Title: The Effect of Jet Speed on Large Volume Jet Injection

Authors: James W. Mckeage[a,*], Bryan P. Ruddy[a,b], Poul M. F. Nielsen[a,b] & Andrew J. Taberner[a,b]

jmck145@aucklanduni.ac.nz, b.ruddy@auckland.ac.nz, p.nielsen@auckland.ac.nz, a.taberner@auckland.ac.nz.

[a] Auckland Bioengineering Institute, The University of Auckland, Auckland, New Zealand
[b] Department of Engineering Science, The University of Auckland, Auckland, New Zealand
*Corresponding Author: jmck145@aucklanduni.ac.nz. Level6, 70 Symonds Street, Auckland, 1010, New Zealand.

Abstract

Jet injection presents a promising alternative to needle and syringe injection for transdermal drug delivery. The controllability of recently-developed jet injection devices now allows jet speed to be modulated during delivery, and has enabled efficient and accurate delivery of volumes up to 0.3 mL. However, recent attempts to inject larger volumes of up to 1 mL using the same methods have highlighted the different requirements for successful delivery at these larger volumes. This study aims to establish the jet speed requirements for delivery of 1 mL of liquid using a controllable, voice coil driven injection device. Additionally, the effectiveness of a two-phase jet speed profile is explored (where jet speed is deliberately decreased toward the end of the injection) and compared to the constant jet speed case.

A controllable jet injection device was developed to deliver volumes of 1 mL of liquid at jet speeds greater than 140 m/s. This device was used to deliver a series of injections into post-mortem porcine tissue in single and two-phase jet speed profiles. Single-phase injections were performed over the range 80 m/s to 140 m/s. Consistent delivery success (>80 % of the liquid delivered) was observed at a jet speed of 130 m/s or greater. Consistent penetration into the muscle layer coincided with delivery success. Two-phase injections of 1 mL were performed with a first phase volume of 0.15 mL, delivered at 140 m/s, while the injection of the remainder of fluid was delivered at a second phase speed that was varied over the range 60 m/s to 120 m/s. Ten two-phase injections were performed with a second phase speed of 100 m/s producing a mean delivery volume of 0.8 mL ± 0.2 mL, while the single-phase injections at 100 m/s achieved a mean delivery volume of 0.4 mL ± 0.3 mL. These results demonstrate that a reduced jet speed can be used in the later stages of a 1 mL injection to achieve delivery success at a reduced energy cost. We found that a jet speed approaching 100 m/s was required following initial penetration to successfully deliver 1 mL, whereas speeds as low as 50 m/s have been used for volumes of less than 0.3 mL. These findings provide valuable insight into the effect of injection volume and speed on delivery success; this information is particularly useful for devices that have the ability to vary jet speed during drug delivery.

Keywords

Jet Injector; Needle-free; Jet Speed; Control; Voice Coil; Transdermal

1. Introduction

Needle and syringe injection has been the standard procedure for transdermal drug delivery since its development in the mid-19th century [1]. While this technique provides an effective way to penetrate the skin and deliver a drug to a chosen tissue layer, the need for a needle presents several drawbacks. These include the spread of infection from accidental needle-stick injury, handling of sharps waste, and reduced patient compliance due to needle-phobia [2].

Jet injection is a promising alternative to needle and syringe injection that avoids the need for a needle by using the liquid drug itself to penetrate the skin. In jet injection systems the liquid drug is pressurised within an ampoule which has a single outlet – an orifice which is typically between 100 μm and 300 μm in diameter [2]. As the pressurised drug is forced out of this orifice it is formed into a high speed jet, which is capable of penetrating the skin and delivering the drug to the underlying tissue. The penetration and delivery of a jet injected liquid depends on both the speed and diameter of the jet [3].

Commercial jet injection efforts have typically used the release of compressed springs or gases to pressurise the liquid and perform the injection [1]. These devices, while energetically efficient, provide little control of the jet speed as the injection takes place [4]. Recent research has focussed on the development of controllable methods such as voice coil actuators [5], [6], piezoelectric actuators [7] or pulsed lasers [8]. These methods provide the ability to control the jet speed during delivery and therefore precisely control the injection volume and depth.

One way in which the controllability of these devices has been used is to deliver the jet injection in two phases [5], [7]. This technique is based on the principle that a high jet speed (120 m/s to 200 m/s) is typically only required at the beginning of the injection while the jet penetrates through the tougher epidermal and dermal layers [4], [7], [9]. The jet speed can thus be reduced later in the injection at no cost to the delivery success, while also reducing the energy input. The energy dissipated during a voice coil driven injection has been to shown to be proportional to the cube of jet speed [10]. Reducing the energy required to perform a jet injection can increase the volume deliverable and/or reduce the size of injection devices.

