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Laser-induced High-Speed Jets in Needle-free Injection Systems: Mechanisms, Applications, and Innovations

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Abstract—Laser-induced jets have garnered significant attention due to their critical role in advancing needle-free injection systems for drug delivery and their potential in various medical and cosmetic applications. This mini-review focuses on the mechanisms and innovations surrounding laser-induced jets, highlighting their advantages over conventional methods. We examine recent research on the dynamics of high-speed liquid jets, emphasizing key aspects such as jet stability and penetration depth. Particular attention is given to the influence of governing parameters, including injection velocity, nozzle geometry, stand-off distance, and fluid properties, on laser-induced jets in needle-free injection systems. This review highlights the transformative potential of these system technologies in delivering precise, painless, and minimally invasive drug treatments by addressing current limitations and exploring improvement strategies. Key areas for future research include advancing laser technology, enhancing predictive capabilities using artificial intelligence to optimize parameters, exploring skin variability, and developing effective methods for jet stabilization.

Keywords- Laser-induced jets; needle-free injection; drug delivery; jet stability.

I. INTRODUCTION

Advancements in healthcare technology are revolutionizing traditional practices, with needle-free injection systems (NFIS) emerging as an outstanding innovation [1]. Needle-free injection systems have proven to be a promising alternative to conventional injections, particularly in the context of mass vaccination and patient comfort [2]. These systems represent a significant innovation in drug delivery, offering a means to administer vaccines, insulin, and other medications without the discomfort or risks associated with traditional needles [3]. However, despite their advantages, these technologies often encounter challenges, such as jet dispersion and inconsistent penetration depth, affecting their efficacy. There is a lack of clinical guidelines for optimal usage parameters, which can lead to variability in treatment outcomes. Further research is needed to establish standardized application protocols [4]. While commercial injectors address some challenges associated with hypodermic needles, their applications remain remarkably limited. A key limitation lies in their constrained ability to adjust the input energy required to displace the liquid. Consequently, these injectors are typically capable of generating jets within a narrow range of volumes and velocities, limiting their versatility and adaptability for broader applications [1].

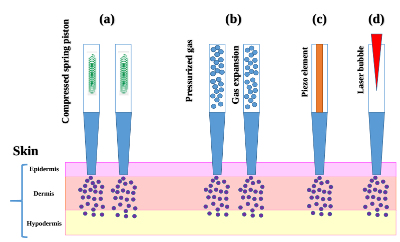

Figure 1. Four types of common jet injectors (JIs) studied in the literature: (a) compressed spring piston, (b) pressurized gas, (c) piezo-element, and (d) laser-induced. The skin layers are characterized by different colors and are named the Epidermis, Dermis, and Hypodermis, respectively. (Reproduced with permission from Ref. [5]. Copyright (2024), Elsevier).

Jet injectors utilize high-speed liquid jets to deliver medications through the skin without a needle, thereby minimizing pain and the risk of needle-stick injuries [6]. Needle-free injector devices use impulse force for targeted vaccine delivery into the intradermal, subcutaneous, and intramuscular regions. Different actuation mechanisms such as spring force

[7], Lorentz coil [8], compressed gas [9], piezoelectric motors [10], pyro-driven [11], and laser-induced cavitation [12, 13] have been used in the development of the needle-free jet injectors, where the working principle is the creation of a high-speed micro scale jet that can puncture the skin and deposit drug into tissues beneath. Figure 1 illustrates four jet injector (JIs) types, including compressed spring piston, pressurized gas, piezo-element, and laser bubble, each showcasing distinct mechanisms for liquid jet formation and skin penetration. Recent studies have demonstrated that laser-induced jets exhibit greater stability compared to those generated by electromechanical methods[14], [15]. In Jansen's investigation [16], high velocity in the laser-induced systems is achieved by focusing a nanosecond-pulsed laser beam into a transparent liquid, such as water, to induce plasma formation via nonlinear absorption. The plasma rapidly heats the liquid, resulting in the formation and collapse of a vapor bubble, emitting pressure waves of several gigapascal [17]. Moreover, despite their high velocity, these jets typically have a small diameter ($10 - 100$ μm), limiting the volume of drug that can be delivered [18].

