A Compound Ampoule for Large-Volume Controllable Jet Injection

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***Abstract*— We present a new design for a needle-free injector ampoule, using two concentric pistons to pressurize the fluid during the injection. The smaller, inner piston is used to provide an initial high-velocity piercing jet; it then engages the outer piston to deliver the remaining drug via a low-velocity jet. The goal of this design is to enable needle-free delivery of relatively large volumes to controlled depths in tissue, a task impractical with conventional ampoules and actuators. We demonstrate this concept by constructing a 1.2 mL ampoule, measuring the jet velocity it produces in free air, and performing a set of injections into post-mortem porcine tissue. The ampoule smoothly produces the two desired phases of an injection, with a smooth transition of jet velocity as the two pistons engage. The injection is able to penetrate porcine skin to a controlled depth and deliver fluid to the subcutaneous and/or intramuscular layers, though further investigation is required to ensure that all of the fluid delivered can be retained at the desired depth.**

I. Introduction

Needle-free jet injection (NFJI) is a technique that delivers liquid drugs through the skin as a narrow, >100 m/s stream, capable of penetrating to depths ranging from epidermal to intramuscular using nothing but the energy of the flowing fluid [1]. It has been established that the depth of the injection is very sensitive to both the jet velocity and the time for which the jet is applied [2]. Furthermore, by reducing the jet velocity once the desired depth has been reached, the injection depth and volume can be controlled independently [3], [4]. Achievement of this control requires that the injector be driven by a very high bandwidth (over 1 kHz) actuator.

At present, commercially-available NFJI systems rely on the uncontrolled expansion of springs or compressed gases [5], [6], delivering volumes up to 5 mL (in devices intended for livestock) but to uncontrolled depths. NFJI devices currently under research can provide sufficient bandwidth to control injection depth with the use of voice coils [4], mechanically-amplified piezoelectric actuators [3], or pulsed lasers [7]. However, these controllable devices are limited in their delivery volume, which ranges from sub-μL for lasers and piezoelectric actuators to about 0.3 mL for voice coils.

Many new drugs, especially protein-based formulations, require low concentrations of their active ingredients to remain effective, yet must also be delivered in large amounts [8]. Therefore, they must be delivered as relatively large volumetric doses, over 1 mL. In animal husbandry, large doses are often required due to the body mass of livestock. Controllable NFJI devices capable of large injection volumes are therefore needed to bring the benefits of control to a wider range of injection contexts.

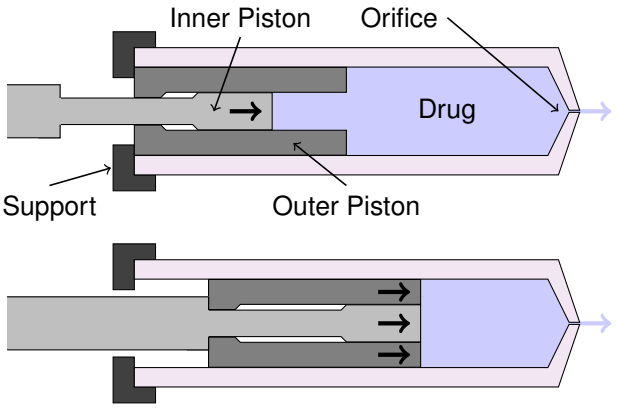

Fig. 1. A schematic of the compound ampoule, showing its operation during the piercing phase of injection (top) and the dispersion phase (bottom). Heavy arrows indicate motion.

We have previously established [9] that, for voice-coil-actuated NFJI systems, there is a fundamental scaling relationship between the injected volume and the required actuator size. For a fixed electrical power input, the required motor mass M is super-linear in injection volume V, with $M \propto V^{6/5}$. Based on the model presented in that work, a motor mass of over 1 kg would be required to deliver 1 mL, and over 40 kg would be needed for 20 mL. Clearly, then, a practical larger-volume system cannot be built simply by using a larger voice coil motor and ampoule.

