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Measurement of a microcapsule vibration having a hard plastic shell in an acoustic standing wave

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ABSTRACT

Observation techniques for measuring the vibration of a single microcapsule with a hard plastic shell in an acoustic standing wave field are discussed. First, optical observation of a microcapsule vibration by using a laser Doppler vibrometer (LDV), which can observe small capsule vibration amplitudes at high-frequency, was investigated. Capsules of tens of micrometer size were trapped at the antinode of an acoustic standing wave generated in an observational cell, and the capsule vibration with displacement amplitude of tens of nano-meters could be measured. The acoustic radiation force acting on microcapsules in the acoustic standing wave was measured from the trapped position of the standing wave and the vibrational displacement amplitude of the capsules was estimated from the theoretical equation of the acoustic radiation force, giving results in good agreement with the LDV measurements. The vibrational amplitude of a capsule was found to be proportional to the amplitude of the driving sound pressure. A larger expansion ratio was observed for capsules closer to the resonance condition under the same driving sound pressure and frequency.

INTRODUCTION

Micrometer-size bubbles are used as contrast agents to enhance diagnostic images for medical ultrasound. The radii of commercial contrast agents in practical use, such as Levovist and Sonazoid, are less than several micrometers, and their resonance frequencies are in the MHz range or higher. These commercial contrast agents are encapsulated and have elastic shells, e.g., Levovist are coated with a palmitic acid shell. The resonance frequencies of the contrast agents, i.e. microcapsules, are higher than that of a free bubble with the same size due to the shell elasticity which restrains the expansion and contraction of the internal gas under ultrasound irradiation. The equations for the motion of a microcapsule including shell effects have been derived by several researchers [1,2]. In recent years, several studies have examined capsule behavior, and destruction under ultrasound irradiation has also been reported [3,4]. Unger et al. have proposed the potential application of microcapsules as drug or gene carries [5]. An ultrasonic drug delivery system (UDDS) using microcapsules would consist of three steps: capsule injection into blood vessels, trapping of the capsules at the target tissue and capsule destruction for drug release [6]. The vibration response of a microcapsule cloud can be predicted through an acoustic signal re-generated by the bubbles under ultrasound irradiation. However, the amplitude of an acoustic signal from a single microbubble is not sufficient for detection by a hydrophone compared with background noise. Therefore, a quantitative evaluation of the shell elasticity of a single microcapsule is difficult since a multi-bubble layer exhibits dispersion of capsule size and shell properties.

The authors have investigated the destruction of a microcapsule with a hard plastic shell and have made a quantitative evaluation of shell elasticity [7]. Our optical observational system consists of a high-speed video camera, which can observe the vibration of a single microbubble when the expansion/contraction ratio is sufficiently large compared with the image resolution. In this paper, we discuss alternative observational techniques for measuring a vibrational displacement amplitude of tens of nanometers for a single microcapsule with a hard plastic shell in an acoustic standing wave field. First, microcapsule vibrations of tens of nanometers amplitude are measured by a laser Doppler vibrometer (LDV). For comparison, the acoustic radiation force acting on microcapsules in the acoustic standing wave is measured from the trapped position of the standing wave, and the vibrational displacement amplitude of the microcapsules is estimated from a theoretical equation of capsule vibration.

OBSERVATIONAL SYSTEM FOR CAPSULE VIBRATION

There are several reports in the literature related to the optical observation of microbubble and microcapsule vibration under ultrasonic radiation using a high-speed video camera [3,4,7]. Although these cameras enable the observation of bubble vibrations in two dimensions, the maximum frame rate of a camera is generally lower than the driving frequency of the bubble and, therefore, a camera system is unsuitable for investigating the details of high-speed bubble vibration and its collapse at high frequencies. Furthermore, it is difficult to

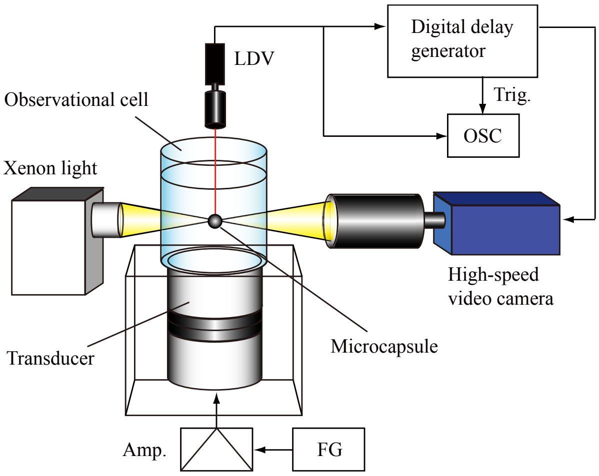

Figure 1. Experimental setup for the optical observation of bubble and capsule vibration using a high-speed video camera and an LDV.

