

고속레이저추진원리를 활용한 무통증 주사기의 개발 및 의료산업으로의 Spin-off

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Development of a painless injector using high speed laser propulsion and its spin-off to medical industry

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ABSTRACT

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 micro scale. 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 μm and the injected microjet reaches an average velocity of 264 m/s. This device adds the time-varying feature of microjet to the current state of liquid injection for drug delivery.

초 록

본 연구진은 레이저-물질 간의 상호작용을 응용하여 새로운 방식의 약물 전달 시스템을 개발하고 있다. 레이저 빔이 마이크로 단위 크기의 고무 챔버 속에 채워져 있는 액체 속에 집광되면 순간적인 고에너지 전달로 인해 기포가 생겨나고, 이로 인한 빠른 부피팽창으로 인해 마이크로 노즐 속의 약물 용액이 빠른 속도의 마이크로 젯의 형태로 분사되는 원리를 이용하는 것이다. 실험에서 노즐 출구의 지름은 125 μm , 측정된 마이크로 젯의 속도는 265 m/s였다. 이 장치의 주요한 특징은 시간에 따른 마이크로 젯의 제어가 가능하다는 것이다.

Key Words : Microjet, Laser induced bubble, Micronozzle, Drug delivery system

1. 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

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and effective injection, they have significant limitations including needle phobia due to pain, contamination from re-use 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. 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 control 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 non-approachable treatment sites in human body. However, microjet injector that can generate a controlled jet from multiple laser pulses has not been developed.

2. Design and Mechanism

In this letter, 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 (NBR) as illustrated in Figure 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, $101.39\ \text{kg}/\text{cm}^2$ 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 Figure 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.

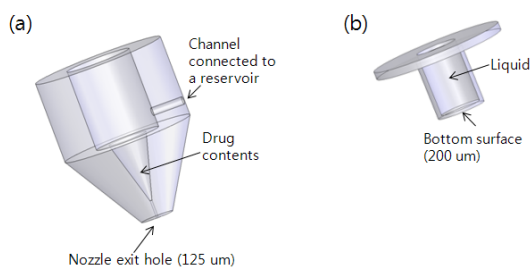


Fig. 1 Illustrations of (a) the micronozzle and (b) the rubber piston

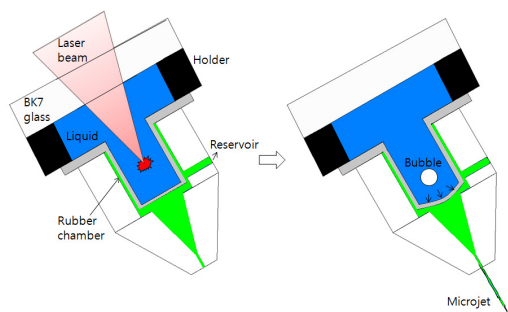


Fig. 2 An illustration of the mechanism of an assembled microjet injection system

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.

3. Experiment and Result

3.1 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 [8]. 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.

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

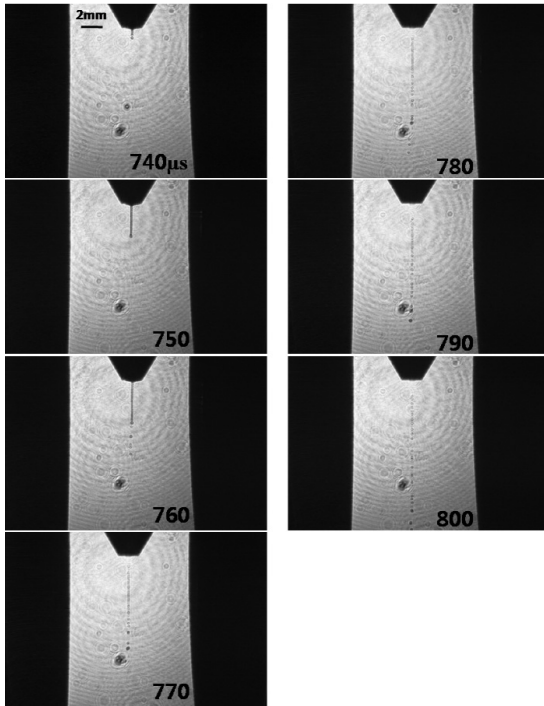


Fig. 3 Sequential images of microjet evolution

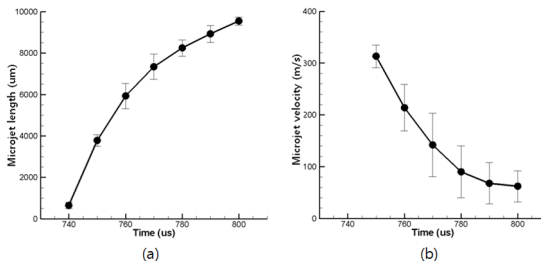


Fig. 4 (a) Distance of a microjet leading edge from the micronozzle exit, and (b) microjet velocity with respect to time after the laser incidence. Error bars indicate standard error above each 5 tries. Jet breakup occurred between 760 μs and 770 μs at 6 mm \sim 7 mm from the nozzle exit.

wavelength, 3~5 ns pulse duration). This setup has a minimum exposure time of 3ns and an image was taken at a try.

3.2 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 Figure 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 Figure 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 [9,10]. The measured average jet velocity before the breakup (740 μs \sim 760 μs) was 264 m/s, which is sufficiently large for delivering drug dose successfully into human soft target³. 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).

4. 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 are aiming to penetrate. Therefore, Future work will focus on fundamental verification of this technique to create less intrusively penetrating microjet in biological tissues.

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