2Pb5-7

Piezoelectric-based compact transducer for low-frequency ultrasound enhanced transdermal drug delivery

Keita Tomioka[1†], Shinya Yamamoto[1], Naohiro Sugita[2], and Tadahiko Shinshi[2]
([1]Dept. of Mech. Eng., Tokyo Institute of Technology; [2]Institute of Innovative Research, Tokyo Institute of Technology)

1. Introduction

Insulin therapy is necessary to regulate blood glucose levels for people with type 1 diabetes and is commonly used in advanced type 2 diabetes. The standard administration method of insulin is hypodermic injection after each meal. The use of needles has disadvantages, such as the fear of pain and the risk of infection due to misuse. To address these disadvantages, transdermal drug delivery has been investigated as a needle-free method. However, biopharmaceuticals with hydrophilic and large molecular weight (>500 Da), such as insulin, do not diffuse passively due to the skin barrier function of the stratum corneum.

Sonophoresis, the physical stimulation of the skin by ultrasound cavitation generated by ultrasound, has been studied to improve drug permeability. However, compact ultrasound devices have not been commercialized due to difficulties in downsizing ultrasound transducers [1].

This study aims to develop a wearable transdermal drug delivery device using ultrasound cavitation. Previously, our research group proposed a concave-shaped acoustic resonator which generates ultrasound cavitation on soft materials [2]. However, it requires an external incident sound source.

In this report, a piezoelectric disk is directly bonded to the acoustic resonator. This mechanism eliminates the need for an external sound source and reduces the transducer size to less than 10 mm in thickness. The proposed transducer can be used at a low frequency of around 100 kHz by converting the radial vibration of a piezoelectric disk to the bending vibration of an acoustic resonator. Modal analysis is simulatively performed to design the transducer profile and dimensions to get desired resonance characteristics. We measure the electric admittance to find the resonance frequencies of the transducer and compare it with the simulated result. Ultrasound cavitation bubbles near the resonance frequencies are observed on an urethan gel by a high-speed video camera.

2. Methods

2.1 Fabrication of ultrasound transducer

Our proof-of-concept is shown in **Fig. 1**. The piezoelectric disk is made of C-204 piezoelectric material (Fuji Ceramics) and is polarized in the thickness direction with a diameter of 20 mm and a thickness of 1.25 mm. Silica glass was used for the acoustic resonator because of its low material damping. Its transparency of the grass allows one to optically observe ultrasound cavitation in the resonator. Epoxy adhesive (SW2214, 3M) was used to bond the piezoelectric disk to the back of the acoustic resonator. The bonded piezoelectric disk was coated with silicone rubber (KE-42T, Shin-Etsu Chemical).

2.2 Numerical method

To understand the basic vibration characteristics of the ultrasound transducer, a finite element analysis based model analysis was performed by numerical software (ANSYS Workbench R19.0, ANSYS) for the model shown in **Fig. 1(A)**. The frequency response of the electrical admittance of the transducer was obtained under the stress-free boundary condition. Material damping of the piezoelectric disk and acoustic resonator are neglected. The epoxy adhesive layer and silicone rubber coating were omitted in the simulation model. The applied voltage is 10 V_{pk}. The simulation result of the electrical admittance is compared with experimental one measured by an LCR tester (3532-50, HIOKI).

2.3 Experimental setup

The experimental setup is shown in **Fig. 2**.

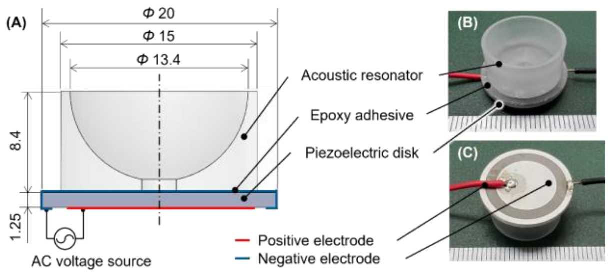

Fig. 1 (A) Profile and dimensions, and (B-C) top and bottom side views of the proposed ultrasound transducer.

E-mail : tomioka.k.aa@m.titech.ac.jp (Keita Tomioka)

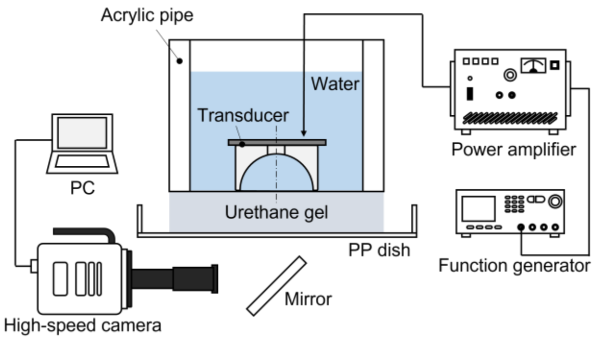

Fig. 2 Schematic of the experimental setup for high-speed imaging under sound irradiation.