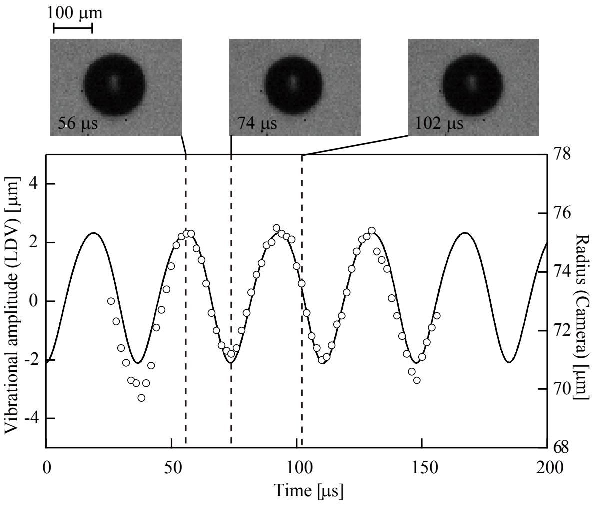

Figure 2. Radius versus time curve for the high-speed video camera and vibrational displacement amplitude measured by the LDV of a microbubble driven with 10 kPa at 27 kHz [8].

obtain a satisfactory image resolution compared with the small vibration amplitude of a microbubble, even using an object lens. It is also difficult to measure a single bubble vibration using a laser scattering method when the volume variation of the bubble is small because the scattered light is insufficient compared with the background noise.

We consider a new system for measuring microcapsule vibration using an LDV. An LDV is a measuring instrument which enables the observation of vibration with an amplitude of nanometers in the MHz range, continuously at a single measuring point. An LDV measures the vibration at a bubble wall at a boundary between water and air in one dimension. To examine the effectiveness of the new system, we made simultaneous optical observations of bubble vibration using a high-speed video camera and an LDV [8]. Several kinds of single-bubble vibrations in an acoustic standing-wave field were investigated by combining observations using the camera and the LDV. Figure 1 shows the experimental setup for the observation of bubble vibration. An acrylic cylindrical cell with an inner diameter of 60 mm and a height of 60 mm filled with degassed water was used as an observational cell. Two transparent flat windows made of quartz glass were placed in the cell wall for the observations. A bolt-clamped Langevin type transducer with a diameter of 45 mm and a resonance frequency of 27 kHz was attached to the bottom of the cell. An acoustic standing wave was generated in the vertical direction in the cell by controlling the water level and maximizing the electrical admittance of the transducer. By disturbing the water surface with a needle, a micrometer-size bubble could be trapped at the antinode of a standing wave. A xenon lamp was used as a continuous light source, focused on the position where the bubble traps. A high-speed video camera (HPV-1, Shimadzu, Kyoto, Japan) with a Barlow lens and a long-distance microscope (QM100, Questar, PA) was arranged along the light axis to receive the light and observe the bubble vibration in a shadow graph. The maximum recording rate and resolution of the camera image were 1 MHz and 4.2 μm/pixel, respectively. A sensor head of an LDV (NLV2500, PI Polytech, Waldbronn, Germany) with a 20-power object lens was arranged above the cell 20 mm from the bubble across the light axis. The focal spot size of the LDV beam was 1.5 μm. The positions of the LDV sensor head and the observational cell were controlled by precise positioning stage controllers to ensure the focal points of the camera and LDV correspond. A trigger signal via a delay generator was input to the camera and a digital oscilloscope to synchronize the signals in the camera and LDV. The sound pressure was measured using a PVDF hydrophone with a diameter of 2 mm, which would not affect the acoustic field. Figure 2 shows representative experimental results of bubble radius versus time curves (R–t curve) measured by the high-speed video camera and the LDV [8]. The driving frequency and sound pressure were 27 kHz and 10 kPa, respectively. The LDV can measure only AC components of the vibration signal through the Doppler effect. The frame rate of the camera was 500 kHz. The spot size of the LDV beam through the object lens (=1.5 μm) was small enough compared with the bubble size that its effect could be neglected. The bubble exhibits harmonic vibration synchronized with the driving sound pressure, and the two experimental results was in good agreement.

