Measurement and calculation of acoustic pressure on the effect of transdermal penetration by sonophoresis

ソノフォレシスによる経皮浸潤効果に及ぼす音圧の測定と計算

Yuta Kurashina[1†], Risa Asano[1], Makoto Matsui[2], Takahiro Nomoto[2], Kentaro Nakamura[2], Nobuhiro Nishiyama[2], and Yoshitaka Kitamoto[1] ([1]School of Mater. & Chem. Technol., Tokyo Tech., [2]Institute of Innovative Research, Tokyo Tech.)

倉科佑太[1†], 浅野梨紗[1], 松井誠[2], 野本貴大[2], 中村健太郎[2], 西山伸宏[2], 北本仁孝[1] ([1]東工大 物質理工学院, [2]東工大 科学技術創成研究院)

1. Introduction

In drug administration, transdermal administration is a stable method of delivering drugs into the bloodstream compared to oral administration. Meanwhile, the skin is the largest organ having a barrier function to protect the human body. In particular, the stratum corneum, which is located on the top surface, is an extremely strong barrier. Only drugs with a molecular weight smaller than 500 can penetrate the stratum corneum[1]. Therefore, macromolecular drugs are unable to penetrate the skin simply by applying the medicine, and require injection or other methods to penetrate through the skin. Injections, the only approved method, are painful and highly invasive. In addition, the drug does not diffuse subcutaneously by injections, making it difficult to administer over a wide area. Therefore, sonophoresis[2] using ultrasound has recently been attracting attention as one of alternative methods.

As for the previous studies on sonophoresis, insulin administered to mice by ultrasonic cleaner[3] and polystyrene particles administered to pig skin[4] have been reported. Thus, the evaluation of sonophoresis using various particles and drugs has been reported. However, measurements of the energy input to the skin when irradiated with ultrasound have not been reported. Therefore, the amount of energy input to the skin is not known.

Here, the acoustic pressure caused by sonophoresis was calculated from the matrix equation of ultrasonic transmission, and a small piezoelectric sensor was fabricated for measurement of the acoustic presssure. The results of the acoustic pressure were compared with the actual test using nanoparticles penetrated by sonophoresis. By changing the hardness of the subcutaneous lining, the acoustic pressure exposed to the skin was varied.

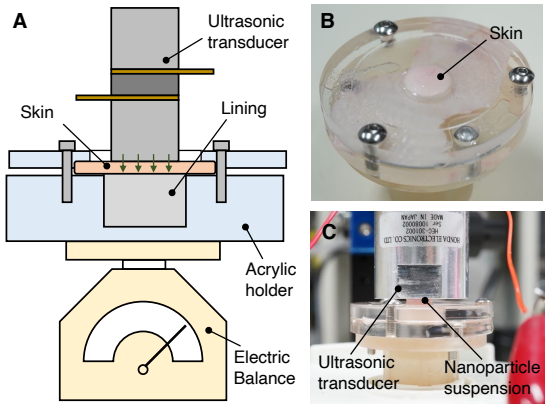

Fig. 1 Experimental setup of an ultrasonic irradiation device for sonophoresis. (A) The skin was placed on an acrylic holder, and the contacts were sensed by an electronic balance. (B) Place the skin in the acrylic holder in a taut position. (C) A suspension of nanoparticles was injected between the ultrasonic transducer and the skin for irradiation of ultrasound.

2. Materials and Methods

2.1 Fabrication of ultrasonic irradiation device

A bolted Langevin transducer with a resonant frequency of 42 ± 1 kHz as an ultrasonic transducer was applied to irradiate the skin on an acrylic holder (Fig. 1A). By placing the acrylic holder on an electronic weighing scale, the weight of the holder was sensed, and the ultrasonic irradiation was carried out at a location just above the contact point. Skin samples harvested from hairless mice were placed in an acrylic holder so that the skin was not wrinkled (Fig. 1B). The nanoparticle suspension was then dropped onto the skin and lowered to the point where the ultrasonic transducer was contacted with the skin (Fig. 1C). This made ultrasonic irradiation possible by keeping the suspension of nanoparticles between the acrylic holder and the ultrasonic transducer.