Uncontrolled injectors (spring or gas driven) have demonstrated delivery of up to 1 mL in humans [11], and up to 5 mL in veterinary applications [12]. Controlled injection systems have typically been associated with much smaller injection volumes. Piezoelectric and laser-based jet injection systems have been used to deliver volumes of 0.1 μL to 6 μL [7], [8], [13] while systems actuated by electric motors have focussed on delivery up to 0.3 mL [4], [5], [14]. Recently, increased focus has been placed on the controlled delivery of volumes of 1 mL or greater. Toward this goal a wide range of controllable electric motors have been trialled [15], [16], and other techniques such as mechanical amplifiers [17] have been investigated. The study reported in [15] represents the first electronically controllable injector to perform delivery of up to 1 mL into humans. The interest in the controlled delivery of larger volumes is motivated by the fact that many common injections in clinical practice are delivered as 1 mL doses, or greater, including some vaccines, monoclonal antibodies and hormones [4], [11], [18].

While the volume deliverable by controllable jet injectors is approaching that of spring and gas driven devices, the previous lack of control at volumes up to 1 mL has meant that the requirements for successful delivery are poorly understood relative to those for volumes <0.3 mL. A previous study attempting to deliver 1 mL was unable to inject the full volume despite using jet speeds which had been shown to successfully deliver 0.3 mL [17]. This revealed that the ability of a liquid jet to penetrate and

remain within skin is dependent upon the delivered volume, an effect that has yet to be explored in the literature. Thus, there is a need to gain a better understanding of the way in which injection volume affects what is required for successful jet injection.

In this work we construct a jet injection device capable of commanding jet speeds of up to 200 m/s for injections of volumes greater than 1 mL. With this device, an investigation into the relationship between jet speed and fluid delivery for volumes of 1 mL is conducted using post-mortem porcine tissue. In addition, we investigate the degree to which jet speed can be reduced following the initial penetration of the jet while ensuring successful (≥80 %) delivery of the target volume.

2. Materials and Methods

2.1. Injection System

The injection device developed for use in this study is shown in Fig. 1. The injector was based on a voice coil actuator (BEI Kimco LA30-75) rigidly connected to a stainless steel piston, which moved within a liquid-filled stainless steel ampoule with an inner diameter of 6 mm. Nitrile-rubber O-rings provided a seal between the piston and the ampoule. At the opposite end of the ampoule, an orifice of 200 µm diameter (O'Keefe Controls Co.) provided the outlet through which the jet was formed. A potentiometer (Omega LP803) was used to monitor the position of the motor.

The voice coil actuator was position-controlled during injections using a field programmable real-time controller (NI cRIO-9024 with LabVIEW RealTime 2011, National Instruments). Motor position was

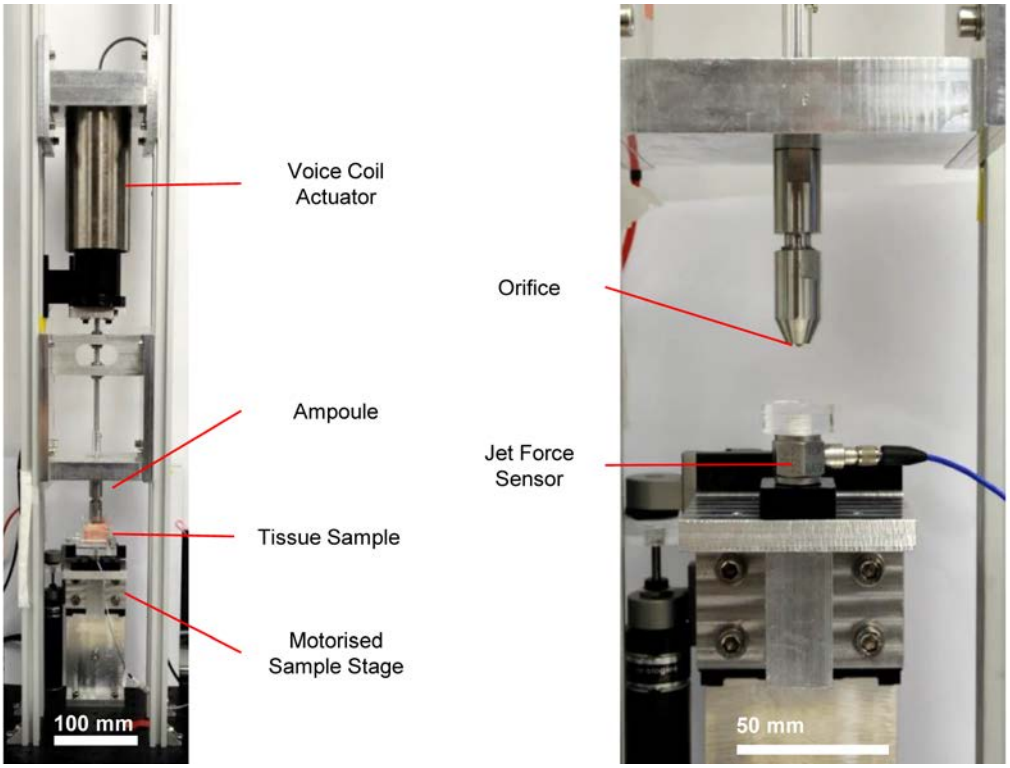

Fig. 1 – The large volume controllable jet injection device. **Left**: The entire device set up to deliver an injection into a tissue sample. **Right**: A close up on the nozzle and sample stage set up to perform a jet force measurement.

