Jet injectors: Perspectives for small volume delivery with lasers

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1. Introduction

Injections using hypodermic needles are among the most common procedures in modern medicine, but pain and phobia affect patient compliance [1–3]. About 3–4% of the world population has a severe blood injury and injection (BII) phobia [4]. BII is found to be the main reason for 11.5% of the Covid-19 vaccine hesitant people in the UK [5]. Moreover, healthcare workers regularly suffer needle-stick incidents with grave consequences for their own health and the economy [6,7]. Furthermore, millions of single-use needles must be processed as sharps waste after use [8,9]. For these reasons, minimally-invasive, and less painful procedures are urgently needed for the delivery of drugs such as vaccines or insulin.

Needle-free jet injectors (NFJIs) have been proposed as an alternative to injections with hypodermic needles. Currently, a handful of commercial needle-free jet injectors already exist. However, these injectors are designed for specific injections, typically limited to large injection volumes into the deeper layers beneath the skin. There is growing evidence of advantages when delivering small volumes into the superficial skin layers, namely the epidermis and dermis. Injections such as vaccines and insulin would benefit from delivery into these superficial layers. Furthermore, the same technology for small volume needle-free injections can serve (medical) tattooing as well as other personalized medicine treatments.

The research dedicated to needle-free jet injectors actuated by laser energy has increased in the last decade. In this case, the absorption of the optical energy by the liquid results in an explosively growing bubble. This bubble displaces the rest of the liquid, resulting in a fast microfluidic jet which can penetrate the skin. This technique allows for precise control over volumes (pL to µL) and penetration depths (µm to mm). Furthermore, these injections can be tuned without changing the device, by varying parameters such as laser power, beam diameter and filling level of the liquid container. Despite the published research on the working principles and capabilities of individual laser-actuated jet injectors, a thorough overview encompassing all of them is lacking. In this perspective, we will discuss the current status of laser-based jet injectors and contrast their advantages and limitations, as well as their potential and challenges.

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ABSTRACT

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efficient, and the required dose could be reduced by a factor of five to ten [19–25]. Another example is insulin, which currently is injected into the subcutis, whereas injections into the dermis is more efficient [26–31].

Recently, there has been a renewed interest in the research of needle-free jet injectors that rely on laser energy [32–37]. The main advantage of these laser-based injectors is the accurate control over the energy deposition and thus, the penetration depth [38]. These injectors work as following: the absorption of the optical energy by the liquid results in an explosively growing bubble. This bubble displaces the rest of the liquid, resulting in a fast microfluidic jet that is able to penetrate the skin. So far, this technique has shown to be capable of creating jets of very small volumes (< 1 nl to 2 μL) [38,39] and penetration depths in the range of μm to mm into hydrogels [40] and porcine skin [41,42]. Furthermore, the volume and injection depth can be controlled without changing the device, by varying parameters such as laser energy, beam diameter and filling level of the liquid container [33,40,43]. This dynamic control over a large range of volumes is key to enabling superficial and personalized injections.

We have identified a knowledge gap in the literature covering laser-based jet injections. Most studies have focused on individual concepts or configurations. Here, we provide an overview and comparison between the results from different research groups, highlighting their potential uses and limitations. First, in Section 2, we review the current status of various needle-free jet injector technologies and their limitations. In Section 3, we will discuss small volume delivery. Here, we will first discuss the applications, continue with the advantages, and finally discuss alternative methods for delivery of small volumes. Section 4 discusses the working principle and current status of laser-based needle-free microjet injectors. Finally, in Section 5 we look at their limitations and propose research needed to accelerate the commercialization of laser-based jet injectors.

2. Current needle-free jet injection technology

Although the first concept of a needle-free jet injector originates from the 19th century [44], the first use was not reported until the second half of the last century. Mechanical needle-free jet injectors had been used for mass-vaccinations [46], until they were banned by the World Health Organization near the end of the 20th century, due to cross-contamination caused by splash-back on the injection nozzle [49]. The move to single-use nozzles has overcome this problem, resulting in the resumed use of needle-free jet injectors from the start of the 21st century [6]. The use of needle-free injection resembles the hype cycle model [63], where currently an increasing number of injectors have become available after an initial peak in the 20th century. An extensive timeline on the use and development of jet injection is shown in Fig. 1.

Table 1 shows the major needle-free jet injection technologies and their characteristics. Fig. 2 shows typical injection volumes and depths for each injection technology. In this table and figure, a clear distinction is shown between two types of jet injectors. The traditional jet injectors inject deeper into the skin and deliver the complete volume in a single jet. More recently, laser-based jet injectors deliver smaller volumes in a single jet, and allow for more superficial injections. An overview of the development of the various technologies is shown in Fig. 3.

In this section, we will discuss the traditional jet injectors and the more recent variations. Traditional technologies make use of a piston to displace the liquid. This liquid is then accelerated through a nozzle, creating a high-speed jet which can penetrate the skin. The main difference between traditional jet injectors is the energy source to displace the piston.

2.1. Mechanical energy

The first jet injectors used mechanical force, such as a compressed spring, to accelerate the liquid (see Fig. 4a). This technology creates jets with a volume in the order of 100 μL (depending on the ampoule) and a typical velocity of 60–140 m/s [92,93]. Several commercial injectors exist that use a compressed spring, such as the Injex 30 and the Bioject Intra-Dermal Pen (Bioject ID pen). One of the main limitations of this method is that the amount of input energy is fixed by the spring, which limits the options to control the jet characteristics [13]. Furthermore, spring-based jet injectors are characterized by a non-uniform acceleration phase [78], which reduces the predictability of the jet and complicates accurate delivery in the superficial layers. Therefore, most spring-based injectors are limited to injecting into the deeper skin layers.

Compressed gas (e.g. air or CO₂) can serve as an alternative mechanical source (Fig. 4b). The Airjet from Union Medical Corps, for example, uses compressed air [94]. Mohizin & Kim [95] compare experimental results with this Airjet, with numerical simulations, to predict optimum nozzle geometry for maximum penetration depth, leading to typical jet velocities of 300 m/s. The jet velocity can be controlled by the volume of compressed gas. This can be done for example by burning gun powder [96]. Miyazaki et al. [97] tested the commercially available pyro-drive jet injector from Actranza. This jet injector creates gas by means of an ignition powder and a smokeless powder, where the smokeless powder generates gas once the ignition powder is burned. By changing the amounts of both powders, the jet characteristics can be controlled. For most jets they observed a large amount of splash-back (> 50%). Only for two specific ratios they found no splash-back (< 5%), which resulted in jets of 226 and 263 m/s and penetration into the subcutis and muscle of porcine tissue (> 8 mm depth). The Enerjet2.0 (successor of Airgent, by PerfAction) is an electronic pneumatic injector, which allows for an adjustable pressure [58]. Bik et al. [98] use this injector for dermal injections of 50 μL into porcine skin, creating a reproducible papule as clinical endpoint. However, for the used pressures (4 and 6 bar), they do not see a clear difference in the resulting dispersion profile. Other work found a pressure dependence in the dispersion for cutaneous injections between 3.1 and 4.6 bar [89], for which reason they hypothesize that for small pressures, the injection depth and dispersion could be controlled by the adjustable gas pressure. Arguably, most compressed-gas needle-free jet injectors are better suited to deliver larger volumes (> 50 μL) into the deeper tissues (subcutaneous fat and muscles).

