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Effects of the molecular film on a microbubble collapsed by ultrasound irradiation

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1. Introduction

In vascular drug therapies, side effects on healthy tissues are problems that need to be overcome. Drug delivery systems (DDS) that enables local drug release have been developed to address this problem. In DDS using ultrasound, drug-containing microbubbles are administered as drug carriers into blood vessels and transported to the target area through the blood flow. Ultrasound excitation can trigger the bubbles to oscillate and collapse to release the drug locally[1]. For a safety criterion on the drug release using ultrasound, the behavior of the molecular film surrounding the microbubble and the process from the vibration to collapse of bubbles under ultrasonication should be clarified to control the drug administration. In this report, we focused on the collapsing microbubbles and investigated the effects of the surrounding molecular film on the sound pressure threshold for the collapse under ultrasound irradiation.

2. Methods

Microbubbles expand and contract repeatedly in synchronization with an incident ultrasound and collapse subsequently via spherical and non-spherical vibrations as the sound pressure amplitude is increased[2]. Acoustic microbubbles such as contrast agents consist of a surrounding molecular film and an internal gas to prevent its dissolution in liquids, and the surface tension on the bubble wall depends on the adsorption of the surfactant molecules. In this report, the contact angle between the bubble and a solid surface θ was measured to investigate the effects of bubble collapse on the adsorption kinetics (**Fig. 1**), which is expressed as[3]

$$\theta = \cos^{-1}(2H/D), \qquad (1)$$

where H is the distance from the center of the microbubble to the solid (glass) surface and D is the horizontal diameter of the microbubble. Adsorption of surfactant molecules on the gas-liquid interface, bubble wall, decreases the surface tension of the bubble, resulting in decrease of the contact angle θ (see right photograph in **Fig. 1**). We measured the contact angle θ to estimate the formation of the surrounding molecular film.

The phospholipid, 1,2-dimyristoyl-*sn*-glycerol-3-phosphocholine (DMPC) was employed as the surfactant. Fluorocarbon gas was used as the internal gas of microbubbles, and the bubbles with a radius of 50 to 230 µm were fabricated using an injector. The vibration and collapse of the microbubbles were observed by the observation system shown in **Fig. 2**. The microbubbles were attached on a glass plate with a thickness of 1.2 mm and immersed in a rectangular glass observational cell filled with the 0.3-mM DMPC solution (or degassed water). Considering the time constant of the adsorption of DMPC molecules to the bubble surface[3], the electric signal was input to the transducer after 1000 s. The microbubbles were exposed to 15-cycle pulsed ultrasonic waves at 38.8 kHz generated by an ultrasound Langevin-type transducer attached on the bottom of the cell. Light from a xenon light was focused to the position where the microbubble was attached so that the vibration and collapse of the bubbles can be observed as shadow graphs. The transmitted light was received by a high-speed camera (Shimadzu, HPV-1; recording frame speed: 63 kfps). For comparison, the same procedure was conducted using fluorocarbon-gas bubbles fabricated in degassed water to investigate the effect of the surrounding molecular film on the bubble collapse. In this report, an ejection of the internal gas from the microbubble (*daughter bubble*) was defined as “collapse of a bubble”.

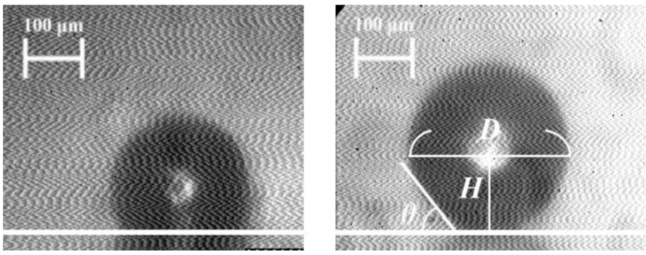

Fig. 1 Contact angle of a microbubble in degassed water (left) and the DMPC solution (right).

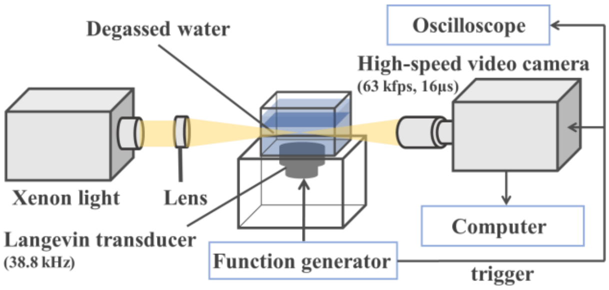

Fig. 2 Optical observation system using a high-speed camera and an ultrasound cell.