In this work, we describe a new design for the injection ampoule that breaks this scaling relationship by providing different piston diameters for the two phases of the injection. We then illustrate the utility of this "compound ampoule" design by constructing a 1.2 mL example and using it with a light-weight voice coil actuator to perform injections into postmortem porcine tissue.

II. Design Considerations

Fig. 1 illustrates our ampoule design, comprising a fluid-filled cylinder, a small-diameter piston directly connected to the actuator, a large-diameter floating piston that carries the

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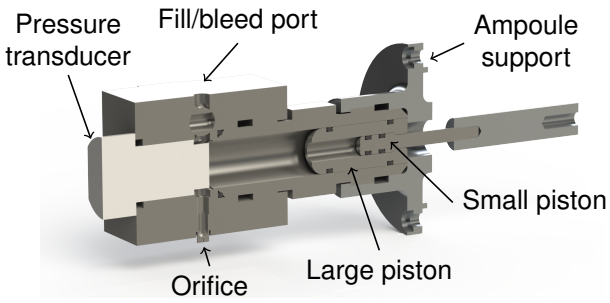

Fig. 2. A cut-away rendering of the instrumented compound ampoule shows the two pistons, the pressure transducer, and the fluid path. Note that there is a 90-degree bend in the flow path to accommodate the pressure transducer.

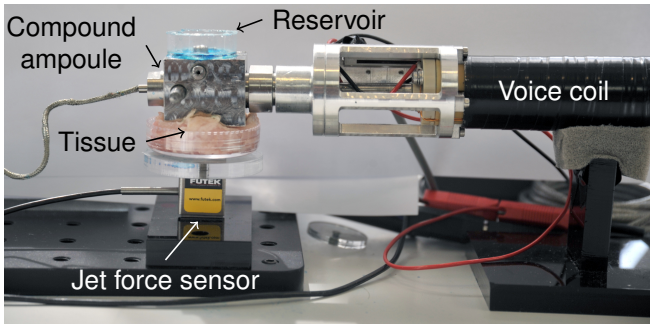

Fig. 3. The compound ampoule is shown connected to our custom-built voice coil actuator (right). A specimen of porcine tissue can be seen below the ampoule with the jet force sensor, and a reservoir for filling the ampoule can be seen above the ampoule.

bore for the small piston, and an ampoule mount that prevents the large piston from escaping the ampoule. During the piercing phase of the injection, the small piston pressurizes the fluid with a large mechanical advantage due to its small area. By the same token, however, this piston only sweeps a small portion of the fluid volume. The force exerted by the fluid on the large piston is supported by the ampoule mount. When the small piston reaches the end of its stroke, a shoulder on its shaft engages with the large piston, now pushing both pistons together as a unit. The mechanical advantage is reduced by the larger piston area, resulting in the lower pressure required during the dispersion phase. If the ampoule needs to be refilled, shoulders can be provided near the small piston head and in the large piston's bore (as shown) that engage to retract the large piston.

The total stroke for both pistons is chosen according to the optimum for the desired motor size [9]. The diameter of the inner piston can then be set to provide an acceptable power demand at the piercing phase pressure, nominally 20 MPa for a desired jet velocity of 200 m/s, neglecting friction. The stroke for the inner piston must be set to provide sufficient piercing volume to reach the desired depth, while also accommodating bulk compression of the fluid. The volume required to pierce the tissue is relatively small, with even 50 μL sufficient to reach intramuscular depths [4]; however, the bulk compression of the fluid can be substantial. Presuming the drug has a bulk modulus comparable to that of water, 2.2 GPa, the drug will compress by approximately 1 %, or 100 μL for a 10 mL delivery volume. If the ampoule is made from plastic, it can also expand significantly under the influence of the injection pressure [10].