2.2. Electro-mechanical energy

A different way to accelerate the liquid is to make use of an electro-mechanical actuator to control the piston. This allows for electronic control over the liquid displacement and the consequent jet velocity. An example is a piezo-element, which expands and contracts depending on the applied voltage. A quick (τ ~ 5 ms) expansion of the piezo-element results in the displacement of the piston and acceleration of the liquid (see Fig. 4c). A piezo-electric micro-jet injector has been developed at the University of California, creating jets of 50–160 m/s [75,99,100]. As the piston is controlled electronically, it is even possible to change its velocity during the jetting phase. This allows to create a jet with a fast tip (~100 m/s), and a slower tail (~20 m/s). These jets allowed for increased control over penetration, and reduced splash-back [77]. Typical jet volumes depend on injector geometry and vary from ~ 10 nl [76] to 100 nl [75,77], with penetration depths of 1 to 10 mm (into poly-acylamide gels with varying concentrations). Although the piezo-electric micro-jet injector allows for small delivery over a large range in injection depths, a few challenges...
remains. First, it requires a voltage amplifier with a voltage range of 
-30 to 150 V and peak current of 4 A, which would make it an
expensive and large device. Furthermore, repetitive jetting has
only been shown for the smallest volumes (2–15 nL), at a
rate of 1 Hz [76], for which reason larger injection volumes
(e.g. 10–100 μL) would require a long time (> 10 min).

A collaboration between MIT and the University of Auckland
has led to the development of a needle-free jet injector actuated
by a voice coil (see Fig. 4d) [78,101–103]. They modified a
commercially available spring-based needle-free jet injector (Injex 30),
such that the piston is moved by Lorentz force. This injector
is further improved by using a feed-back loop, which leads to

Table 1
Overview of various needle-free injection technologies and their characteristics.

| Energy source   | Technique      | Typical jet volume | Typical velocity | Typical depth | Dynamic jet control | Commercially available |
|-----------------|----------------|--------------------|------------------|---------------|---------------------|------------------------|
| Mechanical      | Spring         | 100–1000 μL        | 100 m/s          | 2–10 mm       | No                  | Yes                    |
|                 | Compressed gas | 100–1000 μL        | 100–300 m/s      | 2–10 mm       | Limited             | Yes                    |
| Electromechanical| Piezo-electrical| 1–400 nL           | 50–150 m/s       | 0.3–5 mm      | Yes                 | No                     |
|                 | Lorentz force  | 20–1000 μL         | 50–200 m/s       | 1–20 mm       | Yes                 | No                     |
| Optical         | Pulsed laser   | 1–1000 nL          | 100–300 m/s      | 0.1–5 mm      | Yes                 | Yes                    |
|                 | CW laser       | 1–100 nL           | 20–100 m/s       | 0.1–1 mm      | Yes                 | No                     |

Fig. 1. Progress of needle-free jet injectors over the past 200 years. Copyright images from top to bottom: (1) © La Bibliothèque Interuniversitaire de Médecine, l’Université de Paris V - René Descartes, (2) Reprinted with permission from [62], licensed under CC-BY 2.0, (3) © PATH / WHO, (4) © K-Health.com. (See above-mentioned references for further information.)
decrease in noise during the acceleration-phase compared to other type of injectors [78]. This injector also allows for the injection of more viscous liquids, which has not been demonstrated with mechanical injectors [104]. Similar to the piezo-element jet injector, a two-phase jet (fast jet tip, slower tail) allows for better control over penetration depth [83]. Initially this jet was created by changing the coil voltage, but that required a power amplifier [79]. This problem was solved by replacing the piston with a compound ampoule with two concentric pistons, such that a single constant current results in the same two-phase jets [80,85]. The main focus of these Lorentz force injectors are to inject large volume jets (typically 100–1000 μL) into the deeper layers (subcutis and muscles) [81,84]. Currently, Portal Instruments, a spin-off company from MIT, is working on the commercialization of this method and have performed clinical studies with their PRIME injector [86,105].

3. Small volume injections

Most traditional injections deliver a large volume (> 100 μL) into the deeper body layers, such as the subcutis or muscles. This is also the case for the jet injectors discussed in Section 2. Currently, there is an increased interest in small volume injections into the superficial skin layers (epidermis and dermis), as evidenced by the large body of work on micro-needles [14,106–113]. These small volume injection have many therapeutic advantages and allow for more personalized treatment. We define these small volume injections by their volume (single injection < 5 μL) and injection depth (into the epidermis and/or dermis). If required, multiple of these small volume injections can increase the total delivered volume.

In this section we will first discuss several applications. We will continue with the advantages of splitting an injection up in many
injections of a smaller volume. Finally, we will shortly discuss alternative methods for delivery of these small volumes into the superficial skin layers.

3.1. Applications

Injections can be split in three categories: inert, therapeutic and reactive injections. In this section, these applications will be discussed with a few examples, their characteristic injection depths and volume, as well as the risks and opportunities. A small tabular overview is also shown in Table 2.

3.1.1. Inert injections

Inert injections do not have any clinical effect on the body tissue. As the injectate is not a therapeutic active compound, risk of degradation due to heating or shear stresses is very low. Examples
of inert injections are permanent make-up and other aesthetic injections. These are associated with cosmetic purposes, but can also be used after specific surgeries. Examples are optical mimicking of a nipple after breast removal [117] and camouflaging scars or birthmarks [118]. Most of these small volume inert injections are done using solid needles. However, experiments with needle-free injection showed an increasing injection efficiency and lesser damage to the skin [34,66].

### 3.1.2. Therapeutic injections

These include injections of medication which interact with the body, such as vaccines or insulin. Once the reliability and safety of these therapeutic injections are ensured, there is much to gain from accurate volume and depth control of the injection. However, for hypodermic needles, superficial injections into the dermis are only possible through the Mantoux method. This is a difficult and inconsistent injection method and requires highly trained personnel [119,120]. Furthermore, the patient often experiences more pain during this injection [121]. For this reason, almost all needle injections are done in the deeper skin layers, such as the subcutis and muscles. For some therapeutic agents this deep injection of larger volumes is preferred, such as those treating hypertrophic scars [122] or multiple sclerosis [123]. However, many therapeutic agents work more efficiently in the more superficial layers, leading to improved efficacy and potential dose-sparing.

For example, most vaccines should target Langerhans cells to maximize efficacy [6,8,15,124]. Langerhans cells are dendritic cells, a type of antigen-presenting cells, which are vital in the first stage of the immune system, as they recognize the invading virus or vaccine [17,18]. As shown in Fig. 5, these Langerhans cells are the most potent immune cell in the Stratum Spinousum, which is in the epidermis [10,20,22,125]. Currently, vaccines are often injected intra-muscularly, where these dendritic cells are less numerous [14,16]. By directly targeting these Langerhans cells, only a fraction of the dose is required [22], which makes mass-vaccination programs much cheaper and faster. Examples of vaccine dose reduction are yellow fever [23], influenza [19] and rabies [21], for which the required dose for intradermal injection is at least five times smaller than for intramuscular injection. Preliminary results from Leiden University on the Moderna Covid-19 vaccine indicate that intradermal injection of 1/10th to 1/5th of the intramuscular dose result in a sufficient immune response [126]. Furthermore, it was found that intradermal administration of mRNA vaccines achieved a stronger SARS-CoV-2 pseudovirus neutralization, and more rapidly induced IgM antibodies compared to intra-muscular administration [127].

Alternatively, insulin is usually injected by a single dose into the subcutaneous [29]. However, intradermal insulin injections are advantageous, as the uptake in the dermis is much faster [27,28,128]. This accelerated uptake could be increased further by splitting the dose into multiple smaller injections spread out over a larger area [26,30].

#### 3.1.3. Reactive injections

These include injectates which do not have any therapeutically active compounds, but interact with the tissue in a minor way. For example, medical tattoos containing biomarkers that monitor specific biomolecules such as glucose [129], antibodies [130], pH [131], various electrolytes [132,133], or react to excessive UV-irradiation [134]. The biomarker is injected into the dermis and passively monitors the concentration of a specific biomolecule. Once the concentration is outside of a (specified) safe range, the tattoo color changes, which can be observed by the carrier.