97 controlled by this system at a 20 kHz loop rate, using a combination of feedforward and feedback
98 control. The drive signal for the actuator was generated within the controller and amplified by a pair of
99 linear power amplifiers (AE Techron 7224) operating in parallel mode.

100 A motorised sample stage was used to raise tissue samples to the injector nozzle. A force transducer
101 (Omegadyne Inc LCM-201) positioned underneath the tissue sample was used to measure the contact
102 force applied by the nozzle to the sample. The injection was triggered only when this force equalled or
103 exceeded 0.8 N. During initial calibration, jet speed was confirmed with the use of a piezoelectric force
104 sensor (PCB Piezotronics 208C01), as described in 2.3.

105 *2.2. Control Strategy*

106 The control strategy for this device was the same as that presented in [5] and[19]. It relied primarily on a
107 feedforward model, which estimates the voltage required to attain the desired piston speed. Feedback
108 control (proportional and integral) was included so that the control scheme could respond to
109 disturbances, or small variations in friction, which would otherwise cause differences between the desired
110 and resultant jet speed and volume. Compensation for the motor's position-dependent force sensitivity
111 was also included to sustain the desired piston speed as closely as possible.

112 To avoid oscillations in coil motion and jet speed due to the excitation of the natural frequency (210 Hz)
113 of the electromechanical system, the desired motor position trajectory was low pass filtered (1st order
114 Butterworth) before being presented to the control algorithm. The cutoff frequency of the filter was
115 chosen to be sufficiently high to allow the desired jet speed to develop as quickly as possible, but low
116 enough to avoid peaks above the required steady state jet speed, as determined by the jet force
117 measurement. The viscous damping arising from the production of the jet permitted higher cutoff
118 frequencies at higher nominal jet speeds. The optimal cutoff frequency varied between 40 Hz and
119 150 Hz, depending on the desired initial jet speed, and was empirically determined for each speed of
120 interest using the jet force measurement. When an initial speed of 140 m/s or greater was desired, peaks
121 in jet speed were sufficiently damped by the production of the jet, and therefore the low pass filter was
122 not required.

123 *2.3. Jet Speed Measurement*

124 The measured motor position (our control variable) is used to calculate piston speed, which can be
125 related to the volumetric average jet speed through

126 $$v_j = \frac{v_p . A_p}{A_O},$$

127 where v_j is the jet speed, v_p is the speed of the piston, A_p is the area of the piston and A_o is the area of
128 the orifice. This measurement assumes that the piston speed and volume flow rate are proportionally
129 related, which is true of the vast majority of an injection. It is only the early stages of an injection, as the
130 pressure increases from ~100 kPa to ~20 MPa, that this measurement cannot reliably represent the true
131 speed.

132 Information about the jet speed during dynamic periods of the injection can instead be acquired through
133 the direct measurement of the momentum of the liquid by impinging the jet on a force sensor [20]. The
134 measured force (*F*) can be related to the jet speed through

$$v_j = \sqrt{\frac{F}{A_o . \rho}} \ ,$$

where ρ is the density of the liquid. This measurement provides high bandwidth information but cannot be related to the control variable (motor position) or be performed when injecting tissue samples. The relationship between the momentum-inferred and volumetric jet speed measurements depends on the velocity profile across the diameter of the jet, and thus in turn upon the shape of the orifice. For the orifice used in this study we consistently find the momentum-based estimate of speed is approximately 20 % greater than the volumetric estimate. In the interest of clarity, all quantifications of jet speed in this paper will refer to the volumetric estimate, unless otherwise specified.

2.4. Device Validation

This device was used to perform two styles of injection: single-phase, where a constant jet speed was held throughout the injection (Fig. 2A); and two-phase, where the jet speed was reduced part way through the injection (Fig. 2B). Fig. 2A displays an example of a 1 mL injection where a single volumetric jet speed of 130 m/s was commanded. Fig. 2B displays an example of an injection where 140 m/s was specified for the first 0.15 mL followed by a transition to 100 m/s for the remaining 0.85 mL. In both cases the position measurement follows the set point very closely, indicating the degree of set point control that can be achieved. The momentum-inferred jet speed demonstrates that there is no peak in jet speed above the steady state value, and that the jet speed remains constant throughout the periods where it is commanded to do so.

In order to demonstrate the repeatability of the results shown in Fig. 2, a series of experiments were conducted. In these experiments the device performed repeated ejections of water into containers whose change in mass indicated the volume ejected. Five injections were performed at 140 m/s with a requested total volume of 1 mL. These five injections yielded a mean ejected volume of 1.006 mL with a standard deviation of 0.002 mL.