Despite the extensive research and the growing prominence of needle-free injection systems (NFIS) in medical applications, vital challenges remain in understanding the mechanisms and optimizing injection efficiency. The current review aims to recognize these challenges by providing an up-to-date focus on the specific advancements in laser-induced microjets in NFIS technologies over recent years. By synthesizing recent findings, this review highlights critical parameters, including injection velocity, fluid properties, and nozzle design, which significantly influence jet dispersion shape and penetration depth, two key characteristics that directly impact drug delivery efficiency.

The structure of the paper is organized as follows: Section 2 provides an overview of NFIS types, focusing on the principles of high-speed jet generation and energy conversion. Section 3 examines laser-induced bubble cavitation, detailing the mechanisms of cavitation and jet dynamics and their role in achieving precision and control for drug delivery. Section 4 discusses the critical factors influencing jet performance, including injection velocity, fluid properties, nozzle geometry, and stand-off distance, along with strategies to optimize these parameters for clinical applications. Finally, Section 5 addresses key challenges and offers perspectives on future advancements in NFIS technology.

II. Types of Needle-free Injection Systems

NFIS are categorized into three main types based on their delivery mechanisms [19]:

- Liquid injection: The most common type, which delivers liquid formulations via a high-speed jet. The jet's velocity and pressure can be finely tuned to control penetration depth and dispersal in the tissue [20].
- Powder injection: Uses compressed gas to propel solid drug particles. This method is suited for temperature-sensitive drugs like proteins, as powders maintain stability without refrigeration [20, 21].
- Depot/Projectile injection: Deposits medication in deeper muscle layers, creating a drug reservoir that releases the active compound gradually [22].

Table I demonstrates a list of commercial NFIS systems, along with their approach and application. Among these innovative approaches, liquid jets are remarkable for their widespread application and unique capabilities. This paper focuses on laser-induced liquid jets, opening new possibilities in needle-free injection systems.

III. Laser-induced jets

Various techniques, including laser-induced cavitation [23], thermocavitation [24], spark-induced cavitation [25], and shock wave-induced cavitation [26], are employed to generate controlled cavitation bubbles for diverse applications. These methods exploit different mechanisms to form and collapse bubbles, which under suitable constraints max create high-speed jets. Laser-based techniques have shown significant potential – at least for fundamental studies- among these approaches due to their precise control over bubble generation and repeatable jet formation. The dynamics of bubble expansion and subsequent collapse are central to jet formation. During expansion, the bubble generates a pressure gradient, while during its collapse the surrounding liquid may not symmetrical converge, thereby producing a high-speed jet [27]. In addition, laser-induced jets have been employed in a wide range of applications, including surface cleaning [28], cell targeting [29], enhancement of localized heat transfer [30], forward material transfer processes [31], and the printing of complex liquid materials [32].

TABLE I. A comparative table summarizing different NFIS [19]

Technology	Pressure Source	Depth of Penetration	Applications
Intraject	Compressed gas	Subcutaneous	Delivers drug in <60 milliseconds.
Injex30	Spring	Subcutaneous	Dual safety system for insulin delivery.
Crossject	Spring	Intramuscular, Subcutaneous, Intradermal	Utilizes novel gas technology for a broad range of applications.
Depixol Depot	Compressed gas	Intramuscular	Creates a drug depot in muscle for prolonged release.

