear stresses during jet injection and can therefore minimise the potentially adverse effect of shear on the structural integrity of proteins, vaccines and DNA.

1. Introduction

Skin is recognised as one of the most effective routes for vaccine and drug delivery, offering both immunological and pharmacological advantages due to its multi-layered structure. Since the introduction of the needle and syringe in the mid-19th century, hypodermic injection has become the standard for cutaneous drug administration [1]. However, the pain, anxiety and needle phobia associated with needle injections have manifested in poor patient compliance among both children and adults [2]. Moreover, hypodermic injections are not limited to humans, but are also used in domestic animals such as cattle, sheep and chickens. Here, the use of hypodermic needles has presented difficulties in performing effective injections due to hair or fur, skin thickness, and cross contamination due to reuse of needles, thus resulting in considerable economic loss [3].

To address these drawbacks, alternative cutaneous delivery methods, including transdermal delivery systems and jet injectors, have been investigated. Transdermal patches, which often employ methods such as ultrasound, electroporation and microneedles to increase the permeability of skin, deliver drug molecules across the stratum corneum into the dermis. This delivery method is non-invasive and less painful compared to hypodermic injections, but is limited by a slow delivery rate and requires the use of hydrophobic molecules with low molecular weights [4]. In contrast, jet injection has the advantage of high speed delivery and can be applied to a wide range of liquid drugs including macromolecules. However, the reliability of most commercial spring powered jet injectors has been compromised by the lack of control of jet parameters and by skin variability among different body sites as well as between individuals [5,6].

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More recently, the idea of needle-assisted jet injection has been proposed as an alternative for improving the reliability and effectiveness of conventional jet injectors by first penetrating the skin with a short needle (typically <5 mm) and delivering a fluid jet at high speed. With the needle already penetrating the toughest skin layer, such a system is able to achieve the desired injection depth at a reduced pressure, yet still maintains the high speed nature of jet injection with minimal pain. A lower pressure requirement leads to reduced device size and cost, as well as reduced shear stress during jet injection, thereby reducing the risk a damage to the structural integrity of proteins, vaccines and DNA [7]. Furthermore, factors that have been suggested to compromise jet injection performance such as hair or fur, variability in skin mechanical properties and movement during injection can be minimised by the combination of needle penetration and brief injection time [8].

Currently there is a lack of detailed analyses of injection performance in needle-assisted JI. Particularly absent is an analysis of the effect of jet parameters, needle size and length on penetration depth and injection volume. In addition, experimentation involving smaller needles (>30 G) is also desirable for applications in humans, as shorter and thinner needles are less painful and therefore more likely to yield higher patient compliance. Based on these considerations, this paper evaluates the use of small needles in the range of 30 G to 32 G in needle-assisted jet injections through quantitative analysis of the effect of needle size on jet parameters and injection performance in post-mortem pig skin. The paper also investigates the relationship between fluid pressure and jet velocity developed within the injection system. This knowledge will facilitate the future design and development of needle-assisted jet injectors with better control over jet velocity and injection volume.

2. Materials and methods

2.1. Device development

2.1.1. Voice-coil injector

The jet injector used in this study (Fig. 1) consisted of a custom-made linear voice-coil motor, a linear potentiometer used as a position sensor, a disposable piston and a custom-made stainless steel ampoule [9]. The total DC resistance of the coil was 9.4 Ω and the force constant over the used-stroke of the motor ranged between 9.0 $N \cdot A^{-1}$ and 10.2 $N \cdot A^{-1}$. The piston was attached to the front of the moving coil, with the potentiometer coupled to the edge in order to track the position of the voice-coil actuator. The ampoule head had a threaded compartment at the tip that could accommodate a stainless steel orifice that would typically be between 150 μm and 300 μm in diameter during a standard jet injection (Precision orifices type ZMNS-SS-V, O'Keefe controls Co.).