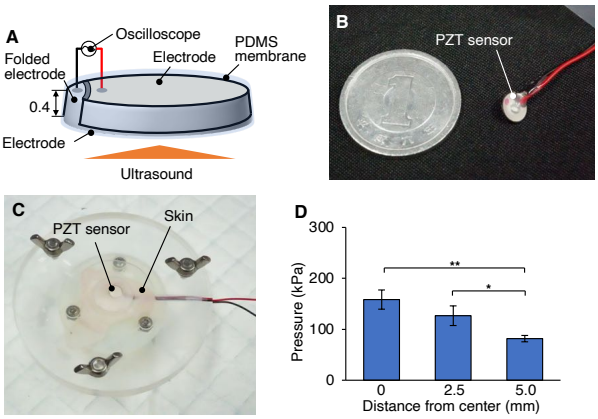

Fig. 2 Acoustic pressure measurement using PZT sensor. (A) Schematic illustration of PZT sensor and (B) a fabricated PZT sensor. (C) PZT sensor placed under the skin. (D) Acoustic pressure measured by PZT sensor.

2.2 Fabrication of piezoelectric sensor

A PZT sensor was fabricated to measure the sound pressure of ultrasonic waves irradiated on the skin. The PZT sensor with the electrode on one side was covered with PDMS to seal the sensor for electrical insulation (Fig. 2A, B). The PZT sensor was connected to an oscilloscope and measured the acoustic pressure. The acoustic pressure was calibrated using a hydrophone, which has a known relationship between current and acoustic pressure. To measure the acoustic pressure, the PZT sensor was placed under the skin and irradiated with ultrasound (Fig. 2C).

2.3 Preparation of sonophoresis

The nanoparticles were infiltrated into the skin using the ultrasonic irradiation system described above. The maximum amplitude of the ultrasonic transducer was adjusted to 1.3 μm, and ultrasonic irradiation was applied for 5 min. A suspension of nanoparticles consisting of 200 nm fluorescent polystyrene nanoparticles was used as a model drug to infiltrate the skin. Note that two types of linings of various hardness (low-density polyethylene (LDPE) and high-density polyethylene (HDPE)) were used under the skin.

3. Results and Discussion

The acoustic pressure measured by the PZT sensor was ~150 kPa at the center (Fig. 2D). This is above the threshold for the occurrence of cavitation (~100 kPa)[5], indicating that cavitation, which is a factor in drug infiltration, also occurs between the skin and the ultrasonic irradiation device. Meanwhile, the acoustic pressure calculated from the particle velocity of the ultrasonic transducer and the ultrasonic transmission equation was ~200 kPa with LDPE as the lining, and ~400 kPa with HDPE.

Kurashina.y.aa@m.titech.ac.jp

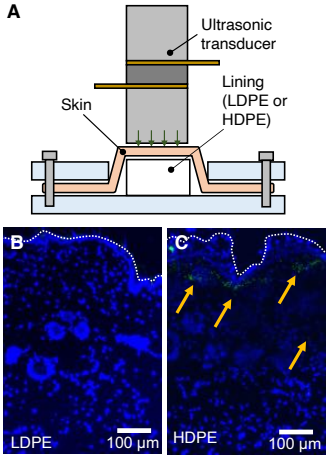

Fig. 3 Two different linings were placed under the skin and polystyrene nanoparticles were infiltrated into the skin. (A) Schematic illustration of sonophoresis with various linings. Polystyrene nanoparticles with 200 nm were infiltrated with (B) LDPE or (C) HDPE.

The measured and calculated values were of the same order, indicating the validity of each value. On the other hand, the discrepancy is due to the error caused by placing the PZT sensor under the skin.

In the infiltration demonstration using polystyrene nanoparticles (Fig. 3), 200 nm polystyrene nanoparticles were observed to infiltrate when HDPE, which was calculated to have higher acoustic pressure, was employed.

4. Conclusion

In this study, the acoustic pressure caused on the skin during the infiltration of nanoparticles by sonophoresis was evaluated by calculation and measurement. The demonstration of the nanoparticle infiltration and the measurement of the acoustic pressure were found to be consistent, indicating the validity of the results.

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