For these tattoos, the degradation of these injectates during injection might be a problem, but the health risks in case of incorrect delivery are much lower compared to the therapeutic injectates. However, all of these above-mentioned medical tattoos are not yet fully developed, for which reason this remains a futuristic application.

#### 3.2. Advantages of repeated small volume injections

All commercial needle-free jet injectors inject the complete injectate in one event (Fig. 6a left). Alternatively, the dose could be split up into multiple micro-boluses, either consecutively (Fig. 6a middle), or simultaneously (Fig. 6a right). Micro-jet injection has several advantages over macro-jet injection:

- **More superficial injections:** Due to the smaller volume of a single jet, it is possible to inject more accurately into the superficial skin layers, such as the epidermis and dermis. This can be seen in Fig. 2; large volume jets (>10 μL) have a larger penetration depth compared to small volume jets (<10 μL) with the same velocity. These superficial injections have many therapeutic advantages (see Section 3.1.2).

- **Improved volume accuracy:** Assuming the relative volume accuracy of a single jet is constant, the error in the volume is linear to 1/√N, where N is the number of jets (see Fig. 6c). Furthermore, the number of jets can be changed for each patient to allow more personalized injections.

- **Larger targeted area:** Injection of many micro-jets result in increased surface area of the injected liquid, whereas for macro-jets, the complete volume is injected as a single large spherical-shaped injection. This increases the total number of
targeted cells. Furthermore, as many small volume injections have a larger combined surface area compared to a single injection of the same total volume, this increases diffusion. Both of these effects result in an accelerated uptake of the medication.

**Improved concentration control in therapeutic window:** By reducing the individual jet volume, it is possible to spread the injections over a longer time span. Frequent jetting of small volumes allows to control the concentration of the medication at a more constant rate, as shown in Fig. 6d. For large volume injections, it is difficult to keep the concentration within the therapeutic window for a long time, which is necessary for safe and effective therapy.

**Less pain and bruising:** Both the dermis and the subcutis contain nerve endings which are sensitive to pain [136], However, pain associated with injections is typically stimulated by the deeper lying nerve receptors [137]. Macro-jet injectors often...
cause pain, which is explained by the diffuse nature of the jet tip and large variance of injection depth [10,138]. As the small volume superficial injections have smaller power (due to jet mass and velocity) and do not come in contact with the subcutaneous nerve endings, they result in less pain and therefore improved patient compliance.

3.3. Current small volume delivery methods

Various methods to deliver small volumes of liquid to the superficial skin layers already exists. These include topical applications, such as patches and creams, laser-assisted drug delivery, and also micro-needles and tattoo injections. These are briefly discussed in the following subsections.

3.3.1. Patches and creams

The first generation of (epi-) dermal delivery consisted of patches and creams. In these delivery systems, the therapeutic compounds are dissolved in a vehicle liquid, often an oil-in-water or water-in-oil emulsion [139]. When the patch or cream is applied onto the skin surface, the vehicle liquids diffuse through the skin. Their non- or minimal-invasiveness and ease of use make creams and patches seemingly ideal (epi-) dermal drug delivery systems [140,141]. However, the transport pathway of the drugs is highly constrained by the structural and solubility requirements for solution and diffusion [142]. The vehicle liquid should be mainly lipophilic to enhance the penetration [143]. Furthermore, the therapeutic compounds cannot have a large molecular weight or viscosity, as that would retard the diffusion [22]. The passive transport could be enhanced using chemical enhancers to soften the stratum corneum, such as DMSO or glycerol [144]. Alternatively, the transport could also be enhanced by ultrasound [145] or electrophoresis/iontophoresis [142]. However, the number of drugs which can be delivered using patches is still limited to twenty [140]. For a more detailed review discussing the progress and current status of patches and creams, we refer to [139,140,142].

3.3.2. Laser-assisted drug delivery

As discussed in the previous subsection, passive transport of drugs through the skin is limited to a few compounds due to solubility and structural requirements. A laser can be used to simplify penetration of drugs through the skin by creating a hole in the epidermis, which is called skin ablation [146,147]. By choosing a wavelength at which the absorption coefficient of water is large (which is in abundance in the skin), only a thin zone is affected [148]. The two mainly used lasers are the Er:YAG (2940 nm, $\alpha \approx 12000 \text{ cm}^{-1}$ [149]) and CO$_2$ laser (10600 nm, $\alpha \approx 800 \text{ cm}^{-1}$ [149]). Laser ablation was first used by exposing a part of the skin with a single laser spot. In this method, the whole exposed area was damaged. More recently, fractional laser ablation has been used to create multiple small microchannels in the epidermis. The laser beam is split in several smaller beams in a specific pattern. The depth, width, and density of the microchannels etched on the skin depend on laser parameters, such as pulse energy, pulse duration, wavelength and number of laser beams [150]. In turn, these microchannel’s characteristics influence the rate and depth of the drug uptake, providing control over the drug delivery profile. For a more detailed review on laser-assisted drug delivery, we refer to [150].

3.3.3. Micro-needles

Micro-needles are needles with a typical length of 150–1500 $\mu$m [151]. They have been developed to penetrate the epidermis specifically, and avoid the deeper tissues [107,108]. This allows controlled injection into the dermis, which besides offering therapeutic advantages, also reduces pain and fear commonly encountered with hypodermic needles. Although the first concept of micro-needles originates from 1976, fabrication was difficult and they were only first applied around 1998 [152]. Micro-needles can be used as individual needles delivering the whole volume at once or in an array. Single micro-needles work similar to hypodermic needles, except they are much smaller, in order to reduce the injection depth.

Micro-needle arrays exist in various ways, such as solid, hollow, dissolvable and coated arrays [110,112,153]. Solid micro-needles create a hole in the epidermis, after which a drug-loaded-patch can be applied [154,155]. The drug can then easily pass the epidermis through these holes. Hollow micro-needles create a hole in the epidermis, and drugs can be injected from a reservoir through these hollow needles [156,157]. Dissolvable or swellable needles can be inserted into the skin after which they will dissolve or swell. The drug is trapped within the needle at the fabrication stage. When the needle dissolves or swells, it releases the drug [158]. Finally, coated micro-needles are similar to solid micro-needles; during their insertion into the skin, the coating will be released from the micro-needle surface [159].

Although micro-needles allow for superficial injections of small volumes, some downsides remain. First of all, they are still invasive, as they create a hole in the epidermis. Due to their size they cause less pain compared to hypodermic needles, but fear of needles may still make people hesitant to get their injection. Second, it is difficult to determine whether the dose has been successfully administered [108]. Furthermore, the manufacturing process is complex. They also cannot be re-used, for which reason, a new patch has to be fabricated for each injection. With the exception of dissolvable needles, they also result in waste. For a more detailed review on micro-needles, we refer to [106,107,109,113,160,161].

3.3.4. Tattooing devices

Tattoo devices are mainly known for the injection of permanent make-up, or pigmentation of the skin (inert injections, see Section 3.1). However, they can also be used for therapeutic injections, such as vaccinations [14]. By a high-frequency oscillating motion of a solid needle, the tattoo device creates punctures into the skin, delivering a fraction of the injectate with each puncture [120]. One of the main advantages of this type of injection, is the large spreading of the injectate. For tattoo vaccination, this likely increases the number of stimulated antigen-presenting cells [162]. However, tattoo injections may cause pain or local trauma at the injection site, due to which compliance might reduce. For a more detailed review discussing tattoo vaccinations, we refer to [111,163–165].

