

A laser based reusable microjet injector for transdermal drug delivery

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(Received 14 March 2010; accepted 18 April 2010; published online 27 May 2010)

A laser based needle-free liquid drug injection device has been developed. A laser beam is focused inside the liquid contained in the rubber chamber of microscale. The focused laser beam causes explosive bubble growth, and the sudden volume increase in a sealed chamber drives a microjet of liquid drug through the micronozzle. The exit diameter of a nozzle is $125\ \mu\text{m}$ and the injected microjet reaches an average velocity of $264\ \text{m/s}$. This device adds the time-varying feature of microjet to the current state of liquid injection for drug delivery. © 2010 American Institute of Physics. [doi:10.1063/1.3430989]

I. INTRODUCTION

Drug delivery system aims at administrating therapeutic agents into a diseased part of a human body for medical treatment. Needles and syringes are mostly used to deliver therapeutics transdermally among various kinds of drug delivery methods. While these devices provide advantages of precise targeting and effective injection, they have significant limitations including needle phobia due to pain, contamination from reuse of needles and syringes in developing countries, and creation of large volumes of medical wastes.^{1,2} These shortcomings have urged many researchers to consider enhanced alternative drug delivery method; namely jet injection that has been considered to overcome current limitations. In this device, a liquid jet is generated to breach skin tissues and then to deliver drug dose to the target region. Since its first development in 1930s, jet injections have been used to deliver a number of different macromolecules, drugs, and vaccines such as insulin and growth hormones; otherwise, they would require needles for the delivery. However, jet injectors did not gain popularity due to the potential for cross-contamination from splash back during injection, poor reliability of delivered dose and depth, and the fact that they are still painful.³⁻⁵

In order to reduce pain and stabilize administrated drug dose, Stachowiak *et al.*⁶ proposed the use of a time-varying jet velocity profile, achieved by a piezoelectric actuator. The beginning jet pulses have adequate velocity for tissue bruising until they achieve the desired injection depth; the latter jet pulses are slower than the former, not to touch the nerves responsible for pain sensing. They are only deposited inside the breached region until the desired dose is delivered.⁶ In other words, a drug delivery process will consist of several time-varying microjet injections. It suggests that this type of real time monitoring of very small amount of jet injections facilitates stabilization and control of liquid jet injection. Therefore, developing a device for real time monitoring jet injection requires the capability of small dose microjet con-

trol so that they are slowly accumulated in the target site allowing the penetration depth and dose profile monitoring during injections.

Unlike jet injection devices based on electrical equipments, a microjet injector using laser induced shock wave has been studied recently.⁷ Laser has advantages that it can concentrate extremely high energy in a very small region with excellent controllability and repeatability. A laser based device can be miniaturized through the use of optical fiber for beam transmitting. In principle, one can administrate drug into currently nonapproachable treatment sites in human body. However, microjet injector that can generate a controlled jet from multiple laser pulses has not been developed.

II. DESIGN AND MECHANISM

We propose a new jet injector using laser pulses, which can achieve time-varying microjets of small doses. This device consists of a tapered micronozzle fabricated from tungsten carbide, a thin rubber chamber molded from nitrile butadiene rubber as illustrated in Fig. 1. The inner diameter of the nozzle exit hole is $125\ \mu\text{m}$, and the inner tapered angle is 32° . The volume of drug content that the micronozzle can contain is about $6\ \mu\text{l}$. The micronozzle is refilled with drug dose from the high pressured reservoir after an injection. The thin rubber chamber, which plays an important role in achieving the reusable microjet system, is fabricated from the base rubber of $200\ \mu\text{m}$ thickness, 53 hardness,

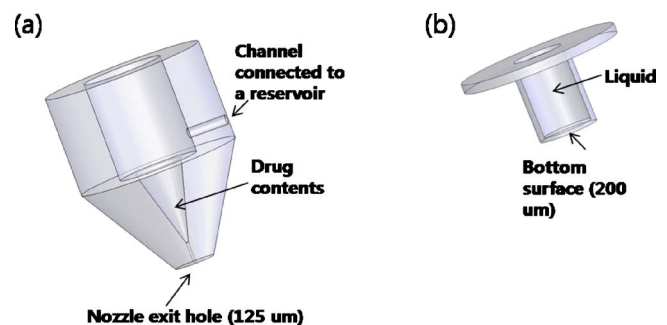


FIG. 1. (Color online) Illustrations of (a) the micronozzle and (b) the rubber piston.

