A compact cavity resonant ultrasound transducer for transdermal drug delivery of biopharmaceuticals

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1. Introduction

Sonophoresis has attracted attention as a minimally invasive alternative to needle injections for transdermal drug administration. The method utilizes ultrasound cavitation to stimulate the skin surface, enhancing drug permeability across the skin[1)]. The skin's barrier function typically allows only lipophilic molecules with molecular weight below 500 Da to penetrate the outermost layer. Generally, inertial cavitation induced by high-pressure ultrasound is employed to enhance the penetration of molecules larger than 500 Da and hydrophilic, such as biopharmaceuticals, which do not normally penetrate the skin surface.

To generate inertial cavitation, high-intensity and low-frequency ultrasound below 100 kHz is effective. However, conventional bolted Langevin-type transducers used for low-frequency sonophoresis are bulky. Additionally, the intensity of the ultrasound is reduced to a moderate level to avoid thermal damage[2)] on the skin, resulting in a longer ultrasound treatment duration. Therefore, a compact low-frequency ultrasonic transducer that can effectively generate ultrasound cavitation on skin surfaces is required for transdermal applications.

In this study, we propose a mechanical design for a compact low-frequency ultrasound transducer capable of effectively generating cavitation for a wearable sonophoresis device. Our design utilizes cavity resonance to enhance acoustic intensity, thereby efficiently generating cavitation on skin surfaces.

2. Materials and methods

2.1 Transducer design concept

The ultrasound transducer consists of a disk-shaped piezoelectric element and a bowl-shaped acoustic resonator. **Fig. 1** shows a schematic illustration of the transducer design concept. A conical slit of the acoustic resonator converts the in-plane vibration of the piezoelectric element to the bending vibration of the acoustic resonator, amplifying the displacement. Utilizing the resonance mode of bending vibration in the acoustic resonator allows the transducer to work in a low-frequency range and irradiate high-intensity ultrasound. Along the steep sound pressure gradient, cavitation nuclei are supplied from the apex of the spherical cavity to the aperture. Due to the presence of cavitation nuclei, the transducer can induce inertial cavitation on material surfaces located in lower sound pressure regions.

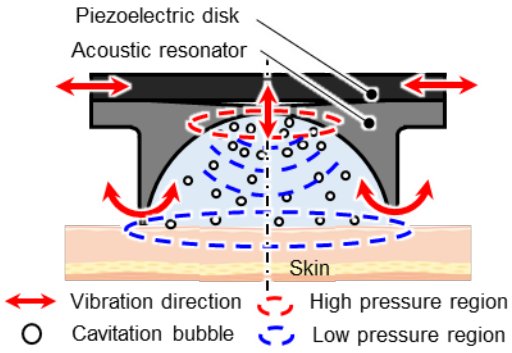

Fig. 1 Schematic illustration of the proposed transducer.

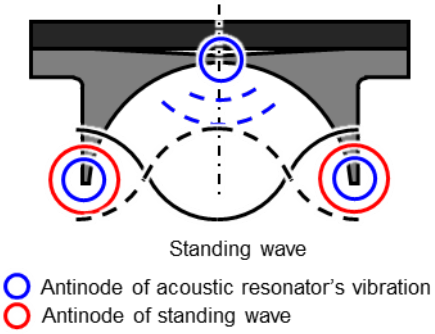

Fig. 2 Schematic illustration of cavity resonance.

Fig. 2 displays a schematic illustration of cavity resonance[3)]. The displacement of the acoustic resonator is at its maximum at the apex of the spherical cavity, and the edge of the aperture vibrates in the radial direction during the resonance vibration mode. We tune the inner diameter of the resonator to form standing waves along the radial direction, pursuing to enhance the intensity of the output sound.

2.2 Transducer fabrication

Fig. 3 displays the transducer prototype. The diameter and thickness are 28 mm and 10 mm, respectively, with a resonance frequency of 78 kHz. The diameter of the aperture matches the wavelength of irradiated ultrasound in water to excite the

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standing wave in the spherical cavity.