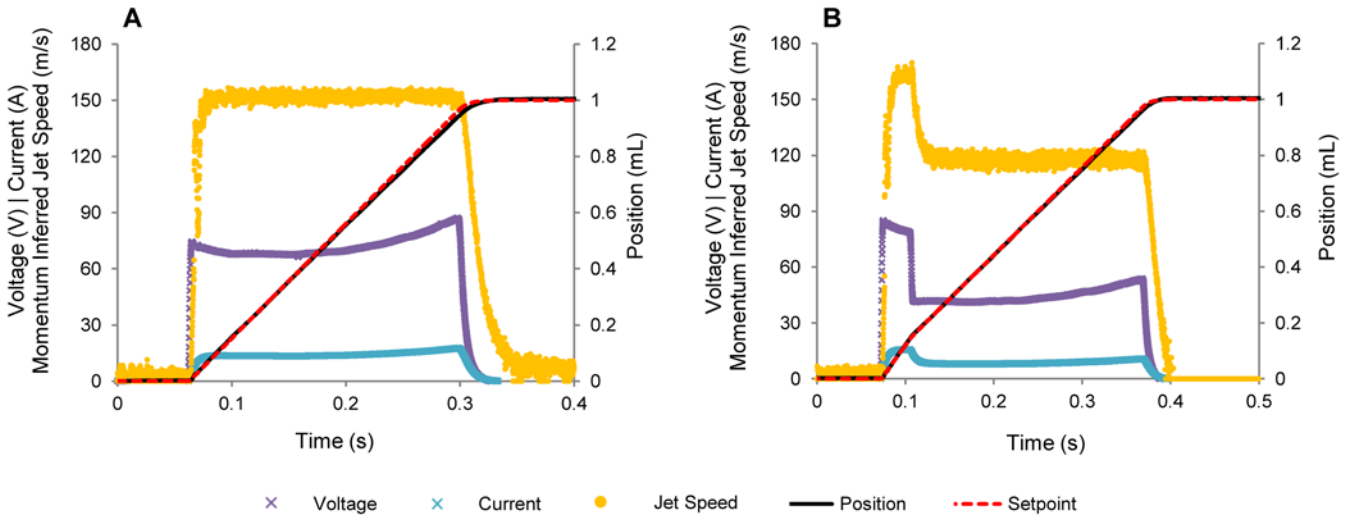

Fig. 2 –Two example injections with the dynamic behaviour of the jet speed inferred from the momentum of the jet. (A) Single-phase injection at a volumetric jet speed of 130 m/s. (B) Two-phase injection beginning at a volumetric jet speed of 140 m/s for 0.15 mL before dropping to 100 m/s.

2.5. Tissue preparation

Porcine tissue is a commonly used model of human tissue in jet injection studies [5], [9], [21], [22]. The thickness of the stratum corneum, total epidermis, and dermis have been shown to be similar between human and pigs [23]. The stiffness of abdominal porcine tissue has also been found to be similar to that of human abdominal tissue [21]. The relationship between volume delivered and jet speed was found to be analogous in both ex-vivo human and porcine tissue. A similar result was observed for the relationship between volume delivered and nozzle diameter [24].

Injections in this study were performed into samples of porcine tissue harvested post-mortem from the abdomen of animals of approximately 3 months of age. Tissue was obtained in accordance with the University of Auckland Code of Ethical Conduct for the Use of Animals for Teaching and Research. Abdominal skin, with subcutaneous fat and at least one muscle layer, was excised (typically to a thickness of 25 mm), vacuum sealed, and stored at -80 °C. In preparation for injection the tissue was thawed to room temperature (~22 °C) and then cut into 30 mm × 30 mm samples. A single injection was performed into each sample using water with 0.1 % blue food colouring (Brilliant Blue FCF, Queen Fine Foods Pty. Ltd.) to allow visualisation of the destination of the injected liquid. This tissue preparation and injection protocol is similar to that of previous jet injections studies [5], [9], [25].

2.6. Injection Experiments

A series of 1 mL single-phase injections were performed at seven different jet speeds: 80 m/s, 90 m/s, 100 m/s, 110 m/s, 120 m/s, 130 m/s, and 140 m/s. A total of 40 injections were performed with at least five injections at each jet speed. An example of such a single-phase injection with a jet force measurement can be seen in Fig. 2A. The volume delivered to each tissue sample was measured by weighing the sample before and after injection. Any liquid on the surface of the sample was removed (via tissue paper) prior to weighing. Following the post-injection mass measurement, the tissue sample was frozen at -80 °C. Once frozen, the injected sample was removed and sectioned through the injection site to observe the destination of the injected liquid. Two measurements were conducted on images of these sections:

the maximum depth reached by the injected liquid, and the deepest tissue layer to which the liquid penetrated.

A two-phase jet speed profile, like that shown in Fig. 2B, was used to perform an additional 25 injections into post-mortem porcine tissue. All of these injections were performed with a first phase speed of 140 m/s and volume of 0.15 mL. The selection of this volume was motivated by a previous study using high speed X-ray, which indicated that this would be sufficient volume to consistently penetrate well past the boundary between the dermis and subcutaneous fat (≥6 mm into the tissue) [26]. A total volume of 1 mL was used for all injections. The 25 injections were performed using four different second-phase speeds: 60 m/s, 80 m/s, 100 m/s, and 120 m/s, with at least five injections at each speed. The volume delivered and injection depth was measured in the same manner as the single-phase injections.

