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Intense laser-induced Lamb waves generated on a spherical shell enough to allow transdermal drug delivery

So Nishida[1†] and Koji Aizawa[1]
([1]Guraduate school of Engineering, Kanazawa Institute of Technology)

1. Background and Motivation

Irradiation of intense pressure waves to the skin has been known to reduce the drug permeability of stratum corneum (SC) [1]. This phenomenon suggests the possibility of minimally invasive transdermal drug delivery (TDD) by a mechanism different from ultrasonically cavitation. Intense pressure waves also reduce the permeability of cell membranes and are therefore also used for gene delivery [2]. Damage to cells, however, causes cellular dysfunction and inflammatory reactions. This study aims to develop a novel TDD system that causes less damage to subcutaneous cells by focusing acoustic energy on the SC.

In the past studies, the use of piezoelectric elements or loudspeakers in contact with the skin have been reported in order to induce surface acoustic waves on the skin [3-5]. These methods can easily control the intensity of surface acoustic waves. However, it is not known whether they are strong enough to alter the drug permeability of the SC. We consider that the use of pulsed laser ablation is advantageous for introducing strong surface acoustic wave. However, direct irradiation of pulsed lasers to the epidermis is not feasible from a view point of non-invasive, therefore we considered acoustic coupling of the strong surface acoustic waves induced by pulsed laser to the skin surface.

In this study, a spherical transducer was used to generate powerful surface acoustic waves. Using spheres is expected to increase the intensity due to the superposition of generated surface acoustic waves. Up to now, we have measured and evaluated Lamb waves generated by irradiating nanosecond laser pulses to a water-immersed black resin spherical shell [6-8]. In this paper, laser-induced Lamb waves generated on a resin spherical shell were measured using a sensor with a piezoelectric membrane/silicone rubber structure bonded to an artificial skin. Through this experiment, we investigated the possibility of minimally invasive TDD with minimal subcutaneous effects.

2. Experimental Procedure

2.1 Intense laser-induced Lamb wave generation on a spherical shell

E-mail: [1†]c6402208@st.kanazawa-it.ac.jp,
[1]aizawa@neptune.kanazawa-it.ac.jp

Laser-induced Lamb waves on the spherical shell are generated by laser ablation on the shell surface by irradiation of a pulsed laser (Spectra-physics, LAB-130-10, wavelength 532 nm, pulse width 10 ns, maximum pulse energy 200 mJ) through a focusing lens (Sigma Koki, SLB-30-80PM, focal length 80 mm) with anti-reflection coating. A commercially available black polypropylene (PP) spherical shells (diameter of 40 mm, shell thickness of 1 mm) was used in this experiment. To stably generate Lamb waves for multiple laser irradiations, the pulsed laser was irradiated to a 0.5-mm-thick black fluoro-elastomer (FKM) (10 mm x 10 mm) plate bonded to the spherical shell surface. **Fig. 1** illustrates a cross-sectional view of spherical shell fixing holder with condenser lens. The spherical shell was fixed by point contact using four screws attached to the holder and placed on the beamline. Furthermore, the lower part of the spherical shell, which is the laser irradiation area, was immersed in pure water to enhance the laser-induced Lamb wave due to the laser plasma confinement effect.

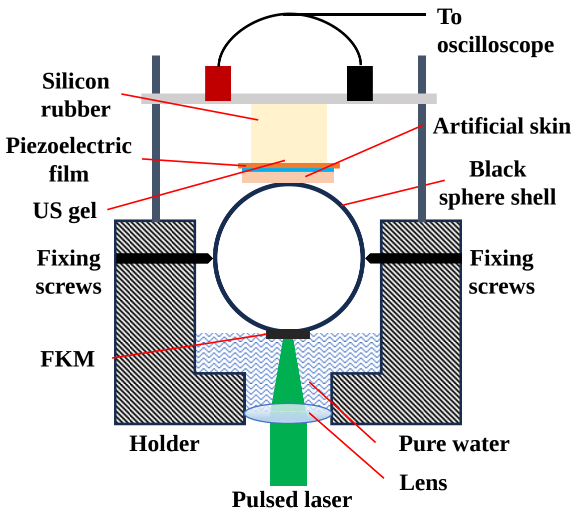

Fig. 1 Cross-sectional view of spherical shell fixing holder with condenser lens.

