A low-frequency ultrasound transducer for creation of transdermal transport region

Shinya Yamamoto[1†‡], Keita Tomioka[1], Naohiro Sugita[2*], and Tadahiko Shinshi[2]
([1]Dept. Mech. Eng., Tokyo Tech; [2]FIRST, Tokyo Tech)

1. Introduction

Ultrasound cavitation is the phenomenon of bubble formation in a liquid due to localized and rapid pressure fluctuation caused by ultrasound irradiation. The cavitation bubbles are subjected to volumetric vibration that repeatedly expands and compresses. Ultrasound cavitation can be classified as stable and inertial cavitation[1)]. In stable cavitation, the bubbles oscillate without collapsing, and emit shockwaves. In inertial cavitation, the bubbles grow with radius expansion and collapse with microjets[2)]. The schematic illustration of cavitation is shown in **Fig. 1**.

Sonophoresis is one of the methods for transdermal drug delivery. Stimulation on the human skin by cavitation generated by ultrasound irradiation enhances drug penetration. The area of increased permeability is called the transdermal transport region. Due to the skin barrier, drug administration is limited to low molecular weight (<500 Da) and hydrophobic drugs. However, in sonophoresis, large molecular weight and hydrophilic drugs can administrate[3)]. Sonophoresis is attracting attention for its minimally invasive method alternative to injections.

Low-frequency ultrasound (<100 kHz) is effective in sonophoresis. On the other hand, in bolted Langevin-type transducers (BLTs), downsizing and low-frequency are trade-offs. Compactness and low-frequency drive are priority issues for medical applications. The transdermal transport region of BLTs is small relative to the irradiated surface. Furthermore, it is sparse. These issues possibly lead to longer treatment times and the inconstant amount of administrated drug.

Our final target is developing a wearable device for transdermal drug delivery. In this research, we propose a compact and low-frequency drive transducer that generates inertial cavitation uniformly on the skin surface, aiming to make larger and uniform transdermal transportation region.

2. Materials and method

A novel compact ultrasound transducer that can work at low-frequency (lower than 100 kHz) is designed and fabricated. The transducer is designed to distribute bubbles to the skin surface. We confirm the occurrence of cavitation by measuring cavitation noise and optically observing cavitation bubbles on a skin-mimicking gel surface.

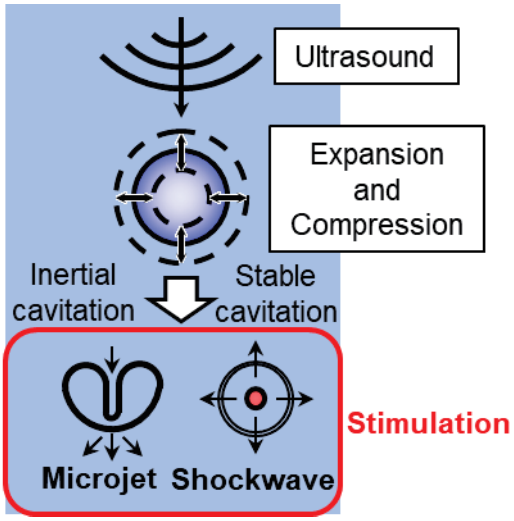

Fig. 1 Schematic illustration of ultrasound cavitation.

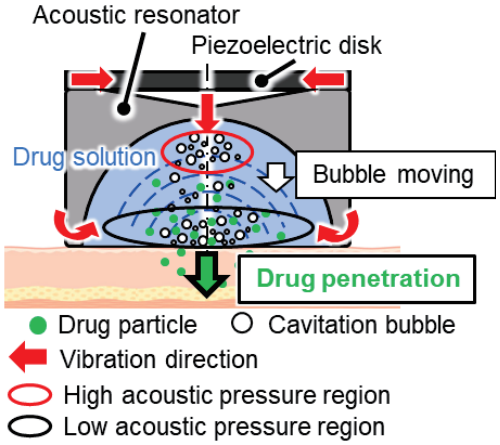

Fig. 2 Schematic illustration of proposal transducer design.