OBSERVATION OF CAPSULE VIBRATION

Microbubble vibrations could be observed using the high-speed camera because the vibrational displacement amplitude of the bubble either equaled or surpassed the image resolution of the camera. In the case of microcapsules with a hard shell, observation by the high-speed camera will be difficult due to the restraints of the capsule vibration by the shell elasticity. Hence, microcapsule vibration was examined using only the LDV. In our experiments, microcapsules (microsphere F-80ED, Matsumotoyushi, Osaka, Japan) constructed of PVC (polyvinyl chloride) having a radius distribution approximately 10 to 100 μm and an average radius of 50 μm were used. The hollow part was approximately 98% of the volume, i.e., the shell thickness was approximately 0.3 μm for a capsule radius of 50 μm. The Young's modulus and Poisson's ratio of the shell material are unknown. The internal gas of the capsule was butane. The PVC-shelled microcapsules F-80ED are useful for observing vibration because of the time-stability properties of the shell in an acoustic standing wave in water, although the capsules cannot be used in in-vivo experiments. The same experimental setup was used for the observation of the capsule vibration except that the driving frequency is chosen considering the fact that the resonance frequency of the capsules is higher than that of a free bubble with the same radius due to the shell effect. A single microcapsule could be trapped by attaching and inserting with a needle at the antinode of the acoustic standing wave driven with the appropriate sound pressure of approximately 30 kPa, which was under the threshold value of capsule destruction [7]. As microbubbles, sufficient reflected light for the LDV could be obtained from the capsule wall. Figure 3 shows the camera image and vibrational displaceme-

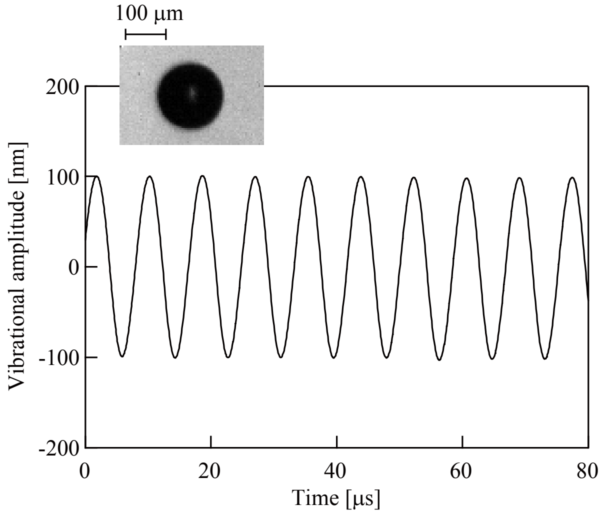

Figure 3. Vibrational displacement amplitude of a capsule measured by the LDV driven with 37 kPa at 115 kHz.

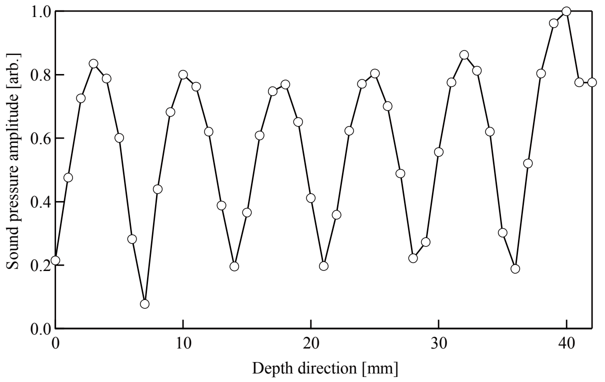

Figure 4. Sound pressure distribution in the vertical direction (z-direction) in the observational cell at 115 kHz.

nt amplitude of a trapped capsule driven with 115 kHz and 37 kPa. The capsule vibration could not be observed by the camera image because of the small vibrational amplitude. In Fig. 3, the capsule exhibits harmonic linear vibration synchronized with the driving sound pressure, and a small capsule vibration with a displacement amplitude of approximately 100 nm could be observed. The displacement amplitude of the capsule vibration was restrained due to the shell effects. The observation by the LDV overcomes the shortcomings of the camera, such as low image resolution and low sampling rate. Using a camera and LDV in combination can obtain detailed information on capsule behavior in an acoustic field.