The diameter of the large piston is then chosen to provide the desired total delivery volume. This also sets the area ratio. Typically, a jet velocity of approximately 50 m/s is used for the dispersion phase, nominally requiring slightly over 1 MPa of fluid pressure. For typical injection pressures, the area ratio must be kept below 16:1 to keep the actuator force required for the dispersion phase below the force required for the piercing phase.

III. Materials and Methods

A. Ampoule Design

A prototype compound ampoule was constructed for a delivery volume of 1.2 mL and actuator stroke of 30 mm, as shown in Fig. 2. A diameter of 3.56 mm and stroke of 10 mm were chosen for the inner bore, yielding a maximum piercing volume of 100 μL. The diameter of the outer piston's bore was chosen as 8.34 mm (21/64 in.) for ease of manufacturing, giving a total delivery volume of 1192 μL.

Fluid was delivered via a 200 μm orifice (O'Keefe Controls ZMNS-8-M3.5-SS-BN), located at right angles to the piston stroke so as to provide space for a pressure transducer. The cross-sectional area of the flow path around the transducer is always significantly larger than the orifice area; as such, the turns in the flow were expected to generate minimal pressure drop. Fluid loading was accomplished through a valve and port above the orifice, for ease of air bubble expulsion. All components with fluid contact were manufactured from grades 303, 304, or 17-4 PH stainless steel, with Buna-N seals lubricated with silicone grease.

B. Instrumentation

The performance of the compound ampoule was initially quantified using a bench-top system, capable of monitoring the fluid pressure, actuator force, and jet force. In this configuration, the ampoule was driven by a commercially available voice coil actuator (BEI Kimco LA25-42-000A, moving mass 540 g), with an inline load cell (Futek LCM300, 250 lb.) and ball-bearing guides. The voice coil was driven via a servomotor drive (National Instruments MID 6752) and FPGA-based control system (National Instruments cRIO-9024), with coil position measured using a potentiometer. Fluid pressure was measured using a diaphragm-based transducer (Omega PXM600MU-700BARGV). The jet velocity was estimated by measuring the force it exerted on a high-sensitivity load cell (Futek LSB200, 10 lb.) with a stand-off distance of 3 mm, and using conservation of momentum (assuming no splash-back and a jet diameter equal to the orifice diameter) to determine the jet velocity, as per [11].

Once the performance of the compound ampoule was initially quantified, it was incorporated into a hand-held in-

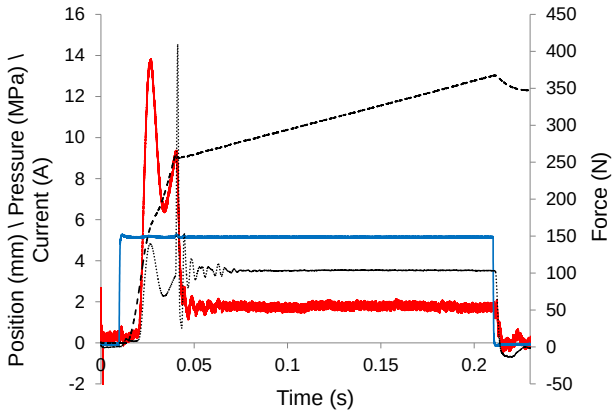

Fig. 4. Performance of the compound ampoule in bench-top configuration is illustrated for a 110 N nominal force, with current (blue), pressure (red), and position (black dashed) indicated by the left axis, and actuator force (black dotted) shown on the right axis.

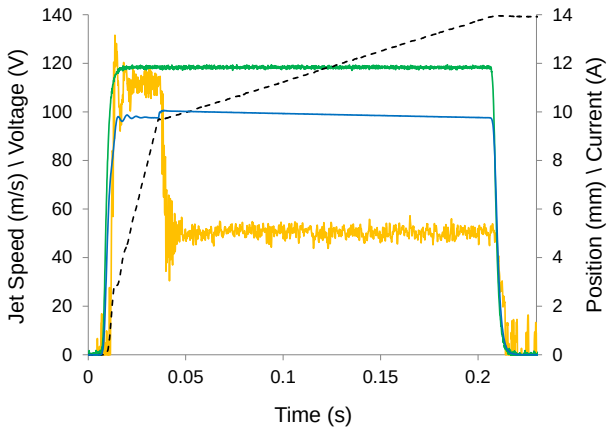

Fig. 5. Performance of the hand-held configuration for the compound ampoule is shown for a 110 N nominal force, with jet velocity (yellow) and voltage (green) on the left axis, and position (black dashed) and current (blue) on the right axis.