3. Results and Discussion

In our previous work[3], we investigated the relationship between the DMPC concentration and the contact angle of a microbubble on a glass plate in DMPC solutions; the contact angle of fluorocarbon-gas bubbles on a glass substrate in 0.3-mM DMPC solution was 32.6 ± 0.5°. In this experiment, we confirmed the contact angle of the bubble before ultrasonication was 33.3 ± 5.9° in the 0.3-mM DMPC solution. **Fig. 3** shows the typical sequential photographs of the vibration and collapse of the microbubble when the sound pressure amplitude was gradually increased. In the case of a low sound pressure (23 kPa in **Fig. 3(a)**), the low resonance vibration mode appeared on the bubble. When the sound pressure amplitude was increased to 25 kPa, the bubble began to behave the non-spherical harmonic vibration mode (**Fig. 3(b)**), and the bubble eventually collapsed (ejected a daughter bubble) at the amplitude threshold at 30 kPa (**Fig. 3(c)**). **Fig. 4** shows the relationship between the initial bubble radius before ultrasonication and the negative sound pressure amplitude threshold for bubble collapse. The results for naked bubbles in degassed water were also plotted. In both cases, the minimum sound pressure threshold existed around 110 µm, indicating the bubbles with the resonance size at 38.8 kHz were collapsed by a smaller sound pressure. There was a significant difference in the sound pressure threshold for collapse between the two cases, implying the encapsulated bubbles with the surfactant require a larger sound pressure for its collapse due to the viscoelasticity of the surrounding molecular film. The contact angle of bubbles just after the collapse was changed to 46.6 ± 6.7°, meaning the DMPC molecules at the bubble surface was desorbed in the process from the vibration to collapse under ultrasonication.

4. Conclusion

We focus on the collapse of microbubbles and investigated the effect of the surrounding molecular film on the sound pressure threshold required for collapse under ultrasonication. The encapsulated bubbles had a larger sound pressure threshold for its collapse, and the surfactant molecules on the bubble wall were desorbed partially in the process from vibration to collapse.

References

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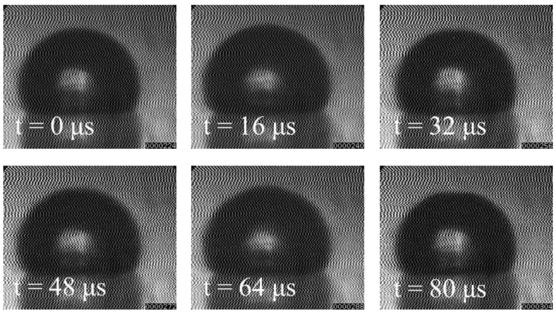
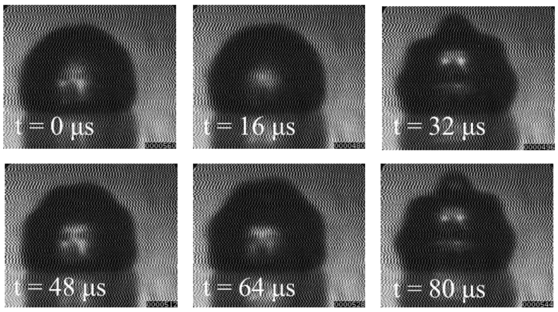
(a) spherical vibration



(b) Non-spherical vibration



(c) collapse

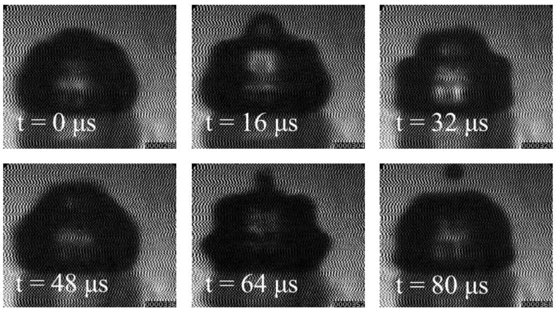


Fig. 3 Non-spherical vibration and collapse of a bubble with an initial radius of 194 µm under ultrasound irradiation of (a) 23 kPa, (b) 25 kPa, and (c) 30 kPa.

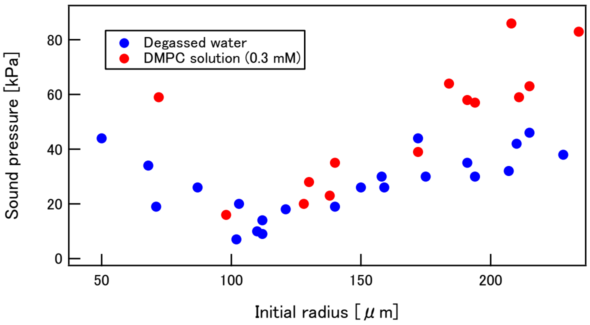


Fig. 4 Relationship between the initial radius of bubble with (red) and without a DMPC molecular film (blue) and the negative sound pressure threshold for collapse.

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