ESTIMATE FROM THE ACOUSTIC RADIATION FORCE

For comparison with the experimental results of capsule vibration by the LDV, we estimated the vibrational displacement amplitude of capsules in an acoustic standing wave from the acoustic radiation force acting on the capsules. There are several reports in the literature on the acoustic radiation force acting on a microbubble in an acoustic standing wave field [9,10]. We consider a microcapsule in an acoustic standing wave field generated in the z-direction as $p_A(z,t)=P_{A0}\sin(2\pi z/\lambda_z)\sin\omega t$ where P_{A0} is the amplitude of the driving sound pressure, λ_z is the wavelength in the z-direction and ω is the driving angular velocity. The acoustic radiation force on a capsule with volume $V(t)$ can be expressed as

$$F_A = -\langle V(t)\cdot\nabla p_A(z,t)\rangle, \quad (1)$$

where the angle brackets indicates the time average and ∇ is the gradient operator. If the vibrational displacement amplitude of the capsule is sufficiently small compared with the capsule radius due to the restraints by the shell effects, the time variation of the capsule radius can be assumed to be a linear vibration and expressed as $R(t)=R_n(1+\varepsilon_0\sin(\omega t+\theta))$ where R_n is the initial capsule radius, ε_0 is the vibrational displacement amplitude coefficient, and θ is the phase difference between the driving sound pressure and the capsule vibration. Additionally, in the case of $R_n \ll R_{res}$ (R_{res} is the resonance radius for the driving frequency), the phase difference θ can be assumed to be π, i.e., if ε_0 is positive, the capsule expands with negative sound pressure and contracts with positive sound pressure. By substituting $V(t)=4\pi R(t)^3/3$ and $p_A(z,t)$ in eq. 1, F_A can be expressed as

$$F_A = \frac{4\pi^2 R_n^3 P_{A0}\varepsilon_0}{\lambda_z}\cos\frac{2\pi\pi}{\lambda_z}\cdot \quad (2)$$

When the capsule radius is smaller than the resonance size for the driving frequency, the acoustic radiation force acts toward the antinode of the standing wave. Strictly speaking, the capsule is trapped at a slightly higher position than the antinode of the standing wave, and in this condition the acoustic radiation force F_A balances the buoyancy force of the capsule $F_B=4\pi R_n^3\rho g/3$ where ρ is the density of the liquid and g is the acceleration due to gravity. Therefore, the vibrational displacement amplitude coefficient ε_0 can be expressed as follows:

$$\varepsilon_0 = \frac{\rho g\lambda_z}{3P_{A0}\pi\cos\frac{2\pi z}{\lambda_z}} \cdot \quad (3)$$

The vibrational displacement amplitude of a capsule was estimated from the trapped position of the capsule in the standing wave and eq. (3). In the experiment, the same observational system was used as in the previous sections. The distance between the position at which the capsule was trapped and the antinode of the standing wave was measured using a hydrophone and the precise positioning stage controllers from the camera image. Figure 4 shows the sound pressure distribution in the vertical direction in the observation cell. The generation of a standing wave with a wavelength of approximately 15 mm was confirmed. The vibration amplitude of capsules measured by the LDV and calculated from the radiation force under several conditions were compared and the results are summarizedin Table 1. Although a difference of approximately 20% exists, the two results show good agreement. Considering the experimental result on free bubbles shown in Fig. 2, we assume that the LDV values are more accurate and the error for the values calculated from eq. 3 can be attributed to the assumptions in the derivation of eq. 3 and the measurement error of the sound pressure amplitude in the standing wave by the hydrophone since the presence of the hydrophone will disturb the standing wave field. The experimental results imply that the vibration amplitude of a capsule trapped in a standing-wave field can be also predicted from eq. 3 (which is an important secondary conclusion of this report). At 115 kHz, a microcapsule with a radius of tens of micrometers was under the reso nance size, which is approximately 100 μm [7], and therefore all the observed capsules were trapped close to the antinode. The trapped position of the capsule and the driving sound pressure change as the input voltage to the transducer changes, and the vibration amplitude of the capsule can also change. The

Table 1. Comparison of the vibrational amplitude of microcapsules measured by the two methods.