The process of laser-induced cavitation begins when a liquid is subjected to rapid heating, particularly through optical means such as ionization or linear absorption by the focused laser beam. For sufficient high intensities a plasma forms at the focal point after focusing the laser pulse through the objective lens. A rapid temperature rise at this point causes localized evaporation of the liquid, leading to bubble nucleation at the laser focal point. The bubble generation creates a significant pressure gradient at the laser focal point, accompanied by the emission of a shock wave that propagates outward at supersonic speed. For cavitation nucleation through linear heating, numerical simulations have indicated nucleation occurs when the temperature in the laser focus reaches approximately 237 °C [41]. This demonstrates the strong correlation between the laser parameters and the liquid's stability conditions.

Laser-induced jets, which are generated through the process of bubble cavitation, can be achieved using either pulsed lasers (typical through the formation of a plasma) or continuous-wave (CW) lasers (through superheating):

- **Pulsed lasers:** When a sufficient intense pulsed laser is focused into a liquid, it leads to a dielectric breakdown, plasma formation, and recombination leaving a vapor core at very high pressure. As a result gas and vapor filled cavity expands explosively that reaches a maximum size before it starts to shrink and collapse [27, 33].
- **Continuous-wave (CW) lasers:** CW lasers can generate bubbles through a process known as thermocavitation. Here, the laser is focused into a highly absorbing solution, superheating the liquid and producing rapidly expanding bubbles. The nucleation is the result of linear heating up to the critical temperature that again results in an explosively expanding cavitation bubble. However because the heating here takes much longer as compared to a pulsed laser, the dynamics can be described with local thermodynamic equilibrium. Still, the collapse of the bubble may result in high-speed jets [6, 34].

Figure 2 depicts the mechanism of laser-induced microjets along with all relevant parameters. The dynamics of laser-induced flow focusing can be explained as follows [35, 36]: at very initial time intervals, a laser pulse is initiated, leading to the rapid absorption of energy by the liquid and subsequent cavitation. The resulting pressure wave spreads through the axisymmetric liquid medium until it reaches the liquid/air interface. The curvature of the meniscus, influenced by capillary-glass wetting, directs the pressure locally toward the axis, thereby contributing to the focusing of the liquid flow. The jet tip's diameter is approximately one-tenth of the capillary diameter. Figure 3 illustrates an example of the liquid jet produced by the laser-induced bubble cavitation. To optimize the liquid jet performance, it is essential to understand the influence of various parameters such as jet velocity, penetration depth, stand-off distance, and jet fluid properties.

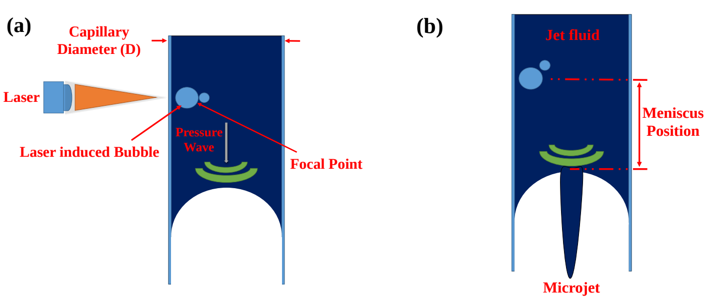

Figure 2. Laser-induced jets' mechanism: A laser-induced bubble propels the liquid out of the nozzle, where it undergoes further acceleration due to the flow-focusing effect at the liquid/air meniscus-shaped interface [37].

IV. EFFECTS OF PARAMETERS IN LASER-INDUCED JETS

Numerous studies have examined the influence of key parameters, including injection velocity, nozzle diameter, stand-off distance, and fluid properties, on laser-induced jets. Below, we provide a detailed overview of each of these parameters and their effects on jet behavior:

A. *Injection Velocity*

Injection velocity is a major parameter to control penetration depth in laser-induced jets in NFIS. Higher jet velocities correspond to increased penetration. However, it is important to carefully assess the stability of the drug formulation at higher velocities to ensure consistent and reliable drug delivery [38]. At velocities around 150 m/s, delivery efficiency exceeded 90% for a 152 µm nozzle diameter in human skin; however, excessively high velocities may reduce efficiency due to fluid instability or jet fragmentation [7]. For laser-induced jets, continuous-wave laser systems have demonstrated the ability to achieve jet velocities of up to 29 m/s, sufficient for penetrating the stratum corneum. In comparison, pulsed laser systems can produce significantly higher jet velocities, ranging from 70 to over 100 m/s [39].

