TRANSLATED PAPER

Development of a switching and focusing mechanism of shock wave and expansion wave using the discharge phenomena of electrically induced microbubbles

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Abstract
A novel needle-free injection system by electrically induced microbubbles has been developed. First of all, we evaluated the depth of injected reagent for evaluating injection performance. Then, the cavitation-induced shock wave has been focused to magnify the injection performance by semispherical reflector. We successfully visualized the shock wave by the schlieren method and succeeded in measuring the pressure of focused shock wave and expansion wave by hydrophone.

KEYWORDS
electrically induced microbubble, expansion wave, shock wave

1 | FOREWORD

Presently, syringes with metal needles are the mainstream in drug administration for medical treatment and prevention of diseases. Drug injection by metal needles is a very useful method featuring easy skin penetration and dose control. However, needles directly contact patient’s mucus and blood, and the spread of infectious diseases through needle sharing has long been a worldwide problem. In addition, many patients suffer a phobia or mental and physical stress because of pain caused by the skin puncture. Furthermore, in addition to the mentioned pain-related problems, when regular injections are needed in treatment of such diseases as diabetes, repeated skin punctures with a needle bring about callus formation in the affected skin area, and injections are accompanied with acute pain.

To resolve these issues, needle-free drug injection systems based on dermal penetration techniques and implantable drug delivery devices are developed worldwide such as drug delivery systems and biomimetic drug administration. Particularly, as regards needle-free syringes, systems are extensively developed for skin perforation and drug injection via high-pressure liquid jet using compressed gas; such systems have been already implemented abroad. However, with the existing needle-free syringes, the use of high-pressure liquid jet is reported to leave bruising in the affected areas and to cause pain. That is, the issues of pain and stress remain unsolved.

The present study is aimed at developing a new needle-free injection system to solve the problems of existing both needle and needle-free syringes. The developed needle-free injection system, as distinct from previous gas-pressure type needle-free injection systems, adopts a new method of skin puncture and drug delivery using microbubbles. This paper reports on proposal of a drug delivery mechanism using microbubbles and actual results of reagent injection. In addition, regarding the use of shock wave for deeper penetration of reagents, the paper explains about shock wave visualization, fabrication of reflectors to generate shock and expansion waves, and results of pressure measurement.
2 | CONCEPT OF SKIN PERFORATION AND DRUG INJECTION

We developed a device called bubble injector to generate microbubbles in electrolyte solution (below referred as “electrically induced microbubbles”) and to directionally inject them. An overall view of the bubble injector and enlarged view of the tip portion are shown in Figure 1. Finite element method (FEM) analysis showed that a strong field of $10^6$–$10^7$ V/m appeared at the device tip when a high pulsed voltage was applied at the voltage application unit of the bubble injector (Figure 2). The instantly generated strong electric field produces minute bubbles in the solution. When a stronger field is applied to the microbubbles, breakdown occurs, plasma is formed, and larger microbubbles are produced. The microbubbles produced by plasma were confirmed to show the same behavior (expansion and compression, and so forth) as conventional microbubbles. Generation and injection of electrically induced microbubbles by the bubble injector are illustrated in Figure 3. Injected microbubbles are crushed nonuniformly, thus producing a high-pressure liquid jet called microjet. Such microjets feature extremely high pressure and perforation capability sufficient even for local metal cutting. This study proposes a new needle-free injection system using the bubble injector as conceptually shown in Figure 4. In the proposed method, skin is perforated by a microjet of electrically induced microbubbles generated by the bubble injector, and a reagent is introduced into the perforated area via the flow of ambient fluid that comes with the microjet.

3 | EXPERIMENTS WITH FLUORESCENT REAGENT INTRODUCTION

First, experiments were conducted to evaluate reagent injection performance of the bubble injector. The experimental system is shown in Figure 5. A power supply—Hyfrecator 2000 used in electrosurgery—was connected to the bubble injector via a noninductive resistance of 10 kΩ. The power source waveforms are shown in Figure 6. A mixture of fluorescent beads (Fluoro-Max by Thermo Scientific; diameter: 2.1 µm) and 0.9% NaCl aqueous solution (below referred to as “physiological saline”) was used as a reagent to inject into chicken meat; reagent penetration depth was measured in real time through fluorescence observation by a stereo zoom microscope. Reagent penetration depth versus power source output is shown in Figure 7. The diagram confirmed that by using the bubble injector, a reagent can be injected to a depth...
of up to about 400 µm. However, drugs must be injected to a depth over 1 mm with typical syringes used for influenza vaccination and so forth. Therefore, drug injection performance in the depth direction must be improved.

4 | USE OF SHOCK WAVES FOR IMPROVEMENT OF REAGENT INJECTION PERFORMANCE

4.1 | Shock wave visualization by schlieren imaging

When microbubbles are crushed by pressure, a great energy accumulated inside the bubbles is instantly released to produce a shock wave. Therefore, one can think of improving reagent injection performance through utilizing the pressure of shock wave for perforation by the bubble injector.