4. Laser based needle-free jet injectors

Over the last decade, NFJIs have been developed making use of optical energy from a pulsed or continuous wave (CW) laser. Table 3 shows typical characteristics of these two laser types. Tables 4 and 5 show all peer-reviewed work on laser based needle-free jet injectors for pulsed and CW lasers respectively, following a thorough literature search. In this section, we will first discuss the working principle of these injectors. Secondly, we will discuss the jet characteristics found in literature, such as the velocity, injection depth, volume and jet coherence, including ways to control and improve them. Finally we will discuss temperature measurements.
lasers. The exact working principle for both type of lasers is slightly different and will be discussed in the upcoming subsections. Lasers with a longer pulse duration (ns-μs) are slightly less expensive, for which reason they are used more. However, the energy absorption by water (diluent for many vaccines [173], at these wavelengths is negligible [174]. Therefore, a dye should be used to increase the linear absorption for lasers in the visible or near-infrared regime.

Alternative, a mid-infrared laser can be used due to the high absorption coefficient of water at these wavelengths. This was done by the group of Yoh with a Er:YAG laser (2940 nm) [39,41,59,171]. These Er:YAG have a relative long pulse duration of 250 μs (compared to ns pulses). The influence of the pulse duration was studied in Ref. [171], where the authors compare the Nd:YAG (7 ns) and Er:YAG laser (250 μs) with identical pulse energies. They found that even though the absorption coefficient is much higher, the longer pulse duration causes a decreased absorption rate. This decreased absorption rate results in a three-times slower bubble growth and also smaller jet velocity (28 compared to 74 m/s). This can be explained by the fact that the nucleation already occurs within 50 microseconds, at which point only twenty percent of the laser energy has been delivered. After the bubble formation, the energy absorption is less efficient, resulting in a reduced bubble growth.

More recently, a ns-pulsed laser at 1570 nm [74] was used for the creation of microfluidic jets. This is the first experiment reported with a relatively cheap and small pulsed laser [175] without the need of a dye, due to the high absorption coefficient of water.

### 4.1. Working principle and energy conversion of laser-based microjet injection

The working principle of laser-based microjet injection is shown in Fig. 7. A laser is focused on a small volume of liquid in the dose chamber, creating a vapor bubble. This bubble displaces the rest of the liquid, resulting in a jet. These laser-based injectors can rely on two types of lasers: pulsed lasers and continuous wave lasers. The exact working principle for both type of lasers is slightly different and will be discussed in the upcoming subsections.

#### 4.1.1. Pulsed lasers

The laser based needle-free jet injectors started with pulsed lasers in 2010 [32]. These pulsed lasers generally deliver an energy of 100 μJ to 1 J within femto- to microseconds, resulting in a very high power density. For extreme power densities, optical breakdown occurs, which is the ionization of the medium due to non-linear absorption, and results in formation of a plasma [166]. This plasma then absorbs the energy through linear absorption, resulting in the formation of a vapor bubble [167]. The energy threshold for this optical breakdown increases with pulse duration [168]. Therefore, the energy threshold is the lowest for lasers with very short pulses (Fs-ps), but these ultra-short pulsed lasers are very expensive, in large size and limited in availability.

Lasers with a longer pulse duration (ns-μs) are slightly less expensive, for which reason they are used more. However, the energy absorption by the plasma alone is relatively low, thus a larger pulse energy is necessary (>1 J). Alternatively, light absorption can be increased by choosing a laser wavelength at which the liquid has a high absorption coefficient. Generally, a ND:YAG laser is used at a wavelength of 532 [32,35,72,169,170] or 1064 nm [171,172]. However, linear absorption by water (diluent for many vaccines [173], at these wavelengths is negligible [174]. Therefore, a dye should be used to increase the linear absorption for lasers in the visible or near-infrared regime.

### Table 3
Comparison of pulsed and continuous wave lasers.

| Parameter                  | Pulsed laser (fs-ps) | Pulsed laser (ns-μs) | CW laser |
|----------------------------|----------------------|----------------------|----------|
| Timescale                  | 100 fs - ps          | ns - 100 μs          | 100 μs-10 ms |
| Origin of breakdown        | Optical              | Optical & thermal    | Thermal  |
| Origin of bubble           | Plasma               | Plasma & superheating| Superheating |
| Cause of absorption        | Non-linear           | Non-linear & linear  | Linear   |
| Laser parameter            | j/cm²                | j/cm²                | W/cm²    |
| Typical energy             | 10 μJ - 10 mJ        | 100 μJ - 1 J        | 0.1-10 mJ |
| Typical (peak) power       | 1-500 MW             | 1 kW - 1 MW         | 0.1-5 W   |
| Price                      | Very expensive       | Expensive            | Inexpensive |

### Table 4
Table shows all peer-reviewed publications on laser-based needle-free jet injection using pulsed lasers, including the corresponding jet characteristics. Not all studies reported a jet volume, and some did not study the injection itself but only the jet formation.

| Research Institution                  | Jet Velocity [m/s] | Jet Volume [nL] | Injection depth [μm] (substrate) | Year & Reference |
|---------------------------------------|--------------------|-----------------|----------------------------------|------------------|
| Seoul National University (South Korea) | 50–320             | ~ 2             | -                               | 2010 [32]        |
|                                       | 230                | -               | 750 (Pork fat)                  | 2011 [183]       |
|                                       | 230                | 100             | 400–1200 (Gelatin)              | 2012 [69]        |
|                                       | 20–45              | 50*             | 1250–5000 (Gel)                 | 2012 [59]        |
|                                       | 28–74              | -               | -                               | 2013 [171]       |
|                                       | 23–50              | 450–2000        | 417 (Porcine Skin)              | 2014 [39]        |
|                                       | 87–120             | 200–600         | 600–1400 (Porcine skin)         | 2014 [71]        |
|                                       | 120–220            | -               | 400–600 (Porcine skin)          | 2016 [42]        |
|                                       | 90–140             | -               | 600–1400 (Porcine skin)         | 2017 [41]        |
|                                       | 10–80              | < 0.2           | 0.250 (Gelatin)                 | 2018 [38]        |
| École Polytechnique Fédérale de Lausanne (Switzerland) | 30–225             | 14              | 1000 (Agarose)                  | 2020 [35]        |
|                                       | 50–450             | 0.01            | 100–1700 (Hydrogel)             | 2020 [40]        |
|                                       | 45                 | 10              | -                               | 2021 [74]        |
| University of Twente (The Netherlands) | 20–850             | 50*             | -                               | 2012 [33,43]     |
|                                       | 30–250             | 75*             | 100–5000 (skin model on gel)    | 2013 [70]        |
| Tokyo University of Agriculture and Technology (Japan) | 20–90             | -               | -                               | 2017 [169]      |
|                                       | 100–180            | -               | 1600–3000 (Gel)                 | 2019 [72]        |
|                                       | 0–40               | 400*            | -                               | 2021 [184]      |
| University of California Riverside (US) | 10–87              | 5               | 570 (Agarose)                   | 2020 [73]        |
| Texas Tech University (US)            | 35–46              | 100–250         | 100–2000 (Gelatin)              | 2020 [37]        |
|                                       | 20–250             | 200–700         | 100–2000 (Gelatin)              | 2020 [37]        |

* Volume not defined by authors, estimate taken from images.
4.1.2. Continuous wave lasers

Alternatively to pulsed lasers, a continuous wave laser can be used to create a vapor bubble. CW lasers have a much lower output power (mW - W) compared to pulsed lasers; therefore, there is no optical breakdown. The liquid is superheated within a few milliseconds \( T > T_{\text{boiling}} \) due to linear absorption, resulting in thermal breakdown and the formation of an explosive growing vapor bubble [176]. Rastopov and Sukhodolsky discovered this process in 1987 and called it thermocavitation [177].