3. Results

3.1. Single-Phase Injections

The volume delivered to each sample, as measured by the change in mass, is plotted against the jet speed in Fig. 3A. At 130 m/s and 140 m/s all injections demonstrated delivery of more than 0.85 mL while all injections at 80 m/s and 90 m/s demonstrated very low volume delivered. Large variability is observed in the volumes delivered at 100 m/s, 110 m/s, and 120 m/s. This variability appears only in those injections which penetrated as far as the subcutaneous fat. Every injection which penetrated into the muscle also recorded a delivered volume of greater than 0.85 mL, while those which did not penetrate through the dermis show little or no volume delivered. This finding is emphasised in Fig. 3B, which shows the delivery

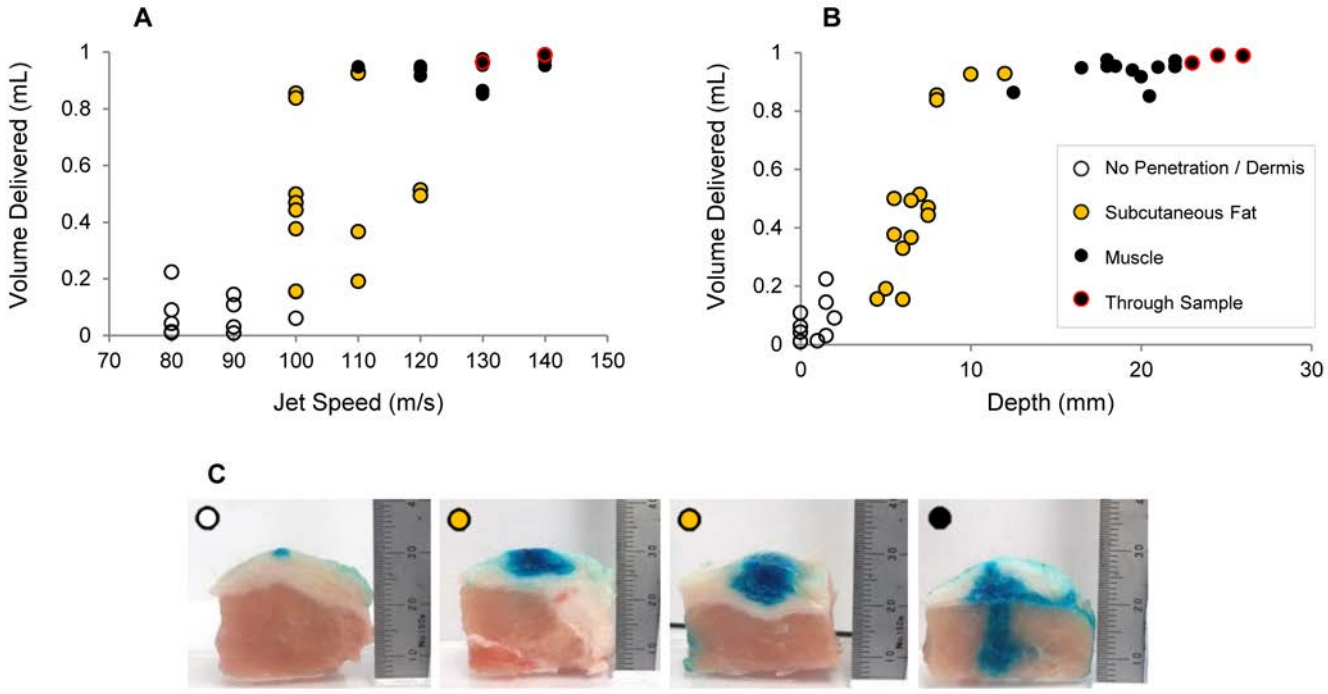

Fig. 3 – Results from the 40 single-phase injections. The legend refers to the deepest tissue layer penetrated by the injection. (A) The volume delivered versus the jet speed. (B) The volume delivered versus the maximum depth. (C) Example images of tissue which has been injected, frozen then sectioned. The ruler represents units of millimetres.