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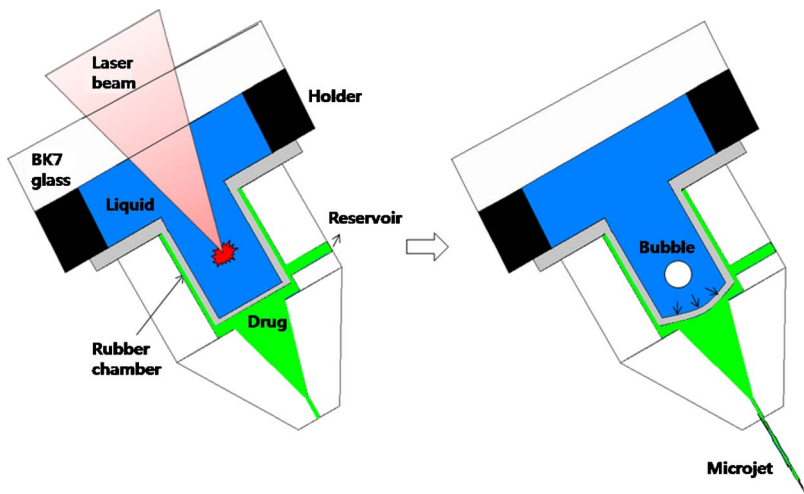


FIG. 2. (Color online) An illustration of the mechanism of an assembled microjet injection system.

101.39 kg/cm² ultimate strength, and 449.79% elongation rate. Its shape is a hat that allows sealed assembly with the micronozzle. The hollow space inside is filled with water confined by a holder and a BK7 glass, both of which are 3 mm in thickness. A schematic of an assembled microjet injection system is depicted in Fig. 2. A laser beam with sufficient irradiance focused in the water inside the rubber chamber through BK7 glass causes explosive growth of vapor bubbles due to optical breakdown in water. The confined vaporized bubbles cause considerable volume change in the chamber such that a shockwave is generated and propagated into the bottom surface of the chamber. The bottom surface is elongated elastically as the shockwave passes through it, and then it drives drug solution inside the micro nozzle toward the nozzle exit. The liquid drug flows out of the nozzle exit in the form of liquid microjet.

The volume of microjet is less than that of the vaporized bubble. The energy of the cavitation bubble can be given by⁸

$$E_B = \frac{4\pi}{3}(p_0 - p_v)R_{\max}^3 \quad (1)$$

where E_B is the cavitation bubble energy, p_0 is the hydrostatic pressure ($=2330$ Pa at 20 °C),⁹ p_v is the vapor pressure inside the bubble ($=0.1$ MPa), and R_{\max} is the maximum radius of the bubble. Since less than 10 percent of the incident energy of 532 nm wavelength is deposited in the bubble, we can deduce from Eq. (1) that the maximum volume of the bubble is on orders of ten nanoliters. Therefore, the volume of microjet would be a few nanoliters considering energy losses by elastic deformation, friction, and so forth.

Since one can choose adequate pulse duration and wavelength of the laser beam, generating high enough jet velocity to penetrate human soft tissue is possible. Also the rubber piston head could protect drug molecules from being damaged by the direct laser heating because of its relatively low heat conductivity. The laser-shed bubbles collapses after an injection is made and the rubber piston is restored by the elasticity of the membrane. This elastic property of injecting chamber is the key to an immediate second injection as the micronozzle is refilled with a new drug dose from a high pressure reservoir.

III. EXPERIMENT

In this work, we employed a visible laser beam emitted from a Q-switched Nd:YAG pulse laser (Powerlite Precision II Plus, 532 nm wavelength, 5–9 ns pulse duration, 10 Hz frequency). The beam was focused by a convex lens (BK Plano Convex lens, focal length 100 mm). The laser beam was not expanded to get lower uncertainty since the range in which the focused laser irradiance is almost uniform (Rayleigh range) becomes longer with the smaller diameter of the beam.¹⁰ We filled pure degassed water inside the rubber chamber as a driving liquid to minimize remaining bubbles before and after an injection. The same water was also filled in the micronozzle as a drug for testing.