jection system actuated by a custom-built voice coil actuator [9] as shown in Fig. 3, with 78 g of moving mass, a coil wound for a coil resistance of 11.5 Ω, and force constant of 10.8 N/A. In this configuration, the inner piston was directly connected to the voice coil, and the fluid pressure was not monitored. The actuator was driven by a more powerful amplifier (2x Techron 7224, connected as a bridged series pair); the other instrumentation was unchanged.

C. Experimental Validation

On the bench-top system, performance was characterized by driving the voice coil with a constant current to eject deionized water against the jet force sensor, measuring all parameters with a sample rate of 100 kHz. Loading of the ampoule was accomplished by filling the reservoir atop the ampoule, then opening the fill valve. The pistons were manually actuated several times over their full travel to expel all air bubbles, then the valve was closed.

Performance of the hand-held injection system was characterized using a similar procedure, but with a 10 kHz sample rate. When testing this system, the motor was driven using a square voltage pulse passed through a first-order low-pass filter at 100 Hz, to minimize excitation of the natural frequency of the system.

The hand-held system was used to inject a blue dye (1.8 % Brilliant Blue FCF, Queen New Zealand Pty. Ltd.) into post mortem porcine tissue, harvested from the chest and upper torso of pigs ranging from 9 to 12 weeks of age in accordance with the University of Auckland Code of Ethical Conduct for the Use of Animals for Teaching and Research. Tissue was frozen at -80 °C immediately post-harvest, and thawed overnight at 4 °C prior to use. Thawed tissue was cut into 40 mm disks, equilibrated to room temperature for 30 minutes, weighed, and placed into rigid plastic containers for injection. The jet force sensor was used as a contact force sensor, and the injector was held against the tissue so as to provide a contact force of 7 N, with the orifice centered on the tissue disk. After injection, the tissue was patted dry to absorb any fluid that did not penetrate the skin, weighed again, and then promptly re-frozen at -80 °C. The frozen tissue was sawed in half through the injection site and photographed to characterize the penetration depth and dispersion of the injection.

IV. Results

The measured performance of the bench-top compound ampoule system is shown for an input current of 5.1 A (nominally 110 N) in Fig. 4. During the piercing phase, there is significant variation in pressure due to the low mechanical resonant frequency of the system, which in turn is caused by the large mass of the actuator coil. When the inner piston reaches the end of its travel and engages with the outer piston, the force spikes dramatically due to the momentum of the actuator coil. This shock does not appear in the pressure data, implying that the load is taken up by the inertia of the outer piston and the static friction of its seals. Instead, the actuator bounces back slightly and the pressure decreases smoothly to its value during the dispersion phase, only then responding to further ringing in piston force. By comparing the areas of the physical pistons to the ratios between force and pressure in each phase of the injection, we find that friction in the seals only uses 4 % of the force provided by the motor during steady-state operation, with the rest available for pressure generation.

Fig. 5 illustrates the compound ampoule performance when driven by our much smaller custom voice coil, with the same nominal force level (120 V input, yielding 110 N). The lower moving mass acts to increase the natural frequency of the system, allowing oscillations in pressure to be more easily controlled. The 100 Hz low-pass filter reduces overshoot in the jet velocity, yielding the desired profile of jet velocity over time.