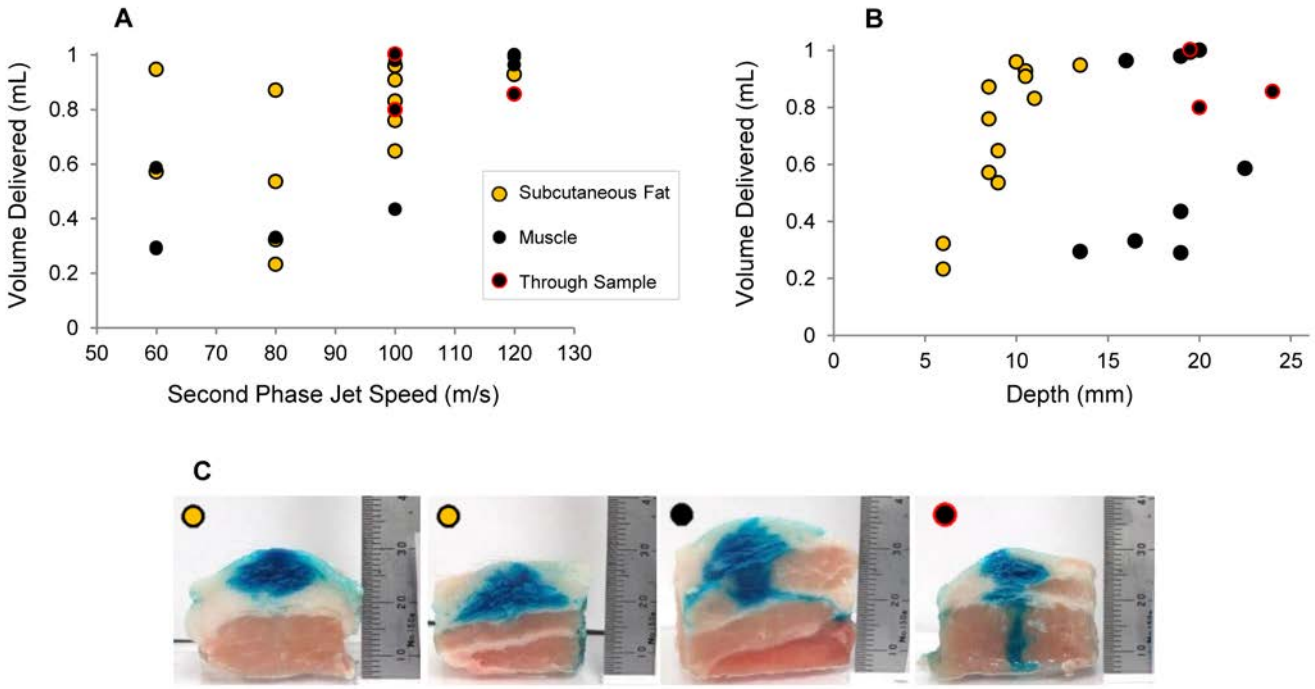

Fig. 4 – Results from the 25 two-phase injections. The legend refers to the deepest tissue layer penetrated by the injection. (A) The volume delivered versus the second phase jet speed. (B) The volume delivered versus the maximum depth. (C) Example images of samples which have been injected, frozen then sectioned. The ruler represents units of millimetres.

volume versus the maximum depth. The transition from low to high delivery volume occurs exclusively within the injections which penetrated into the subcutaneous fat. Within this transition region the volume delivered appears to be correlated with the maximum depth. Example images of sectioned samples in which the jet penetrated to the three different tissue layers are shown in Fig. 3C.

3.2. Two-Phase Injections

The volume delivered versus the second phase jet speed for the 25 two-phase injections is shown in Fig. 4A. Those injections conducted at 120 m/s consistently show greater than 0.8 mL of the volume delivered. The injections at 100 m/s are also mostly successful with 8/10 demonstrating delivery of more than 0.75 mL, while the injections at 60 m/s and 80 m/s were mostly unsuccessful and quite variable.

Fig. 4B plots the volume delivered versus the maximum depth; unlike the single-phase injections (Fig. 3B), there is no obvious grouping that relates to the layer to which each injection penetrated. However, there does again appear to be some correlation between volume delivered and maximum depth for those injections which penetrated as far as the subcutaneous fat (Fig. 4B, yellow circles).

Of the injections which penetrated into the muscle, 8/13 were associated with a delivered volume of greater than 0.8 mL. The other 5/13 injections demonstrated a volume delivered of less than 0.6 mL; four of these had second phase speeds of 60 m/s or 80 m/s. It is likely that for these four injections, the maximum depth was determined by the 140 m/s first phase, while the following speed was insufficient to maintain liquid flow to this depth, resulting in low volume delivered.

4. Discussion

4.1. Single-Phase vs Two-Phase

The effectiveness of the two-phase approach can be evaluated by comparing the energy input required for successful delivery relative to single-phase injection. Electrical energy consumption (E) was calculated from the voltage (V) and current (I) measurements over the time (t) course of the injections based on:

$$E = \int VI\, dt$$

Energy consumption is plotted against volume delivered for all single and two-phase injections in Fig. 5A. The two-phase data appear shifted to the left relative to that of the single-phase, indicating that using a two-phase jet speed profile has achieved delivery success at a reduced energy cost.

Injection in two phases provided success at an energy cost of 140 J, whereas over 200 J was required before similar, or improved, delivery was observed with a single-phase profile. Reductions in energy expenditure can enable existing injectors to deliver greater volumes and/or reduce the size of these devices. The two-phase approach could also allow more energy to be available during the first phase. In some situations, such as the injection of highly viscous formulations, much greater motor effort may be required to bring the jet to penetration speeds. By making more energy available at the beginning of the injection, the two-phase approach may facilitate the improved delivery of such formulations.

The data associated with a jet speed of 100 m/s, in both the single and two-phase results, is highlighted in Fig. 5A. Comparing these two groups, we see that introducing the 140 m/s, 0.15 mL first phase has come at an energy cost of 23 J, but resulted in an increase in volume delivered from 0.4 mL ± 0.3 mL to 0.8 mL ± 0.2 mL. A paired *t*-test between these two groups provided very strong evidence against the hypothesis that the two means are the same by returning a *p* value of 0.0041. This demonstrates that, for the injection of 1 mL, the required second phase jet speed during a two-phase injection is less than the jet speed required for success in a single-phase injection.