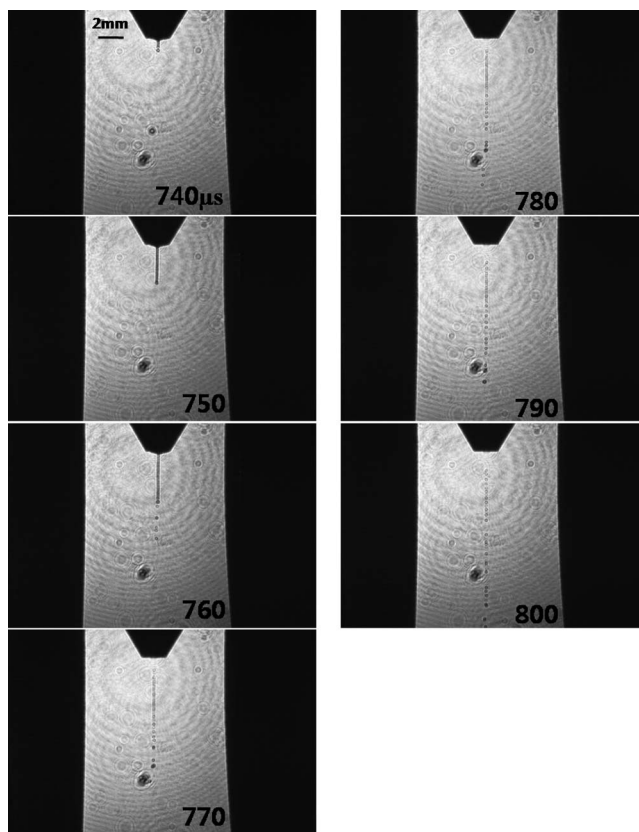


FIG. 3. Sequential images of microjet evolution.

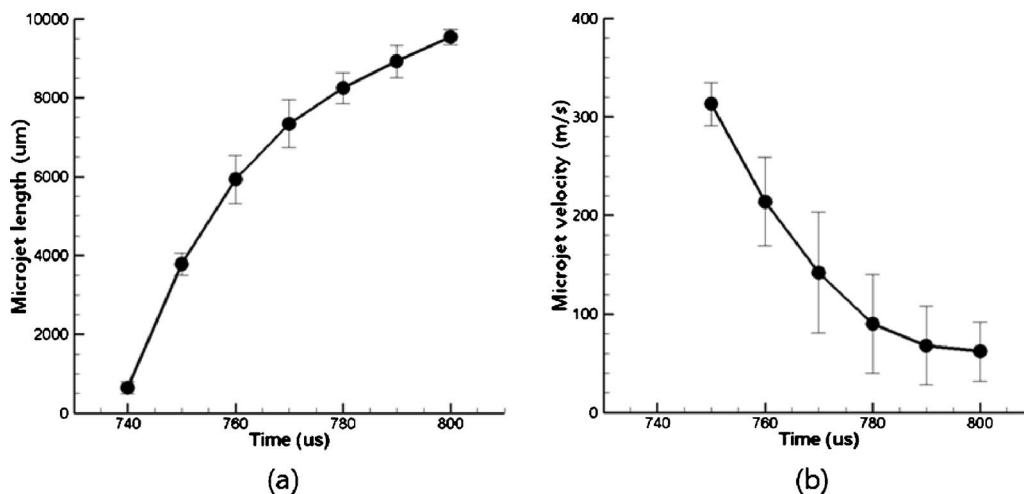


FIG. 4. (a) Distance of a microjet leading edge from the micronozzle exit, and (b) microjet velocity with respect to time after the laser incidence. Error bars indicate standard error above each 5 tries. Jet breakup occurred between 760 and 770 μs at 6–7 mm from the nozzle exit.

The microjet emanated from the nozzle exit was visualized using a commercial camera (Nikon D90), a pulse generator (BNC 565–8CG: RMS, 250 ps jitter, 500 ps delay time), and a flashlight emitted from a Q-switched Nd:YAG pulse laser (>Minilite, Powerlite, 532 nm wavelength, 3–5 ns pulse duration). This setup has a minimum exposure time of 3 ns and an image was taken at a try.