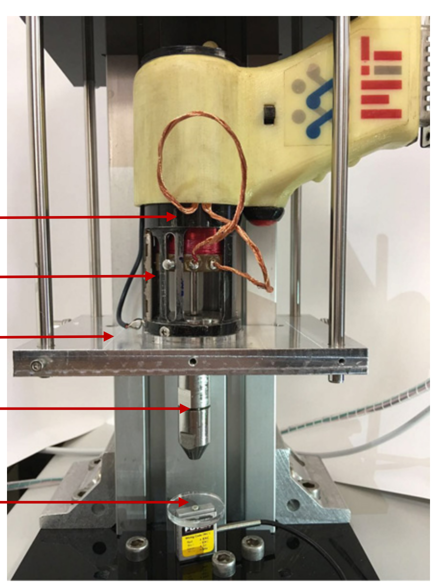

Fig. 1. Needle-assisted jet injector experimental apparatus.

High speed monitoring and control of the coil position was achieved using a system comprising a real-time controller (cRIO-9024, National Instruments) embedded in a reconfigurable field-programmable gate-array (FPGA) chassis (cRIO-9113). The motor was driven by a linear power amplifier (AE Techron 7224), controlled by a PC-based data acquisition and control system running in National Instruments LabVIEW™ 11.1.

2.1.2. Tissue force measurement

The force applied by the injector to the tissue was measured with a small load cell (Futek, stock # FSH00104) with 44.5 N capacity fixed to the base of the vertical stand aligned with the needle. An acrylic plate was fixed on top of the sensor to avoid direct contact of fluid and the sensor (Fig. 1). The sensor was connected to a bridge analog input module (NI 9237), and force data were sampled at 20 kHz, recorded by the FPGA "target" application at 10 kHz and filtered by a 10-point moving-average prior to display.

2.1.3. Needle-assisted jet injector

Three of the smallest needles that are commercially available were selected for this study. These were the BD Microlance™ 30 G needles, BD Micro-Fine™ 31 G pen needles and BD Micro-Fine™ 32 G pen needles respectively (Fig. 2A–C). 5 needles of each size were randomly selected and imaged using a SKYSCAN 1172 X-ray micro-computed tomography (Micro-CT) machine to determine their outer and inner diameters (o.d. & i.d.). A comparison of the measured diameters and the nominal diameters provided in the Birmingham Wire Gauge Table is presented in Table 1.

The needles were trimmed to a shorter length in order to minimise the resistance to flow as well as to ensure adequate penetration depth into the skin for effective injection. Laurent et al. measured human skin thickness (epidermis and dermis) at different body sites and found the mean and 95% confidence interval values of skin thickness across the deltoid, suprascapular region, waist, and thigh are >1.5 mm regardless of gender, age (18–70 years old), ethnic origin and body mass index [10]. Based on these considerations, each needle was trimmed to 4 mm, inserted, and soldered into an orifice with 2 mm remaining above the orifice surface (Fig. 2D–F). The assembly of the needle-orifice to the jet injector is shown in Fig. 3.

2.2. Estimation of jet velocity

As voltage is applied to the voice coil actuator, the resulting current generates force to propel the piston forward and thereby accelerate fluid through the needle. Jet velocity can be estimated based on the conservation of volume, where the volume of fluid moved by the piston in the ampoule must equal the volume ejected through the needle, assuming there is no dead volume left within the injector system. By equating volumetric flow rates in the ampoule and needle, jet velocity can be obtained by

$$v_{jet} = \frac{r_{ampoule}^2}{r_{jet}^2} v_{piston}$$

where $r_{ampoule}$ is the radius of the ampoule shaft, r_{jet} is the radius of the jet as it exits the needle tip and v_{piston} is the piston velocity measured in $m \cdot s^{-1}$. High speed video (Phantom Micro LC 110 camera) of the fluid jet revealed the cylindrical shape of the fluid jet as it exits the needle tip and that the jet diameter closely matches the i.d. of the needle (Fig. 4). Therefore the inner radius of the needle can be used as an