At the resonance frequencies found in the admittance measurement experiment, ultrasound cavitation yield was observed using high-speed photography. A square acrylic pipe (internal dimensions 40 mm × 40 mm) was fixed on a 10 mm thick urethane gel phantom (IP-10, Exseal) and filled with deionized water. The ultrasound transducer was placed on the urethane gel. A continuous square voltage signal with a duty ratio of 0.5 generated by a function generator was amplified by a power amplifier and input to the ultrasound transducer. A high-speed video camera (FASTCAM Nova S12, Photron) was used to capture images of cavitation bubbles generated on the surface of the urethane gel through a mirror placed under the object.

3. Results

3.1 Frequency response

A comparison of the experimental and simulated electrical admittance results is shown in **Fig. 3**. In the experiment, the ultrasound transducer was suspended in the air. Four resonance admittance peaks were found in the simulation at 72.7, 122, 133, and 144 kHz. These resonance peaks correspond to axisymmetric vibration modes of the ultrasound transducer. The experimental result has two resonance frequencies at 69.2 and 127 kHz. The experimental electrical admittance is smaller than the simulated value over the whole frequency range due to damping effects.

3.2 Cavitation observation

Ultrasound cavitation was observed near the experimentally measured resonance frequencies of 69.2 and 127 kHz at the applied voltage of more than 20 V_{pk}. Especially, ultrasound cavitation occurred with a low voltage of 10 V_{pk} at 127 kHz. **Fig. 4** shows examples of ultrasound cavitation yield. The applied voltage to the ultrasound transducer were 10 and 40 V_{pk}, and both operating frequencies were 127 kHz. Ultrasound cavitation generated inside the acoustic resonator and moved onto the urethane gel.

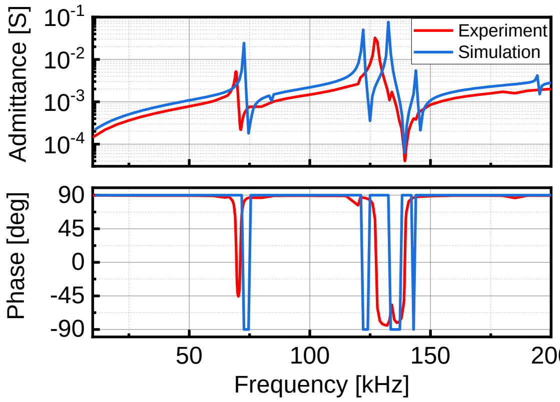

Fig. 3 Experimental (red) and simulated (blue) frequency responses of electrical admittance.

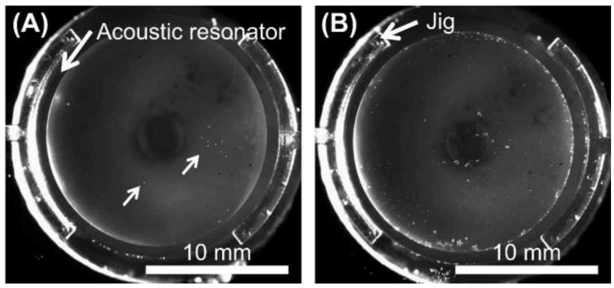

Fig. 4 Ultrasound cavitation on urethane gel under ultrasound irradiation photographed for 10 sec by high-speed camera at 250 frame/sec: Applied voltage are (A) 10 V_{pk} and (B) 40 V_{pk}. The operating frequency for both (A) and (B) is 127 kHz. The inside of the acoustic resonator is illuminated by a high-brightness LED. The arrows indicate the location of ultrasound cavitation yield.

4. Conclusion

A compact ultrasound transducer less than 10 mm thick was designed and fabricated, aiming to develop a wearable transdermal drug delivery device to improve the skin permeability of biopharmaceuticals such as insulin. Cavitation generation was observed using a high-speed video camera, and it was confirmed that cavitation could be generated on the urethane gel surface with an applied voltage of 20 V_{pk} or higher around the experimentally measured admittance resonance frequencies of 69.2 and 127 kHz. Especially, ultrasound cavitation occurred with a low voltage of 10 V_{pk} at 127 kHz. These results contribute to the realization of a wearable transdermal drug delivery device that utilizes ultrasound cavitation.

Acknowledgment

This work was supported in part by ASAHI KASEI Corporation.

References

1. C. Schoellhammer et al.: Expert Opin Drug Deliv, **11** (2014) 393.
2. N. Sugita et al.: Proc. USE2021, 2E2-3, (2021).