2.2 Measurement method of laser-induced Lamb waves

Lamb waves generated by pulsed laser irradiation in the lower part of the spherical shell propagate through the spherical shell and overlap on the spherical shell on the opposite side of the laser irradiation area. For the detection of the Lamb waves, a sensor fabricated from a 28-μm-thick piezoelectric film (10 × 20 mm) bonded to a 10 mm square of silicone rubber was used. In addition, an artificial skin was placed on top of the spherical shell, which was designed to acoustically couple the strong Lamb waves to the SC. The contact surface between the artificial skin and the sensor was coated with ultrasound gel. Signals from the sensor were detected using a digital oscilloscope (Iwatsu, DS-5654A) with a data sampling rate of 10 M and a data length of 100 k points. The signal was subjected to time-frequency characteristic (scalogram) analysis with a continuous wavelet transform using generalized Morse wavelet in MATLAB®. In addition, the Lamb wave components were analyzed in detail by filtering specific frequency regions and performing an inverse wavelet transform.

3. Results and Discussion

Figure 2 shows a typical scalogram obtained from the time waveform measured by the sensor. The scalograms measured under the same conditions were obtained with good reproducibility in this measurement. This result shows a strong component around 7 kHz to 20 kHz, which is considered to be a Lamb wave. Prosser *et al.* have reported in the modal dispersion analysis of Lamb waves in aluminum plates that large amplitude signals in the low frequency region are characteristic of A0-mode Lamb wave signals [9]. From the time waveforms obtained by inverse wavelet transform filtered in the frequency range from 7 kHz to 20 kHz, the signal intensity reached a maximum amplitude of 27.5 mV at 0.38 ms after laser irradiation and decayed with a time constant of a few ms. This tendency was similar to that observed in the Lamb wave analysis of A0 modes traveling in a 2.5-mm-thick aluminum plate reported by Cai *et al* [10].

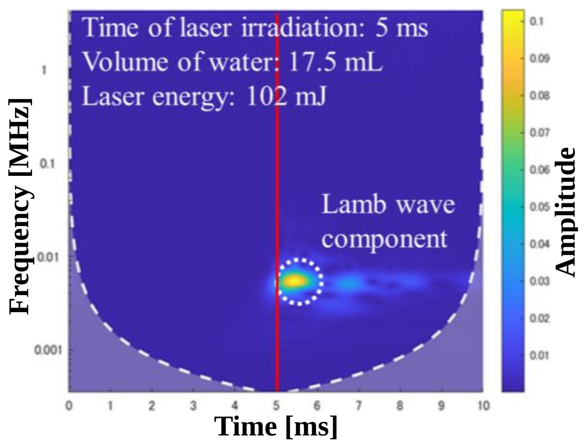

Fig. 2 A scalogram of time waveform measured by the sensor with piezoelectric film/silicon rubber structure.

Finally, we compared the intensity of the laser-induced Lamb waves generated on the spherical shell with the laser-induced stress waves used for TDD. In a report by Ogura *et al*. that confirmed the enhanced penetration of photosensitizers into the skin, a structure consisting of a 1-mm-thick PET plate bonded together with a natural rubber was used to generate the laser-induced stress wave [11]. We placed the rubber surface of this structure in contact with the artificial skin shown in Fig. 1 and measured the sensor signal when a pulsed laser was irradiated to the PET surface of this structure. As a result, the maximum amplitude of the obtained signal intensity was 31.2 mV, which is close to the magnitude of the signal intensity we observed. We suppose that our devised spherical shell vibrator has the ability to enable TDD if we focus only on the signal intensity.

4. Conclusion

Laser-induced Lamb waves generated in a water-immersed black resin spherical shell were measured and evaluated, and the signal intensity was confirmed to be promising for TDD applications.

Acknowledgments

This work was supported in part by Grant-in-Aid for Scientific Research (21K04202, 24K07614).

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