Berrospe-Rodriguez et al. [64] were the first to use CW lasers to create fast microfluidic jets for jet injection. Due to the low output power compared to pulsed lasers, they are smaller, cheaper and do not require active cooling, which makes them ideal for needle-free injection [36]. However, as thermocavitation only relies on the linear absorption and thus requires a high absorption coefficient, the laser wavelength and liquid have to be matched. Typical absorption coefficient values used in literature are \( \alpha \approx 100 \text{ cm}^{-1} \) [65,178].

As water is transparent for visible (400–700 nm) and near-infrared light (700–1300 nm) [174], a dye is needed to increase the absorption coefficient. In literature, this was either achieved by a combination of a near-infrared laser and a copper-nitrate solution [64,65,67], or alternatively a blue laser and a red dye (Direct Red 81) [34,36,66,68]. However, for jet injection, these chemical dyes are unwanted, as copper nitrate is corrosive [179] and the medical safety of Direct Red 81 is not guaranteed [180]. Recently, Afanador-Delgado et al. [181] used a non-toxic natural dye from a dried flower (Hibiscus Sabdariff). Using a green laser (\( \lambda = 532 \text{ nm} \)), they created vapor bubbles initiated by thermocavitation. For this study, only the bubble formation in bulk liquid was observed. To investigate jet formation, the experiment has to be repeated in the vicinity of a liquid–air interface.

Similar to pulsed lasers (Section 4.1.1), it is possible to use a mid-IR laser and omit the dye. For wavelengths of \( \lambda > 1900 \text{ nm} \), the absorption coefficient is comparable to the previously mentioned laser-dye combinations (\( \alpha > 100 \text{ cm}^{-1} \)). Chudnovski et al. [182] create vapor bubbles initiated by thermocavitation with a 1940 nm laser; but similar to the natural dye, further studies are necessary to proof the capability to create microfluidic jets with the right characteristics to deliver a payload into the skin.

4.2. Jet velocity

The velocity of the tip or front of the jet is the most studied jet characteristic and has therefore been reported extensively (see Table 5 below). This table shows all peer-reviewed publications on laser-based needle-free jet injection using continuous wave lasers, including the corresponding jet characteristics.

Table 5: Research Institution | Jet Velocity [m/s] | Jet Volume [nl] | Injection depth [μm] (substrate) | Year & Reference
---|---|---|---|---
Instituto Nacional de Astrofísica (Mexico) | 1–12 | ~ 1000* | - | 2013 [185]
2 | ~ 1000* | - | 2017 [186]
20 | ~ 200* | - | 2020 [67]
15–30 | 35 | 500–1000 (Agarose) | 2016 [64]
15–94 | 50 | 400–1000 (Agarose) | 2019 [34]
10–50 | 40 | 100–400 (Porcine skin) | 2019 [66]
15–65 | 40 | - | 2020 [36]
8–35 | 10 | - | 2021 [68]

* Volume not defined by authors, estimate taken from images.

Fig. 7. Schematic of working principle of laser-based needle-free jet injection. (a) Set-up with laser focused through an objective on dose chamber filled with liquid. Parameters relevant for jet velocity are: spot area 'S', filling level 'H', contact angle '\( \theta \)', channel diameter 'D'. (b) Moment of nucleation and jet formation. (c) Bubble growth and jet with velocity 'V'. (d) Jet splits from liquid and impacts on substrate. (e) Liquid volume 'Vol.' injected into substrate at depth 'd'. Liquid in channel is back at rest. A typical injection takes place within a millisecond.
It was found that the jet velocity is influenced by various parameters such as the laser, geometry of the dose chamber and the liquid. This was first extensively studied for pulsed lasers [33,40,59,171] and more recently also for CW lasers [36,64,65].

### Pulsed lasers

In an experimental study on the jet velocity, Tagawa et al. [33] proposed a shock-wave model, in which the jet velocity is proportional to the overpressure of this shock-wave. They confirmed these experimental results with a numerical model [43] and later also expanded this shock-wave model by finding that the velocity depends on the pressure impulse (pressure integrated over time) [169,187]. Ultimately, the jet velocity changes with multiple parameters: pulse energy, liquid volume, contact angle (curvature of meniscus), as shown in Eq. 1 and Fig. 7, where $V_j$ is the jet velocity, $E$ the pulse energy, $E_{heat}$ the minimum amount of energy needed to create the plasma, $\theta$ the liquid-capillary contact angle, $H$ the stand-off distance, $D$ the capillary diameter and $C_0$ and $\beta$ are constants. $S$ is the area of the laser spot, later added by Krizek et al. [35].

$$V_j = C_0 \times \frac{(E - E_{heat})(1 + \beta \cos \theta)}{HDS}$$

This equation shows that the jet velocity can be controlled by only changing the laser pulse energy. This allows for a change in jet velocity (and thus penetration depth) without changing the device or the liquid volume. It is also possible to increase the liquid volume (filling level $H$ or capillary diameter $D$) and keep the velocity constant, by changing the effective energy ($E - E_{heat}$) by the same ratio. This allows to reach jet velocities in a range larger by one order of magnitude with the same injector geometries, by only changing the laser pulse energy.

### CW laser

Similar to the results with pulsed lasers (see Eq. 1), for CW lasers the jet velocity increases with a decrease in channel width $D$ [64] and a decrease in filling level $H$ [65]. This can be explained by the reduction in liquid volume with lesser mass that needs to be displaced, resulting in an increased jet velocity. The influence of the laser power on the jet velocities has not yet been fully characterized. However, experiments show that, for continuous wave lasers, a decrease in laser power results in an increase in bubble size [64].

Additionally, including a tapered nozzle allows to decrease the nozzle diameter and can increase the jet velocity. Due to incompressibility of the liquid, a nozzle results in an acceleration, as the same liquid volume is squeezed through a smaller cross-sectional area. Oyarte-Galvez et al. [36] investigated the influence of the taper angle, and found that the velocity increased with increasing taper angle, both numerically and experimentally. However, in contrast to (electro-) mechanical needle-free jet injectors (such as spring, gas, or piezo-electric based), a nozzle is not required to create a fast and thin microfluidic jet. Due to the small volume and curved liquid–air interface, flow focussing already results in a fast and thin jet without the use of a nozzle [13]. Furthermore, nozzles can result in less stable and focused jets, which will be discussed in 4.5.

### 4.3. Injection depth

Tables 4 & 5 show a large range in injection depths, with typical depths of 100–2000 μm. However, these numbers are reported on a large range of substrates. Most injection studies use a gel, such as agarose or gelatin, or they use porcine skin. These substrates are often chosen due to their ease of use; the gels also allow for visualization of the injection. Although these substrates are often used to mimic human skin, it is difficult to make a direct comparison between the different studies. The mechanical properties of these tested substrates are mainly studied at the macro-scale. The elasticity of human skin however depends on the length scale [190,191], for which reason, it is unclear whether these skin models accurately mimic skin at the length- and timescale of microjet injection.

Krizek et al. [40] observe a linear relation between the jet velocity and the injection depth. They find this relation for hydrogels of multiple stiffness, also indicating that their injector can penetrate substrates similar to fat-like tissue (13 kPa) as well as the epidermis (462 kPa). The maximum injection depth also increases with the number of jet injections. A 40% increase was found already for the second jet (from 1200 to 1700 μm in 1% agarose) [34]. The injection depth was found to stabilise at an approximate 100% increase after 20 jets in various hydrogels [40] and 150 jets in porcine skin [41].