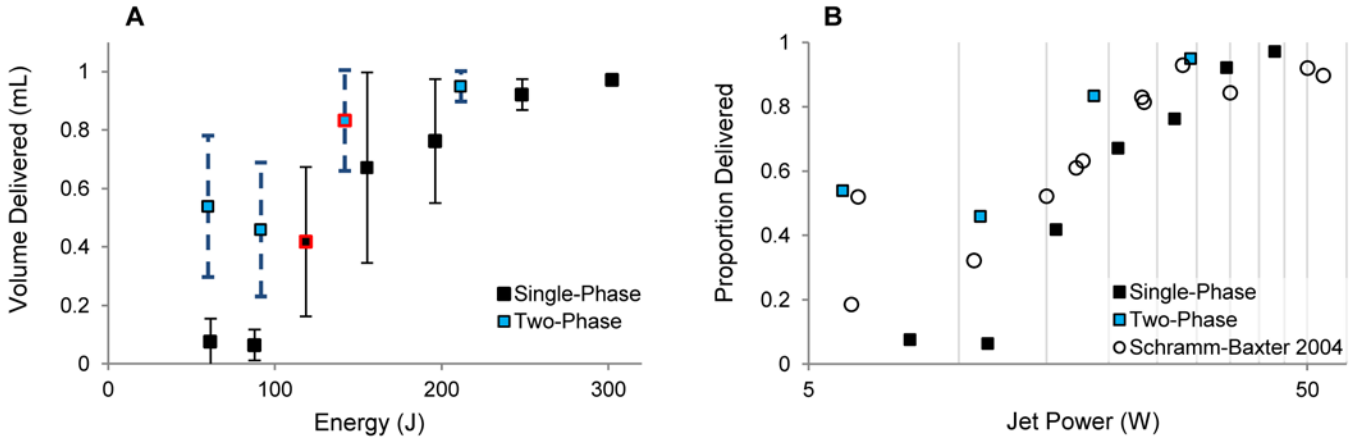

Fig. 5 – (A) The volume delivered for both the single and two-phase injections plotted against the total energy expended. The groups associated with 100 m/s are highlighted with red outline. Error bars indicate one standard deviation. (B) The proportion delivered versus the average jet power (log scale) for the single and two-phase results. These are compared to data presented by Schramm-Baxter et al [3] for the delivery of much smaller volumes (<100 µL) with a spring-driven injection device. Error bars were omitted for clarity.

Previously, second phase speeds as low as 50 m/s have been successfully employed by controllable injection devices for injection volumes up to 0.3 mL into porcine tissue [5],[27], [28]. However, attempts at using this speed during the injection of 1 mL were unsuccessful, even at second phase speeds of up to 60 m/s [17]. The results presented here suggest that the second phase jet speed must approach 100 m/s for successful delivery of 1 mL. This demonstrates that larger delivery volumes require greater second phase jet speeds in order to achieve substantial delivery.

4.2. Jet Power

The average jet power (*P*) was calculated for the single and two-phase injections using,

$$P = \frac{1}{8}\pi\rho D_o v_j,$$

where ρ is the liquid density, D_o is the orifice diameter and v_j is the average volumetric jet speed over the entire injection. The metric of jet power was first presented in [3], and was shown to correlate well with injection depth and delivery proportion.

To observe the jet power requirements of the injections presented here relative to lower volumes, the proportion delivered versus the average jet power is plotted in Fig. 5B, which includes results previously presented by Schramm-Baxter et al in 2004 [3]. The results taken from [3] are primarily from 0.07 mL injections into human cadaver tissue using a spring-driven injector (Vitajet 3, Bioject, Portland, OR).

Given the uncontrolled nature of the device used in [3] it would have performed injections that included a peak in jet speed at the very beginning of the injection [20], [24] that would have assisted in the initial penetration. Fig 5B indicates that the single-phase, 1 mL injections generally required a greater average jet power to achieve a given proportion delivered relative to the data from [18]. The greater delivery volume could be an explanation for this difference. However, the peak in jet speed would have also assisted the Schramm-Baxter results in reaching complete delivery at a reduced jet power.

We have already established that the delivery of 1 mL required a much larger second phase jet speed than that previously reported for the delivery of up to 0.3 mL with a controllable injection device [5], [27], [28]. Despite this, the two-phase results in Fig. 5B appear to be associated with a marginally reduced average jet power relative to the Schramm-Baxter data [18]. This could be due to the difference in the initial jet speed applied by each of the injectors. The longer, controlled first phase of jet speed produced by our device may have presented a greater benefit to delivery relative to the very short, uncontrolled peak applied by the spring-driven injector.

At this stage little else is known about how the volume and speed associated with the first phase impacts upon the required second phase speed. It would seem that increasing the first phase volume or speed could only improve the delivery characteristics and permit a reduced second phase speed. However, this would come at an energetic cost ($E \propto v_j^3$ [10]) and requires further testing to properly evaluate. Other system characteristics, particularly the jet size [3] and shape [28], would also be expected to affect the liquid delivery.