IV. RESULT

Figure 3 shows the sequential images during injections taken by several tests at 100 mJ laser energy. The average distance from the micronozzle exit and velocity of the jet, based on its leading edge, are also measured from the time resolved images. They are plotted in Fig. 4 with respect to time after the laser incidence. The microjet began at the micronozzle exit about 740 μs after the laser incidence. Reasons for this time delay include growth of bubbles, propagation of the shockwave, and existence of the relatively high attraction force between liquid and the nozzle surface at the exit hole. Its measured diameter and initial velocity were about 135 μm and higher than 300 m/s, respectively. As the microjet flows downstream, it slowed down and was broken up at a point between 6 and 7 mm. Among several breakup regimes that have been identified corresponding to different combination of liquid inertia, surface tension, and aerodynamic forces acting on the jet, images after 770 μs shown in Fig. 3 are clearly demonstrated to be in the Rayleigh regime. At the low velocity of the jet downstream, the growth of long-wavelength, small-amplitude disturbances on the liquid jet surface, promoted by the interaction between the liquid and ambient air, is believed to initiate the liquid breakup process.^{11,12} The measured average jet velocity before the breakup (740–760 μs) was 264 m/s, which is sufficiently large for delivering drug dose successfully into human soft target.³ Therefore, the pressurized microjet injector can be used as an effective drug delivery device within the standoff distance (the distance between the micronozzle and the target surface) shorter than the jet breakup distance (about 6 mm in this experiment).

V. CONCLUSION

In conclusion, we have designed a laser based device for needle-free liquid drug injection. This device is capable of generating time-varying microjets of small doses. It facilitates real time monitoring of jet injection such that they can compose the desired penetration depth and dose profiles. Therefore, we expect that it enhances the stability and the controllability of liquid jet injection as well as reduces the pain and splash backs during injection. The performance of the device was demonstrated with the visualization of the microjets. The measured microjet diameter was comparable to the nozzle exit, and the measured velocity in air was high enough to penetrate a human soft tissue. However, the same microjet velocity may not be achieved in biological tissues which we aim to penetrate. Therefore, future work will focus on fundamental verification of this technique to create less intrusively penetrating microjet in biological tissues.

ACKNOWLEDGMENTS

This work was supported by the Korea Science and Engineering Foundation (Grant Nos. KOSEF-2009-0076557 and KOSEF-2009-0059432) through IAAT at Seoul National University. Authors thank technical assistance of T. K. Choi.

¹Y. Nir, A. Paz, E. Sabo, and I. Potasman, *Am. J. Trop. Med. Hyg.* **68**, 341 (2003).

²M. Kermodé, *Health Promot. Int.* **19**, 95 (2004).

³S. Mitragotri, *Nat. Rev. Drug Discovery* **5**, 543 (2006).

⁴P. N. Hoffman, R. A. Abuknesha, N. J. Andrews, D. Samuel, and J. S. Lloyd, *Vaccine* **19**, 4020 (2001).

⁵G. E. Theintz and P. C. Sizonenko, *Eur. J. Pediatr.* **150**, 554 (1991).

⁶J. C. Stachowiak, T. H. Li, A. Arora, S. Mitragotri, and D. A. Fletcher, *J. Controlled Release* **135**, 104 (2009).

⁷V. Menezes, S. Kumar, and K. Takayama, *J. Appl. Phys.* **106**, 086102 (2009).

⁸A. E. Siegman, *Lasers* (University Science Books, Sausalito, CA, 1986).

⁹A. Vogel, J. Noack, K. Nahen, D. Theisen, S. Busch, U. Parlitz, D. X. Hammer, G. D. Noojin, B. A. Rockwell, and R. Birngruber, *Appl. Phys. B: Lasers Opt.* **68**, 271 (1999).

¹⁰R. C. Weast, *CRC Handbook of Chemistry and Physics* (CRC, Boca Raton, 1998).

¹¹S. P. Lin and R. D. Reitz, *Annu. Rev. Fluid Mech.* **30**, 85 (1998).

¹²L. Rayleigh, *Proc. London Math. Soc.* **s1-10**, 4 (1878).