#### 4.3.1. Strategies to enhance injection depth

Penetration enhancing methods can be used for applications where the injection depth has to be increased. Chemicals and other non-invasive methods are already discussed in Section 3.3.1. These could be applied prior to or during jet injection.

As discussed in section 3.3.2, skin ablation can be used as an alternative invasive method to simplify penetration of the skin. Jang et al. [71] have used their Er:YAG laser to ablate the skin prior to jet injection. Using a beamsplitter, mirror and lens, 20% of the optical energy was directly focused onto the skin, the other 80% was focused on the water for normal bubble and jet formation. As this results in a smaller amount of energy absorbed by the liquid (20% reduction), the resulting jet velocity is slightly smaller (87 m/s instead of 120 m/s). However, they observe approximately a two-times increase in injection efficiency (which is defined as the delivered volume per pulse energy), making it an interesting technique to enhance the injection parameters. Various skin-ablation methods were further investigated in Ref. [192], with the goal to improve injection efficiency, while minimizing damage to the skin.

Bulk ablation of the whole area results in the largest penetration depth (625 ± 98 μm, compared to 443 ± 104 μm for normal jet injection), but also results in the most damage. Their fractional-rotational method, where dots in a circular pattern are ablated, only damages about 20% of the area, but has almost the same increase in penetration depth (595 ± 141 μm). For this reason they conclude that fractional-rotational ablation is a useful addition to the micro-jet injector.

#### 4.4. Jet volume

For pulsed laser injectors, the typical volume of a single jet is in the order of 1 nl to 2 μl (see Table 4). For CW laser injectors, this volume is 10–50 nl (see Table 5). For CW laser injectors, larger volume jets (~1 μl) are achieved, but only for small velocities (<2 m/s) which are not fast enough for jet injection. This smaller range of volume is explained by the limited number of publications for CW lasers, but also by the reduced inertia, leading to small jet velocities (<20 m/s) for larger volumes. For both injector types, it applies that the volume of a single jet depends on the injector geometry and liquid filling level [37,65]. However, most studies do not mention a detailed jet volume, and in most cases where it is mentioned, it is only calculated from the total liquid volume in the chamber. A reason for this could be that it is difficult to calculate the jet volume from 2D videos, especially in cases where the
video only contains a few frames of the jet. Alternatively, it is pos-

tible to determine the jet volume from the expelled liquid. How-

ever, in case of refilling during the jetting phase, this is in-

accurate and not possible. Furthermore, in case of incomplete
delivery due to jet break-up or splash-back, this also results in an
inaccurate value.

4.4.1. Repetitive jetting

For some applications, a single micro-jet will not deliver suffi-
cient liquid volume. An example for this would be vaccina-
tions, where approximately 50 μL is required (see examples in
Table 2). For these applications, repetitive jetting is a solution to increase
the total delivered volume. Due to the short timescale of a single
bubble and jet formation (∼ 1 ms), it is possible to create fast con-
secutive jets, with demonstrated frequencies of 10 [39,41] and
15 Hz [40,74]. However, creating these jets at a high frequency
results in two challenges. First of all, the channel has to be refilled
between each jet. This can be done either with continuous filling
[40], or with a discrete stepper motor [39]. The second challenge
is to prevent entrapped air bubbles. During the bubble collapse,
air might flow into the injector, resulting in trapped air bubbles
near the cavitation site. These bubbles might affect the next vapor
bubble and subsequent jet, or prevent cavitation from occurring at
all. These air bubbles can be prevented in two ways. One option is
to eject the whole liquid volume in the capillary in one jet and refill
the channel in between the pulses. As there is no liquid remaining,
there are no remaining air bubbles [40]. Alternatively, researchers
from Seoul National University tried to prevent air bubbles by
increasing the flow rate [39]. They found two critical flow rates.
The first critical flow rate is equal to the total ejected volume, at
which point the back-flow of air was strongly reduced and the
problem rarely occurred. The second critical flow rate is when a dro-
plet grows at the nozzle tip and eventually detaches from the injec-
tor. In an improved injector design, they included a check-valve in
the nozzle [41]. This check-valve prevented back-flow of air, resolv-
ing any remaining problems with air bubbles. The jet veloc-
ity was constant (∼ 140 m/s) for 600 jets (60 s).

4.5. Jet stability

For jet injection, it is important that the microfluidic jet remains
stable until it impacts the skin. However, long cylindrical jets break
up into smaller droplets to reduce the surface area, which is called
the Plateau-Rayleigh instability [193]. The limit for this break-up is
when the aspect ratio $\Lambda = \frac{L}{r}$ exceeds $\pi$, where $L$ is the length and $r$
is the radius of the jet [186]. As these droplets have less momen-
tum and increased viscous dissipation, the penetration power is
smaller compared to the initial jet, which can result in a smaller
penetration depth and/or splash-back. Jet break-up makes the pen-
etration less predictable, and is therefore unwanted [70]. This phe-

omena is widely known, and observed for other jet injectors,
including gas- [60,96] and spring-based needle-free jet injectors
[194,195].

Although this phenomena is widely known, it’s exact influence
on laser-based microfluidic jets has not been investigated thor-
oughly. Padilla-Martinez et al. were able to create jets with aspect
ratios of $\Lambda > 40$ just before break-up [185]. They also found that
the maximum length of a jet increases with the Weber number
(We), which represents the dominance of the fluids inertia com-
pared to the surface tension:

$$We = \frac{\rho V^2 R}{\sigma}$$  \hspace{1cm} (2)

This influence on the jet stability is explained as the reduction in
surface energy, which is the main cause of jet break-up. For small
jet radii $R$, or large surface tension $\sigma$, the jet will break-up faster,
whereas for jets with high density $\rho$, break-up will be delayed
and an increase of velocity $V$ will result in an elongated jet during
the timescale of break-up.

The addition of a tapered nozzle allows to decrease the jet
diameter, producing a thin jet and increased jet velocity, see sec-
tion 4.2. For macro-jet injectors a nozzle is required to make such
a thin jet. For laser-based microjet injectors this is not strictly nec-
essary, as the self-focusing interface already results in a focused jet
tip. Nonetheless, a nozzle can be included to increase the jet veloc-
ity even further, up to a limit. The inclusion of such nozzles can
lead to viscous losses and a reduced energy transfer efficiency
[104]. Furthermore, a nozzle with a large taper angle can induce
this Plateau-Rayleigh instability faster, resulting in a diffuse or
spray-like jet tip, which is observed for micro-jet injectors [38],
as well as macro-jet injectors [60,96,194,195]. Such a diffuse jet
tip has a smaller jet power, which results in a decrease in depth
and predictability of the injection compared to a focused jet tip
[36,70], as shown in Fig. 8. Although for jets with a focused tip,
the tail has often a smaller velocity. Especially for larger volume
jets, the difference in velocity between the tip and the tail is larger,
resulting in poor penetration of the tail and a smaller injection effi-
ciency [35].

As all cylindrical jets break-up over time, it is difficult to ensure
jet stability for each individual injection. A spacer can be placed in
between the injector and the substrate to ensure a specific stand-
off distance (see Fig. 9), creating identical jet conditions for each
injection. By choosing a stand-off distance over which the coher-
ence of the jet is guaranteed, chances of poor penetration are min-
imized. Additionally, potential splash-back will be confined within
the spacer, thereby preventing contamination. It has been shown
that for a spring-powered jet injector, that minimizing this
stand-off distance results in the best penetration [196]. Further-
more, the use of a spacer to ensure contact between the injector
and the skin allows to apply a load on the targeted skin area. Ref.
[93] shows that a normal load of 9.8 N results in an optimum
injection efficiency, as it slightly tensions the skin for puncture
and liquid dispersion. Axial loads or normal loads larger than the
optimum result in excessive stress and reduced injection efficiency.