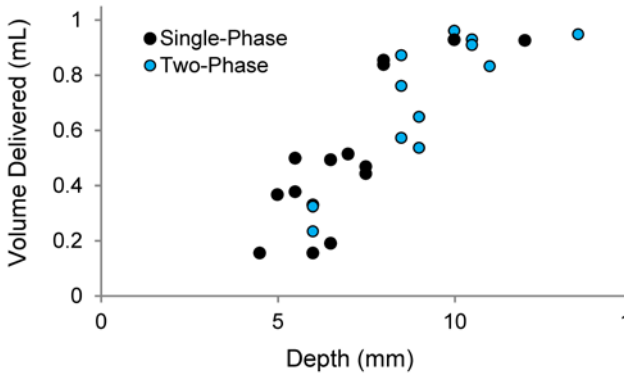

Fig. 6 – The volume delivered plotted against the maximum depth for all subcutaneous injections.

4.3. Tissue Layer Effects

4.3.1. Tissue Permeability During Penetration

The single-phase results indicate that all those injections which penetrated into the muscle also had a very high volume delivered whereas those in the subcutaneous fat were less successful and quite variable. Could this observation be due to muscle tissue being more permeable to an injected liquid than the subcutaneous fat? In rats, the permeability of muscle tissue (abdominal muscle) has been reported as being two orders of magnitude greater than that of subcutaneous fat tissue [29], [30]. However, in dogs, the permeability of subcutaneous fat has been shown to rise steeply and nonlinearly with the interstitial pressure [30], [31]. This was supported by an injection study into porcine adipose tissue, which found the formation of micro-cracks during injection caused the permeability of the fat to increase by more than 2 orders of magnitude [22].

These reports provide some insight into the relative permeability of the subcutaneous fat and muscle tissue at rest, and the way in which an injection increases the permeability of the subcutaneous fat. What we are missing is an understanding of how a jet injection affects the permeability of the muscle. It is reasonable, however, to expect that the disruption resulting from an injection would increase the permeability. This expectation, and the observations made in this paper, suggests the hypothesis that the muscle tissue accepts a jet injected liquid more readily than the subcutaneous fat. This would require further investigation to properly evaluate, and there is the need to confirm that this behaviour is also reflected in human tissue.

4.3.2. Subcutaneous Fat

In both the single-phase and two-phase injections a strong correlation between volume delivered and maximum depth was observed for those injections which penetrated as far as the subcutaneous fat. The volume delivered versus maximum depth for all injections (single and two-phase) which penetrated into the subcutaneous fat can be seen in Fig. 6. This relationship appears to be similar for both injection profiles and fairly linear (R^2=0.75); a linear fit to this data has a gradient of 0.1 L/m.

This gradient could be interpreted as suggesting that for every millimetre of penetration into the subcutaneous fat up to 0.1 mL of liquid can be delivered. However, an increased volume dispersed in the tissue would itself increase the measurement of maximum depth. This confounding fact makes it difficult to accurately quantify the benefit to delivery achieved by deeper penetration. A centroid-based depth

measurement could reduce this effect, but this would require a more sophisticated imaging technique. One option may be the use of micro-CT imaging, as conducted in previous injection studies [22], [25].

5. Conclusions

A controllable voice-coil driven jet injection device was developed and used to deliver 1 mL into post-mortem porcine tissue using single- and two-phase jet speed profiles. These injections demonstrated that a two-phase jet speed profile can be used during 1 mL injections to achieve delivery success at a reduced energy cost. The use of a two-phase jet speed profile achieved a mean volume delivered of over 0.8 mL while expending just 140 J, whereas similar success with a single-phase profile required over 200 J. The advantage of two-phase delivery is much less significant than that previously demonstrated at lower injection volumes, suggesting a greater second phase jet speed is required with greater injection volumes. For the injection system presented here, a second phase speed of 100 m/s or greater was required for delivery success. Despite this increase in required second phase speed with volume, the delivery of 1 mL in two-phases was found to require a reduced average jet power relative to the uncontrolled delivery of 0.07 mL. This suggests that there may be a benefit to delivery when injecting with a controlled two-phase jet speed profile.

The delivery volume was observed to be correlated with the tissue layer, as well as with depth into the subcutaneous fat. Both these observations raise important questions for future investigation related to large volume jet injection: Is there a minimum depth associated with a given delivery volume that must be achieved for success; and, is the muscle tissue inherently better able to support the delivery of larger volumes of a jet injected liquid relative to the subcutaneous fat?

Acknowledgements

The authors would like to thank Mr Stephen Olding for his assistance with the construction of the large-volume injection device, and, Mr Samuel Richardson for his help with the collection of post-mortem porcine tissue. This work was supported by the MedTech Centre of Research Excellence, funded by the Tertiary Education Commission of New Zealand; and the Science for Technological Innovation National Science Challenge, funded by the New Zealand Ministry of Business, Innovation and Employment.

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