2.1 Transducer design and fabrication

The transducer consists of a piezoelectric disk (type C-21, Fuji Ceramics) and a bowl-shaped acoustic resonator of titanium alloy. The piezoelectric disk and the acoustic resonator are adhered to by epoxy resin adhesive. The schematic illustration of the transducer is shown in **Fig. 2**. The

E-mail: †yamamoto.s.bm@m.titech.ac.jp,
*sugita.n.aa@m.titech.ac.jp

outer diameter is 28 mm and the height is 10 mm. The radius of curvature of the spherical cavity is 16.3 mm. The transducer provides an acoustic pressure gradient in the spherical cavity. The high-pressure region is formed at the upper side of the cavity as seen in **Fig**. **1**, and the low-pressure region is formed at the bottom side where the skin surface is located. Due to the pressure gradient, the cavitation bubbles on the upper side move toward the skin surface. This bubble movement can increase the skin permeability without exposing the skin to a high-intensity ultrasound.

2.2 Cavitation noise detection

To confirm the cavitation occurrence, we measured cavitation noise by using a piezoelectric pressure sensor. In a frequency spectrum of the pressure signal, an increase in the broadband noise is a critical indicator of the occurrence of inertial cavitation, -inertial cavitation occurs[4]. The sensitivity of the sensor is 39.8 μV/Pa. The input signal is burst sinusoidal waves, and the frequency is a resonant frequency of the transducer. Input voltage is 20 to 120 V_{pp} (each 20 V_{pp}).

2.3 Cavitation observation by a high-speed camera

We used a urethane gel instead of human skin to estimate cavitation bubbles distribution on the skin surface. We took photography on the gel surface by a high-speed video camera. The transducer was put on the gel. The input signal is sinusoidal waves, and the frequency the is resonance frequency of the transducer. Input voltage is 20 to120 V_{pp} (each 20 V_{pp}). The frame rate of the camera is 2000 fps and the exposure time is 1/2000 s.

3. Result

A transducer prototype is shown in **Fig**. **3**. The resonance frequency in the water is 80 kHz.

The frequency spectrum of the pressure signal is shown in **Fig**. **4**. When the input voltage is 80 V_{pp}, the broadband noise increases. It can concludes that inertial cavitation occurs at the input voltage larger than 80 V_{pp}.

The photograph of cavitation on the urethane gel is shown in **Fig**. **5**. The region surrounded by red dashed lines presents the region where cavitation bubbles were observed on the gel surface. When the input voltage is 80 V_{pp}, cavitation bubbles sharply increase, and the bubble distribution becomes more uniform.

4. Conclusion

We proposed a novel compact and low-frequency drive transducer for developing a wearable device for transdermal drug delivery. We demonstrated the generation of inertial cavitation and achieved uniform bubble distribution.

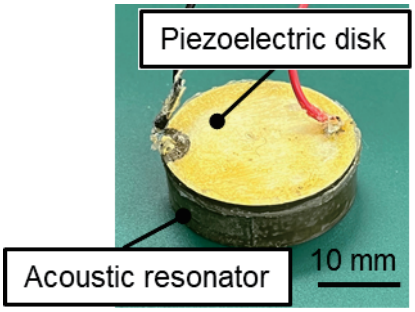

Fig. 3 Photograph of the transducer.

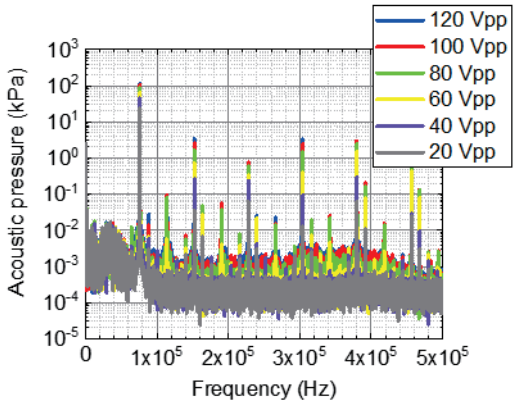

Fig. 4 Acoustic pressure spectrum of the prototype transducer driven at 80 kHz.

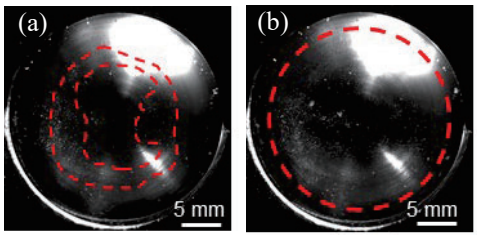

Fig. 5 Photographs of cavitation generated at the input voltage of (a) 60 V_{pp} and (b) 80 V_{pp}.

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