4.6. Liquid temperature and potential degradation of injectate

To use the laser based needle-free jet injector for therapeutic
purposes, the therapeutic compounds have to remain functional
during and after the injection. As part of the liquid is heated
beyond the boiling temperature, there is a risk of degradation of
any active compounds in the injectate. Temperature measure-
ments as well as proposed solutions have been investigated in
literature.

4.6.1. Temperature measurements

Pulsed laser

Fig. 10 shows a temperature profile after the bubble collapse
created by a pulsed laser, taken from Ref. [197]. This profile shows
an increase in temperature of only about 10 °C, which most likely
will not result in any major degradation of the therapeutic agents.
However, the pulse energy in this study is only 8.6 μJ, which is at
least one or two orders of magnitudes smaller than the typical
pulse energy in experiments from Table 4, which are at least 100
μJ to 1 mJ [35,37,169]. As the temperature increases with pulse
energy, the temperature profile has to be measured at the relevant
pulse energies.

Krizek et al. [35,74] also measured the influence of heating on the
therapeutic compounds indirectly. In Ref [35], they compared
heat-sensitive biomolecules using fluorescence microscopy before
and after jetting. The results suggest that the biomolecules did not change. In Ref. [74] they used proton nuclear magnetic resonance ($^1$H NMR) to find any degradation due to heating of δ-Aminolevulinic acid (ALA) and Lidocaine (both small molecules used in therapy), but they did not find any noticeable degradation. In these studies the laser pulse energies were 330 μJ and 2.25 mJ, which suggest that these biomolecules could be injected with this technique without degradation.

Fig. 8. A nozzle can result in an earlier onset of the Plateau-Rayleigh instability and create diffuse tip and/or a spray-like jet [36], which reduces the reliability of penetration leading to potential splash-back (see the video in the Supplementary Material). For injectors without a nozzle, the curvature of the liquid–air interface results in a focused jet, which increases the stability and reliability of the injection. However, for larger volumes, the tail of this focused jet has a smaller velocity, which also could result in poor penetration [35].

Fig. 9. Various additions have improved the laser-based jet injector, such as optical fiber [40,74], the use of a membrane [32] and a spacer [93].
CW-laser

Banks et al. used fluorescent imaging to measure the temperature increase due to thermocavitation [198]. They find a maximum temperature of 98 °C just 1 ms before bubble formation, which decreases to 57 °C at 5 ms after bubble collapse, as shown in Fig. 11. Importantly, the maximum calculated temperature was extrapolated from the calibration (which could only be done until 85 °C). Furthermore, it was found that only the liquid in close proximity to the wall is heated ($x < 200 \mu m$), for which reason, at least a large part of the injectate is unaffected, for which reason, at least a large part of the injectate is unaffected, as the typical length of the dose chamber is about 500–1000 μm [34,66]. Also, it is unclear whether the active compounds would already degrade within this short timescale, as the average temperature near the nucleation site decreases to below 50 °C within a few milliseconds. For this reason, more experiments will be necessary in the relevant length and timescales.

4.6.2. Protecting membrane

A membrane separating the liquid to be injected from the heated liquid has been proposed to overcome potential temperature-related problems (see Fig. 9). Such a membrane has been implemented by the group from Seoul National University [39,69]. The device consists of two chambers, one for the bubble growth, and one for the injectate. During the bubble growth, the membrane will be pushed outwards, accelerating the injectate. This way, the liquid containing the medication is not heated, which prevents any kind of temperature related degradation. However, a numerical study has shown that the jet velocity decreases with increasing membrane thickness [199]. For this reason, the energy efficiency decreases and a larger pulse energy is required to get the same jet velocity. Furthermore, the fabrication of a device with a membrane is more complex, especially for very thin membranes.

Fig. 10. Temperature profile during cavitation and after bubble collapse. Bubble is generated with a pulsed laser (A) Fluorescent images of the temperature profile during and after cavitation (at $t = 0$). (B) Radial temperature for three timestamps after cavitation. The maximum temperature difference is approximately 10 °C. However, the pulse energy is 8.6 μJ, which is at least ten times lower than the typical used pulse energies. Figure reprinted with permission from Ref. [197], licensed under Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Fig. 11. Temperature profile just before and after a bubble generated by a continuous wave laser. Bubble formation is at 263 ms after start of laser output. Maximum bubble size is shown in white, and its size is several times greater than the thermal boundary layer thickness. The maximum found temperature just prior to bubble formation is 98 °C. Already a few milliseconds after bubble collapse, the thermal boundary layer appears nearly absent. Figure reprinted with permission from Ref. [198].
5. Outlook

In this section, the focus will be on the development of the laser-based needle-free jet injectors in the near future. First, we will discuss development related to the input energy and conversion efficiency. This includes the development of both laser systems, as well as alternative cavitation methods. Second, we will discuss the improvement of injection rate and jet stability. Then we will discuss research related to skin properties and impact studies to further control the injection depth. Finally we will discuss a futuristic idea of combining needle-free jet injection with micro-needles to simplify the skin penetration for low power jet injectors.

5.1. Improvement of energy conversion

5.1.1. Development of new laser systems

Currently, the choice of laser system is often still limited by the availability of wavelength and power/pulse energy. However, further development of these lasers in industry as well as fundamental research in academia could result in cheaper, more efficient and smaller lasers, as well as a wider range in wavelength and power/pulse energy, as discussed in this subsection.

Portable pulsed lasers

The main practical limitation of pulsed lasers for its adoption in treatments where portability is needed, is their size. Pulsed lasers are becoming more efficient, are requiring less cooling and are reducing in size. First portable and battery-operated pulsed lasers are available on the market [175,200]. As mentioned in Section 4.1.1, this has led to the first jet injections with a portable pulsed NIR laser (1570 nm) coupled to an optical fiber [74]. Furthermore, new pulsed lasers might allow for increased repetition rates, resulting in more jets (thus increased total delivered volume) per second.

Vertical Cavity Surface Emitting Lasers (VCSEL)

VCSELs are microscopic 2D structures emitting CW laser light with efficiencies up to 60% and a high beam quality [201,202]. Due to their small size, they can be fabricated in 2D arrays with powers over 1 kW. Initially most VCSELs were developed in the NIR regime (800–1064 nm). However, over the last 15 years there has been increased interest in fabrication of mid-IR (2000–3500 nm) VCSELs [203–205], where the energy absorption of water is very high ($\chi > 100$ cm$^{-1}$). The commercialization of mid-IR VCSELs could lead to a cost reduction of CW mid-IR lasers, which at the moment are still about ten times as expensive compared to visible and near-IR lasers [206], due to their more complex fabrication requirements.

5.1.2. Alternative cavitation methods

Plasmonic bubbles

Alternative to optical absorption by the liquid itself, nanoparticles can absorb optical energy, using the so-called plasmonic effect [189,207,208]. These particles can either be immersed in the liquid itself [209], or bonded to the channel surface [210]. Irradiation near their plasmonic resonance, results in a temperature increase and the heating of the surrounding liquid, with a high energy conversion efficiency from light to dynamic energy of up to 12% [210]. For jet injection, surface-bonded nanoparticles are preferred over nanoparticles immersed in the liquid for two reasons. First of all, deposition on the surface results in faster growing bubbles compared to liquid immersed nanoparticles due to more localized heating [211]. Secondly, in the case of immersed nanoparticles, the injectate will also contain these nanoparticles, which is undesired.