Figure 3. A sequence of liquid jet snapshots captured by an ultrafast camera operating at 60,000 frames per second reveals that flow focusing induces significant acceleration and results in the liquid jet adopting a sharply defined geometrical shape (© 2019. This work is openly licensed via CC BY 4.0) [37].

B. *Nozzle Diameter*

Nozzle (capillary) diameter directly influences jet diameter, velocity, and subsequently, the jet penetration depth. Larger capillary diameters (152–229 µm) generate broader jets, enabling near-complete drug delivery rates exceeding 90% [38]. The penetration depth of the jet also varies with nozzle diameter, ranging from shallow skin penetration (<1 mm) to deep dermal penetration (2–4 mm) [38]. Research indicates that optimal delivery efficiency exceeding 90% is often achieved with nozzle diameters within the 152–229 µm range [38]. A nozzle diameter of approximately 0.3 mm is ideal for achieving efficient drug diffusion in subcutaneous tissues [40]. Moreover, mathematical models are being developed to identify the optimal nozzle diameters for improved delivery efficiency and performance [41]. Smaller nozzle diameters generate higher shear stresses, potentially affecting the structural integrity of sensitive drugs such as proteins, vaccines, and DNA [38]. However, the shorter exposure time to shear stress in jet injectors, compared to conventional needles, mitigates some of these effects [38].

C. Stand-off Distance

To mitigate contamination caused by blood on the skin, a 'stand-off distance', i.e., the gap between the injector nozzle and the target surface, is employed [42]. The stand-off distance affects the jet velocity upon impact. While the initial jet velocity is high (often greater than 100 m/s), the velocity can decrease as the jet travels through the air due to divergence and interaction with the atmosphere. However, the impact velocity remains sufficient to penetrate the skin or soft material if the stand-off distance is optimized [43]. Also, a stand-off distance of about 3 mm has been identified as effective for maximizing penetration depth while maintaining jet quality [44].

D. Fluid Properties

The jet fluid typically contains the drug or therapeutic material being delivered, while the ambient medium serves as a model or simulator for the injection environment. For instance, ambient mediums may range from artificial constructs like gels to biological materials such as animal skin, depending on the experimental setup for considering human skin [45]. Studies in this area aim to replicate realistic injection scenarios to evaluate the behavior of the jet fluid and its interaction with the ambient medium [46, 47]. By controlling the properties of both the jet fluid and ambient medium, researchers have been able to simulate various clinical scenarios and refine system performance for applications ranging from vaccines to specialized drug therapies. Han et al. [48] demonstrated that variations in fluid properties can significantly influence jet behavior, with viscosity showing a weak inverse correlation to jet velocity ($V_{jet} \sim \mu^{-0.08}$). For example, high-viscosity fluids, such as 80% glycerol, produce narrower jet spreads compared to water, which helps maintain jet integrity during injection. This highlights the importance of fluid viscosity in achieving precise drug delivery. Berrospe-Rodriguez et al. [39] reported that denser fluids increase the penetration depth by increasing the jet's momentum. Table II presents a summary of parametric studies on laser-induced NFISs.