Capsule radius [μm]	Sound pressure amplitude [kPa]	Vibrational amplitude (LDV) [nm]	Vibrational amplitude (Radiation force) [nm]
46	52	88.5	65.0
63	53	130	148
76	37	101	125

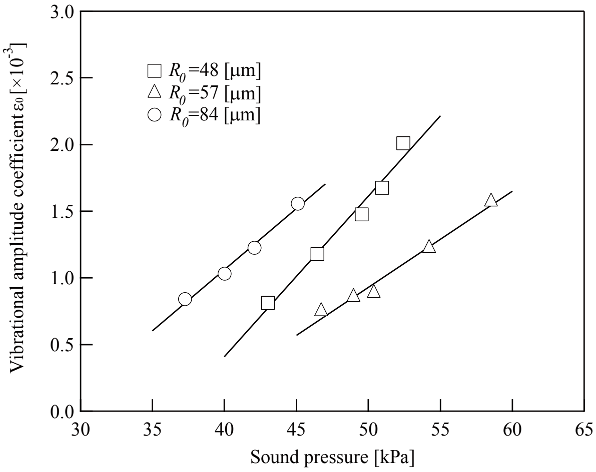

Figure 5. Relationship between driving sound pressure amplitude and vibrational displacement amplitude of capsules driven at 115 kHz.

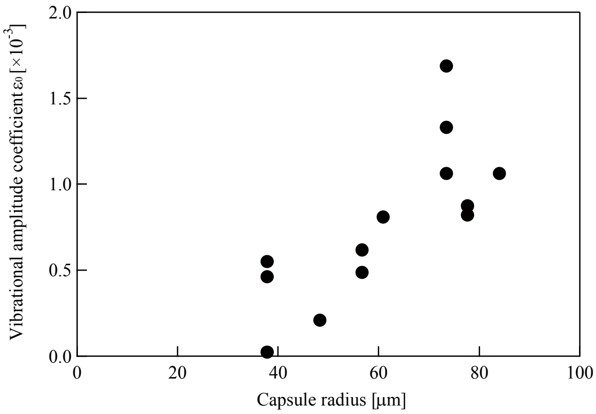

Figure 6. Relationship between initial capsule radius and expansion ratio driven with 40 kPa at 115 kHz.

nodal point as the input voltage increases because the acoustic radiation force toward the antinode increases.

The relationship between the driving sound pressure and the vibrational displacement amplitude coefficient ε_0 is shown in Fig. 5. The results for several samples with different radii are plotted. For all the measured capsules, the vibration amplitudes were proportional to the driving sound pressure, and the gradients in the graph are all different. If a larger sound pressure is applied, the capsule exhibits a circling movement and eventually collapses near the antinode [7]. Figure 6 shows the relationship between the initial capsule radius and ε_0 at 115 kHz and 40 kPa. A larger value of ε_0, which corresponds to a larger expansion ratio in the capsule vibration, was observed for larger capsules due to the fact that larger capsules are closer to the resonance condition in the standing wave. It is well-known that when the driving sound pressure is small and the bubble exhibits linear harmonic vibration, the relationship between the initial bubble radius R_0 and the normalized maximum radius by the initial radius R_{max}/R_0 shows a Λ-shape which is called the resonance curve. At the top of the resonance curve, a bubble with the resonance radius has the maximum expansion ratio [11]. In Fig. 6, therefore, we observed the left-side of the Λ-shape because only capsules smaller than the resonance size of 100 μm could be trapped around the antinode of the standing wave, while capsules larger than the resonance size will be trapped at the nodal points. However, it should be noted that the shell effects on the capsule vibration are different for each capsule because the shell thickness is different and largely depends on the capsule size.

CONCLUSIONS

A method for observing microcapsule vibration in an acoustic standing wave field was discussed. First, the vibration of microcapsules with a hard plastic shell was observed by the LDV and vibrations with a displacement amplitude of tens of nano-meters could be observed. For comparison, the vibration amplitude was estimated from the acoustic radiation force acting on capsules in the acoustic standing wave field. The measured value by the LDV was in good agreement with the estimated value. A larger vibration amplitude was observed with a larger driving sound pressure, and a larger expansion ratio was observed the closer the capsule was to the resonance condition.

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