As regards the use of shock wave, we confirmed generation of shock waves with crushing of electrically induced microbubbles produced by the bubble injector. The experimental system for shock wave visualization is shown schematically in Figure 8. In order to visualize a density change in liquid caused by shock wave generation, we fabricated an optical system for schlieren imaging in microfluidic environment, and captured images by a high-speed camera (Phantom v2512 by Nobby Tech). Thus acquired image of shock wave is shown in Figure 9. In the diagram, propagation of shock wave is confirmed via the difference in density.

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**FIGURE 5** Experimental setup for measuring depth of injected reagent [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 6** Power output waveform (below: enlarged view of one pulse) [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 7** Experimental result of measuring depth [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 8** Experimental setup for micro-schlieren to visualize shock wave [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 9** Result of visualizing shock wave
4.2 Concept of shock wave convergence

In the previous subsection, it was confirmed that a shock wave occurs when electrically induced microbubbles are crushed, same as with conventional microbubbles. This subsection considers a method to amplify pressure by reflecting a shock wave that spreads from an origin, and making it converge at a single point.

Figure 10 illustrates the concept of providing the bubble injector with a reflector to focus shock waves. As regards reflector’s shape, we adopted an elliptic reflector used for shock wave focusing in extracorporeal shock wave lithotripsy.10,11 When the bubble injector tip (shock wave origin) is placed at a focus of an ellipse, generated shock waves reflect from the wall and converge at the other focus. Perforation capability of electrically induced microbubbles is amplified when this other focus is put on the surface of perforation.

4.3 Selection of materials and fabrication of reflectors

When shock waves arrive to an interface with an object different from their propagation medium, two phenomena occur—reflection and transmission. Reflection and transmission that occur near reflector are illustrated in Figure 11. The ratio between transmission and reflection is defined by reflection coefficient \( R \) that can be expressed via acoustic impedance of objects as shown below.

\[
R = \frac{A_2 - A_1}{A_2 + A_1}
\]

Here, \( A_1 \) is acoustic impedance of a medium where shock waves propagate, and \( A_2 \) is acoustic impedance of an object existing in the way. As indicated by Equation (1), the bigger is the difference in acoustic impedance of two objects, the higher is reflection coefficient, and the stronger is reflection of shock wave. Besides, reflection coefficient \( R \) is negative when \( A_2 \) is smaller than \( A_1 \). In this case, a shock wave inverts its phase to form an expansion wave.12 A shock wave (positive pressure) pushes objects in its way, while an expansion wave (negative pressure) pulls objects in the direction opposite to propagation.

Unless reflection coefficient \( R \) is extremely high or extremely low, a wave separates into reflected and transmitted waves. This separation results in a pressure drop. Therefore, materials of reflectors must be chosen so that reflection coefficient \( R \) is very low in case of transmission and high in case of reflection. A structure with changeable reflection conditions was fabricated to compare shock and expansion waves in terms of utility for a needle-free injection system.

Table 1 lists acoustic impedance values of selected reflector materials as well as physiological saline and air making reflection boundaries. Physiological saline and PDMS (polydimethylsiloxane) have almost same acoustic impedance; therefore, a shock wave generated in physiological saline goes through PDMS. Acoustic impedance of air is very small as compared to PDMS, and a shock wave reflects as an expansion wave at PDMS–air interface. On the other hand, acoustic impedance of tin is higher than that of PDMS, and a shock wave reflects as it is at PDMS–tin interface. Thus, switching between shock and expansion waves can be implemented if two kinds of reflectors are made of PDMS and tin so that the latter can be placed and removed outside of the former.

The two reflectors were fabricated in the following way.

As regards the PDMS reflector, a template of the corresponding shape was first fabricated using a stereolithographic 3D printer (Form 2 by Formlabs; layer thickness: 25 µm).
Then, PDMS mix with 10:1 weight ratio of SILPOT 184 (Dow Corning Toray) to hardener was poured into the template and cured in an oven. After curing, PDMS was removed from the template to complete the fabrication of reflector.

As regards the tin reflector, a template was fabricated using a 3D printer, and reflector was formed by rolling. Photographs of the reflectors made of PDMS and tin are shown in Figure 12. The focal distance of the ellipse is 2 cm; when measuring pressure, the gauge is sufficiently apart from the bubble injector so that microjet pressure is not measured. The thickness of PDMS and tin reflectors was 15 mm and 1 mm, respectively.