V. Challenges and Future Directions

As previously discussed, Laser-induced jet technology has shown promise as a transformative approach to needle-free injection systems. While significant potential has been realized, several challenges remain, making future research critical to advancing this technology for broader clinical adoption. The key challenges and potential directions for future work are outlined below:

A. Nozzle Design

Nozzle diameter and shape variations can lead to differences in flow rates and jet stability. Considerable research has examined the effects of varying jet velocity, injection pressure, and nozzle aperture on the injection effect to study needle-free injection parameters under different skin characteristics [49]. However, further studies are needed to explore micro- and nanoscale nozzle designs for precise control of jet dynamics and to understand nozzle-skin interactions under diverse skin conditions [4]. Additionally, using advanced materials in nozzle fabrication could enhance durability and biocompatibility, ensuring consistent performance over repeated use. Future innovations in adjustable and multifunctional nozzles hold promise for facilitating clinical adoption and personalized drug delivery.

B. Prediction Enhancement

Current systems struggle with precise control over jet velocity, penetration depth, and dose accuracy due to the variability in tissue properties and patient-specific conditions. Adaptive laser technologies that adjust operational parameters during injection can address these challenges effectively [45, 50]. To further advance this approach, incorporating artificial intelligence and machine learning algorithms could enable real-time monitoring and optimization of injection parameters, improving precision and patient-specific customization.

TABLE II. Characterization of some studies on laser-induced jet injectors

Ref.	Velocity (m/s)	Studied parameters	Jet fluid	Ambient medium
[51]	10-150	Jet-fluid viscosity, Capillary diameter	Water, Glycerol solution 50 and 80 %w/w	Gelatin, porcine tissue
[27]	25-225	Laser fiber Optic diameter, jet-fluid properties	Water, sun flower oil, glycerol, Ethanol	Agarose gel
[12]	0-350	Ambient medium properties	Water	Gelatin, artificial human skin
[36]	20-850	Laser-focal point in the jet fluid chamber	Water	Air

C. Jet instability

Controlling jet flow properties, such as stability, radius, shape, and tip velocity, is critical for ensuring the effectiveness of needle-free injection systems. Wider dispersion and instabilities of the jet and the subsequent issues (e.g. inhomogeneous penetration into the skin [52] and the cross-contamination of the skin due to the splash-back of the medication [4]) are associated with severe bruising, pain, and bleeding [53]. Jet instabilities, including Kelvin-Helmholtz instability, can lead to jet breakup into smaller droplets, reducing penetration depth, injection precision, and surface area coverage [54, 55]. These disruptions diminish the jet's momentum and increase viscous dissipation, resulting in splash-back and inconsistent drug delivery [12]. Therefore, stabilizing jets is a key challenge for future research, and finding the most effective solution remains a top priority for advancing the technology.

D. Skin Research

Investigating skin properties, including elasticity, hydration levels, thickness, and density, is critical for optimizing jet parameters. Also, developing standardized skin substrates, such as ex-vivo human skin samples or reconstructed human skin models, is essential to enable consistent and reliable comparisons of injection performance. Future research could leverage advanced imaging and diagnostic tools to characterize skin properties in real-time, enabling dynamic adjustments during the injection process.

VI. CONCLUSION

Laser-induced jets in NFIS represent a transformative advancement in drug delivery technologies, offering precise, painless, and minimally invasive alternatives to traditional methods. By utilizing high-speed liquid jets from laser-induced cavitation, these systems have demonstrated the ability to mitigate challenges such as inconsistent penetration depth, certain forms of jet instability, and tissue damage. However, these issues have not yet been fully resolved. This review explored key parameters, including jet velocity, penetration depth, fluid properties, and nozzle diameter, that govern the performance of laser-induced jets in NFIS, highlighting their pivotal roles in ensuring efficiency and accuracy in drug delivery. Despite their potential, laser-induced jets in NFIS face several challenges, including optimizing nozzle designs for diverse clinical applications, achieving precise control over jet parameters, and, most critically, developing effective strategies to stabilize jets and address instability issues. Future research should focus on standardizing evaluation methods, skin research, and developing adaptive laser systems and stabilizers. By addressing these challenges and fostering interdisciplinary innovation, laser-induced cavitation promises to revolutionize drug delivery, offering significant improvements in patient safety, comfort, and therapeutic outcomes.

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