Besides the high energy efficiency, a second advantage of using these plasmonic bubbles is that it allows for CW lasers in the visible regime. For example, gold nanoparticles can be heated with a green laser (532 nm) [189,207], which are more widely available than mid-IR CW lasers needed for heating of pure water ($\lambda > 2000$ nm). Similar to CW lasers, it is also possible to heat these nanoparticles with pulsed lasers [209,211,212].

Dielectric breakdown

Alternative to laser-generated cavitation, dielectric breakdown of the liquid also results in a bubble. Dielectric breakdown can be achieved by inserting two electrodes in the liquid closely together. By applying an extreme voltage difference, the liquid becomes conductive, creating a plasma. In 2001 Fletcher et al. were the first to investigate this method for needle-free drug delivery [213,214], but shifted to piezo-electric jet injectors (see Section 2.2). Later, C.D. Ohl et al. used this method to generate nanoliter-volume jets at velocities in the order of 100 m/s [215]. However, since then their interest shifted back to laser generated bubbles [216–219], the dielectric method was not further explored. Very recently, this method has received renewed interest with two studies. The first study investigated the wear at the electrodes and the electrode stability was improved [220]. In the second study, the authors compared jets from dielectric breakdown and laser-induced cavitation (keeping other parameters constant) [221]. In this work, they find a 21 times increased energy efficiency for the dielectric breakdown compared to the pulsed laser set-up. The volume and repetition rates are similar to their earlier work with the laser-generated jets ($f \sim 10$ Hz, $V \sim 1$ $\mu$L [39,41]). More research is required to further develop this technique and make a better comparison.

5.2. Investigation of jet characteristics

Increase of injection rate

Currently, the maximum reported injection rate with a laser-based jet injector is in the order of 1–10 $\mu$L/s (details are discussed in Section 4.4). For large volumes (> 100 $\mu$L), the injection could take tens of seconds, which might be unwanted. There are three ways to increase the injection rate and volume. First, it is possible to increase the volume of a single jet, for example by increasing the length or diameter of the channel. Then, by changing other parameters such as the input energy, the jet velocity and penetration depth can be kept constant. Second, it is possible to increase the repetition rate. Current repetitive jet injectors can create ten [41] and fifteen [40] jets per second. The repetition rate is currently limited by the pulsed lasers, but that could be increased in the future. For CW lasers, with a typical timescale of 1–5 ms for bubble and jet formation, the repetition rate could be up to 100–1000 Hz. Finally, an option would be to increase the number of microfluidic channels. Due to the size of a single microfluidic channel ($D < 1$ mm), it is possible to fabricate a device with multiple channels in a 2-D array (e.g. a 10x10 array on 1 cm$^2$). Using a beam-splitter, a single laser can be used to focus on these parallel channels, resulting in multiple simultaneous jets (see Fig. 6a). This approach of numbering-up is commonly used in microfluidics [222–224] and more specifically in inkjet printing [225–228].

Jet Stability

As described in Section 4.5, cylindrical jets may break-up into smaller droplets due to surface tension, which would result in reduced penetration and predictability of the jet. The influence of liquid parameters such as surface tension, viscosity and elasticity should be investigated further. A reduction in surface tension and increase in viscosity is expected to delay this break-up. Non-Newtonian liquids (whose viscosity changes with shear rate) are of interest as they allow to control the viscosity of the jet in-flight, while keeping the viscosity at rest constant. Shear-thickening
liquids create a highly viscous jet, resulting in increased jet stability. However this increased viscosity also results in more losses due to viscous dissipation, and a reduced jet velocity. Alternatively, viscoelastic liquids are of interest as they are expected to increase jet stability and delay break-up due to their resistance against deformation.

5.3. Skin research

A direct comparison between different injection studies is difficult, as a large range of substrates is used, such as gelatin [60], porcine skin [41,59], rat skin [72] and agarose [34]. The use of a single substrate is required to enable a better comparison of injection depths between studies. Of the mentioned substrates, ex-vivo skin is preferred as it has a higher complexity compared to gels and therefore a better comparison to real injections. Porcine skin is an inexpensive and relatively easy to obtain alternative to ex-vivo human skin [229]. Once the ex-vivo injection characteristics are fully understood, injections into in vitro human skin should be studied. Reconstructed human skin [230] or other human skin equivalents should be used as it results in a more realistic penetration [41,59], rat skin [72] and agarose [34]. The use of a single jet stability and delay break-up due to their resistance against viscoelastic liquids are of interest as they are expected to increase viscous dissipation, and a reduced jet velocity. Alternatively, however this increased viscosity also results in more losses due to liquids create a highly viscous jet, resulting in increased jet stability. Hollow micro-needles and laser-ablation, it results in damage to the epidermis, as it is an invasive method.

6. Conclusion

We have covered in this review a gap in published studies on laser-based microjet injection. We started off with a brief overview of the reported jet injection technologies and their limitations. Next, we established how conventional jet injection are less effective in accurately controlling the injection volume and depth, especially for superficial injections. This remains a difficult challenge that can be overcome by microjet injections.

Microjet injectors offer a potential solution for superficial injections. The increased accuracy in delivered volume and depth control enable targeting superficial skin layers, namely, the epidermis and dermis. These superficial skin layers allow for dose-sparing of vaccines for among others: influenza, yellow fever, rabies and possibly Covid-19, resulting in a cheaper and faster mass-vaccination program. Furthermore, it has been reported that these shallow injections improve the uptake of insulin for diabetes patients. Finally, small volume and shallow injections reduce the pain and waste of many injections, including aesthetic injections such as tattoos.

For these reasons, there has been a lot of interest in laser-based jet injectors over the past decades. Most research currently focus on the precise control of injection depth and on the increase in delivered volume. It has been reported that the jet velocity and injection depth increase linearly with the laser pulse energy. This makes it an ideal technique to create specific jets over a wide range of velocities with a single injector. Furthermore, by injection of multiple small volume jet at a high repetition rate, the volume is controlled accurately. Individual jets typically contain hundreds of nL, but repetitive jetting allows a delivered volume as high as 20 μL per second. Typical injection depth is in the order of 100–2000 μm. This corresponds to injecting in the epidermis (~0–200 μm) and dermis (~200–3000 μm). However, a direct comparison between studies is difficult, as a wide range of substrates is used. Nonetheless, individual studies show a high controllability and reproducibility of injection depth, which is very promising.

The research on laser-based jet injection has led to Mirajet, which is the first commercial laser-based injector. The Mirajet is mainly used for intradermal injections aimed at skin rejuvenation, which has a relatively low risk. For therapeutic and reactive injections, more research will be needed. For some injectors, splash-back is still a problem, as it results in an unpredictable delivered volume and risk of contamination. Furthermore, the stability of therapeutic compounds in the injectate must be ensured. Temperature measurements showed a limited increase in temperature, but it is yet unclear whether this holds for typically used pulse energies. Studies showed that several biomolecules were not affected by the heating and jetting phase. However, for completeness, these studies have to be repeated for each relevant biomolecule and injection parameters. Alternatively the inclusion of a membrane overcomes degradation by heating, but results in a reduced energy efficiency. Besides thermal degradation, the shear stress might affect some injectates, and has to be studied further.

Finally, continuous wave (CW) lasers have been proposed as an alternative to the more commonly used pulsed lasers. Due to their low power, CW lasers are typically more affordable compared to the pulsed lasers. Furthermore, as they do not require active cooling, they are much smaller in size. For these reasons, CW lasers could result in an inexpensive handheld device, which allows for use in low-resource settings, such as vaccination campaigns in developing countries or personal use for insulin. However, the controllability of the jet characteristics is still limited and requires more understanding of the energy transfer from the CW lasers into the bubble and jet.
Competing interest

D.F.R. is co-founder of FlowBeams, a spin-off company of the University of Twente on needle-free injection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.addr.2021.114109.

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