4.4 Measurement of convergence pressure in shock and expansion waves

The pressure measurement system is shown schematically in Figure 13. Pressure was measured by a fast-response hydrophone (Muller-plate needle probe by Nobby Tech) widely used in shock wave measurement. The pressure probe (hydrophone tip) was fixed at the reflector’s focus using a PDMS support placed between the reflector and the hydrophone. After setting up the experimental system, the inner part of the reflector was filled with physiological saline; then the bubble injector was inserted in the reflector’s upper part and its position was aligned and fixed at the reflector’s focus using a precision manipulator. First, pressure of expansion wave generated by the PDMS reflector was measured; after that, the tin reflector was attached to measure shock wave pressure. In addition, pressure of unfocused shock wave was measured without the reflector for comparison.

Pressure of nonfocused shock wave is shown in Figure 14. These results confirmed that pressure of nonfocused shock wave was around 500 kPa. Measured results for expansion wave pressure are presented in Figure 15. In this case, a negative pressure of –1.5 MPa was obtained. Thus, nearly a threefold negative pressure was achieved using the PDMS reflector. Besides, thus obtained negative pressure confirmed successful realization of the idea that shock waves can be converted into expansion waves through reflection between PDMS and air. Measured results for shock wave pressure are presented in Figure 16. In this case, a positive pressure of 2 MPa was obtained. Thus, approximately fourfold pressure amplification effect by using the tin reflector was confirmed. As regards the negative pressure showed by circle in Figure 16, one can assume that an air layer appeared between tin and PDMS because of poor adhesion, and expansion wave was generated there. Thus, when using a tin reflector, one can expect further pressure improvement due to evacuation of air from the gap (e.g., using a vacuum device) to enhance adhesion. Besides, two pressure peaks were observed in Figure 16. This
can be attributed to characteristics of the power supply. With the power source used in this study, 600 voltage pulses are outputted at a time. Thus, bubble generation timing is irregular, and two peaks might be observed because bubbles and shock waves were generated twice in a short period of time.

Results of pressure measurement for both reflectors confirm successful switching between positive and negative pressure. In addition, comparison in pressure between shock wave and expansion wave demonstrated that pressure was greater in shock wave. However, reflection coefficient is 99.9% between PDMS and air, and 88.3% between PDMS and tin, which means that pressure loss theoretically increases when the tin reflector is used. That is, the experimental results are inconsistent with theory. This can be attributed to positional errors that occur when the tip of bubble injector is aligned with the reflector’s focus using a manipulator. One can also think of pressure loss due to microroughness of PDMS outer surface produced by layer shifting in 3D layered printing of PDMS template. Because PDMS is poured into the template and then cured, the template’s surface pattern is reproduced; on the other hand, tin is formed by rolling, and microstructure is not transferred to the reflector. Thus, pressure in the experiments can be increased through more precisely aligning the tip of bubble injector with the reflector’s focus, and polishing the template surface to make it smoother.

5 | CONCLUSION AND FUTURE DIRECTIONS

This study was aimed at development of a needle-free injection system using electrically induced microbubbles. We evaluated reagent injection performance; in addition, we fabricated reflectors and measured pressure to examine the use of shock wave to improve injection performance. Thus obtained results confirmed that reagent injection performance of the bubble injector, as it is, provided a penetration depth about 400 µm, which is not sufficient for typical injections. In order to improve perforation performance, we proposed using shock waves that occur around microbubbles when they are crushed. Micro-schlieren imaging showed that shock waves also occur with crushing of electrically induced microbubbles generated by the bubble injector. After that, we fabricated reflectors to focus diverging shock waves. In so doing, we selected PDMS and tin as reflector materials with appropriate acoustic impedance. The reflectors were designed and fabricated so that convergence can be switched between positive-pressure shock waves and negative-pressure expansion waves in a single device. Measurement showed that pressure of 500 kPa of nonfocused shock wave was amplified three times up to 1.5 MPa (negative) in expansion wave focused with PDMS reflector, and four times up to 2 MPa (positive) in shock wave focused with tin reflector. These results confirmed that pressured can be amplified using the fabricated reflectors. It also should be noted that in this study, switching between shock and expansion waves can be performed in a single device by changing reflectors. Existing reflector-based focusing devices are often intended to generate either shock waves or expansion waves, while switching between positive and negative pressure in a single system can be applied not only to needle-free injection systems but to a wide range of other applications. On the other hand, results of pressure measurement revealed a number of problems related to the present methods of reflector fabrication and setup, for example, influence exerted by surface profile of 3D-printed template on PDMS surface, and alignment between bubble injector and reflector’s focus. Solving these problems promises further increase of pressure.

In future, we will solve the reflector’s problems identified through the experiments to get the most out of the pressure amplification effect. In addition, we will examine how reagent injection performance in Figure 7 changes when an optimized reflector is used. We will also compare shock and expansion waves in terms of improving reagent injection performance. As regards the switching between shock and expansion waves by the proposed method, we will continue research toward wider applications of such devices.

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