Two cross-sections of injected porcine tissue are shown in Fig. 6. The specimen on the left was injected using parameters that give a piercing jet velocity of 125 m/s, a

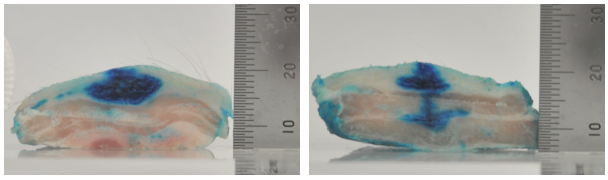

Fig. 6. Two examples of injected tissue cross-sections: Left – 180 V, 0.3 s. Right – 210 V, 0.8 s. The rulers are marked in millimeters.

dispersion velocity of 51 m/s, and a total delivery volume of 541 μL. Of the delivered volume, 501 μL remained in the tissue, entirely within the subcutaneous fat. The specimen on the right was injected with a 130 m/s piercing jet velocity, a dispersion velocity of 52 m/s, and a total delivery volume of 1077 μL. Of that volume, only 394 μL remained in the tissue, though the injection did penetrate through the subcutaneous fat and into the muscle.

The results of nine tissue injections, at a variety of jet speeds and total volumes, are shown in Fig. 7. It is clear that the amount of fluid retained by the tissue did not depend on the amount that was delivered by the injector, and ranged from 200 μL to 500 μL. The injection depth increased with the voltage (jet velocity) as expected, however, reaching 11 mm at 210 V. All injections at 150 V were subcutaneous, some of the 180 V injections penetrated the muscle slightly, and all injections at 210 V were intramuscular.

V. Discussion

The compound ampoule concept has proven to be reliable and effective at ejecting large volumes of fluid according to jet velocity-time profiles considered appropriate for jet injection. Our measurements of the jet velocity and pressure show that the injection sequence is not disrupted by the sudden impact of the actuator with the large piston, following the desired velocity profile even as the actuator bounces back slightly. The remaining challenge in using this system for a controllable jet injection is the development of a suitable closed-loop control system, capable of maintaining stability across the transition from the piercing phase to the dispersion phase. As we have found control architectures dominated by feed-forward action to be most appropriate for jet injection [4], this challenge should not be difficult to overcome.

We are surprised by the inability of the tissue to absorb the full dose of fluid during the injection. The awkward contact between the flat surface of the instrumented ampoule and the tissue may have led to poor contact pressure around the nozzle itself, allowing the injected fluid to escape. Alternatively, we have also noticed significant motion of hand-held voice-coil NFJI systems caused by the inertial reaction force at the beginning of the injection. The unusual configuration of our experimental compound ampoule causes this motion to manifest as a shear perpendicular to the injection hole, which may be sufficient to disrupt the continued delivery of fluid during the dispersion phase. Further investigation using a rigidly-mounted injector and a conventional orifice arrangement will be required to pinpoint the cause of these "wet" injections.

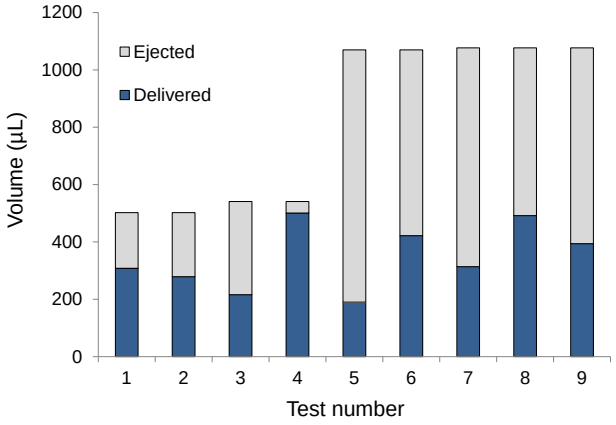

Fig. 7. The volume delivered and the volume retained in the tissue are shown for nine injections: 1 and 2 using 150 V for 0.3 s, 3 and 4 using 180 V for 0.3 s, 5 and 6 using 180 V for 0.8 s, and 7–9 using 210 V for 0.8 s. Tests 4 and 9 are shown on the left and right of Fig. 6, respectively.

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