2.3 Cavitation scatter noise measurement

To verify that the transducer prototype can induce inertial cavitation, we measured the scatter noise from cavitation bubbles. The ultra-harmonic response and rapid increase of broadband noise represent the generation of stable and inertial cavitation, respectively. The transducer was driven at 76 kHz in pure water, with input voltages ranging from 20 V_{pp} to 120 V_{pp} in increments of 20 V_{pp}. The scatter signal was measured 0.5 s after the irradiation started.

2.4 Drug permeation across an artificial membrane

To verify the device performance in enhancing drug permeability, we permeated FITC-dextran4 (4000 Da) across the artificial membrane. The diffusion characteristics of the membrane are similar to those of human skin. Before drug permeation, ultrasound treatment was applied for 3 mins to the membrane in PBS solution. The transducer was driven at the resonance frequency of 78 kHz with input voltages of 20, 60, and 120 V_{pp}. The duty ratio and repetition period were set at 0.5 and 1 s, respectively. The concentration of the FITC-dextran solution was 1 g/L.

3. Results

Fig. 4 shows the frequency spectrum of cavitation noise. The broadband noise rapidly increased between 40 V_{pp} and 60 V_{pp}. These results indicate that the transducer prototype can induce inertial cavitation.

Fig. 5 shows the permeated amount of FITC-dextran4 across the artificial membrane at different input voltages. Without ultrasound treatment, the drug did not permeate across the membrane. However, with ultrasound treatment, the drug permeated across the membrane. Interestingly, the permeated amount was saturated at the lowest voltage of 20 V_{pp}. This implies that we could further reduce the applied voltage for ultrasound irradiation in the future study.

4. Conclusion

We developed a cavity resonant ultrasound transducer with a diameter of 28 mm, a thickness of 10 mm, and a resonance frequency of 78 kHz. The transducer prototype effectively induced inertial cavitation and enhanced drug permeability across the skin through ultrasound treatment.

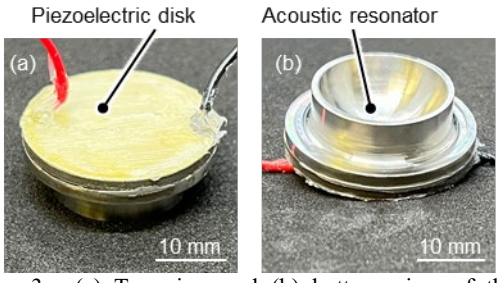

Fig. 3 (a) Top view and (b) bottom view of the transducer prototype.

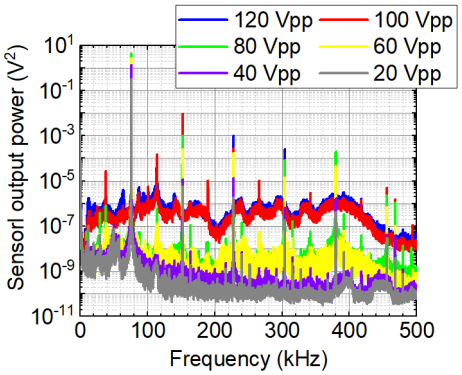

Fig. 4 Frequency spectrum of scatter noise from cavitation bubbles at difference applied voltage.

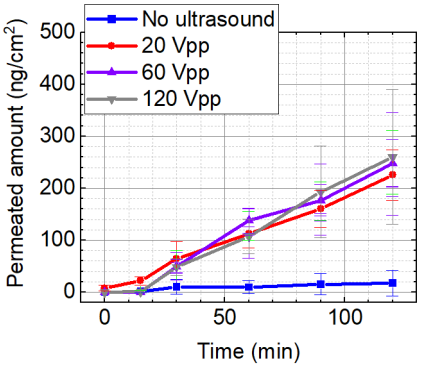

Fig. 5 Permeated amount of FITC-dextran4 across the artificial membrane.

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