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Development of Functional Microbubbles for Ultrasound Therapy

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SUMMARY

Microbubbles are well-known contrast agent for ultrasound diagnosis. They can be also used for the therapy. In the case of therapy, there are several ways to use microbubbles with high intensity focused ultrasound (HIFU), such as cauterizing cancers, drug delivery, gene transfection etc. For this type of applications, the microbubbles need to have some special treatment on their surface, such as surface coating or modifications with lipid molecules, ligand proteins etc.

In this study, aiming at the wide variety of the medical applications of microbubbles with ultrasound field, we are developing the methods to give many functions to microbubbles. That is, T-junction type microchannels with a special configuration are developed to generate well-controlled mono-dispersed size microbubbles with/without surface coating. The vesicles containing microbubbles are also developed and the breaking up of vesicles is achieved using ultrasound field. The current stage of the development of these functional microbubbles is presented in this talk. Furthermore, related to the above study, numerical and theoretical analysis of the shape instability of an encapsulated (membrane-coated) bubble is also presented. The analysis shows that the shape instability is more easily triggered by choosing the bubble size which has shape instability integer-multiplication to the radial bubble volume oscillation.

INTRODUCTION

Microbubbles are well-known contrast agent for ultrasound diagnosis[1], because their ultrasonic scattering property is excellent in comparison with other contrast agents. In particular, monodisperse bubbles with the diameter of less than 5 μm are required for the capability of passing through blood capillaries and for the well-defined frequency response to ultrasound.

It is also known that they are available not only for the diagnosis, but also for the therapy. In the case of therapy, there are several ways to use microbubbles with high intensity focused ultrasound (HIFU) field. For example, they can be used to enhance the heating effect for cauterizing cancers. Fig.1 corresponds to the experimental results conducted by the authors' research group. The results indicate that microbubbles enhance the heat release at the focal area of ultrasound and the temperature rise around the area is much effectively done by using microbubble contrast agents. This is because acoustic energy given by the ultrasound is effectively converted to thermal energy through the volume oscillation of micro bubbles.

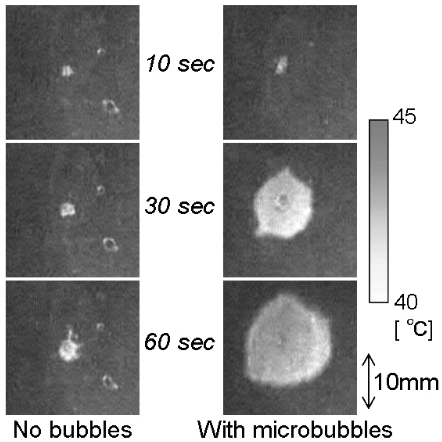


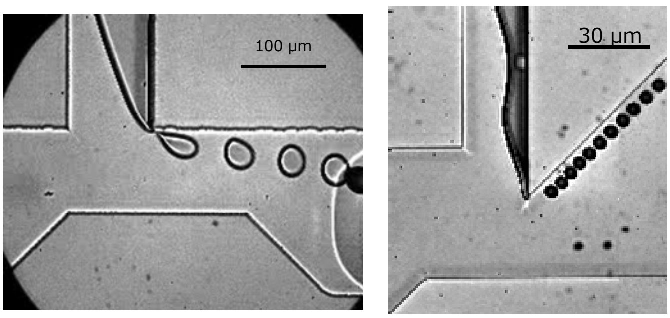
Figure 1: Heating effect by microbubbles

Micro bubbles are also expected to be used as the agents for ultrasound-guided drug delivery systems or gene transfection [2, 3]. For these applications, the microbubbles need to have some special treatment on their surface, such as surface coating or modifications with lipid molecules, ligand proteins etc. In this study, aiming at the wide variety of the medical applications of microbubbles with ultrasound field, we are developing the methods to give many functions to microbubbles. That is, T-junction type microchannels with a special configuration are developed to generate well-controlled mono-dispersed size microbubbles with/without surface coating. The vesicles containing microbubbles are also developed and the breaking up of vesicles is achieved using ultrasound field. Here, we call these types of microbubbles developed for the future medical applications, the functional microbubbles. The current stage of the development of functional microbubbles is presented in this talk. Furthermore, related to the above study, numerical and theoretical analysis of the shape instability of an encapsulated (membrane-coated) bubble is also presented. The analysis shows that the shape instability is more easily triggered by choosing the bubble size which has shape instability integer-multiplication to the radial bubble volume oscillation.

MICROBUBBLE GENERATION BY MICROCHANNEL

A novel technique to generate micrometer-order bubbles was developed using a microchannel with a squeezed T-junction. The mechanism of bubble generation was investigated with observation by the developed Ultra high-speed micron-resolution particle tracking velocimetry (UH-μPTV) method[4]. The experiments were conducted by using several kinds of channels with the different cross-section sizes to examine the effect of the cross-section size of the channels.

Two of the typical snapshots of generated microbubbles are shown in Fig.2. In the experiment shown in right figure (b), bubbles of mono-dispersed 6.1μm diameter were generated through the suitable design of channel shape for generating smaller bubbles. The experimental results show that the proposed technique enables the generation of 2 ~ 70 μm diameter bubbles at frequency of 1 ~ 10^2 kHz. The results indicate that the diameter of the generated bubble becomes smaller with increasing of the liquid velocity and with decreasing of the interfacial tension of the gas-liquid interface. The bubble diameter at the upper limit velocity shows interesting scaling characteristics with Weber number defined using an equivalent diameter of the channel and the mean velocity of the liquid phase. Furthermore, the high-speed observation indicates that the bubble generation consists of two stages; intruding stage and squeezing stage. Different kinds of flow field in front of bubble are observed for these two stages.

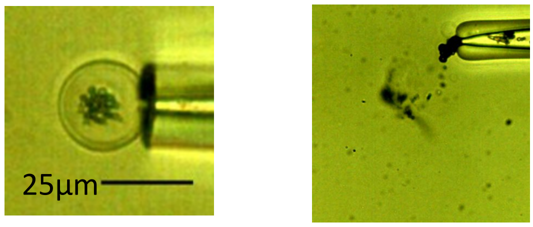


(a) Simple T-Shape (b) Orifice Type

Fig.2 Microbubble generation in T-Junction-type Microchannel

BREAKUP OF VESICLES WITH MICROBUBBLES UNDER ULTRASOUND FIELD

We are also working on the vesicle breakup using microbubbles. The vesicles containing microbubbles were developed and the breaking up of vesicles is achieved using ultrasound field. The experimental investigation reveal that the primary Bjerknes force is effectively used to break up the bubbles. Microbubbles-endohedral vesicles is shown in Fig.3(a) and the snapshot of breakup using ultrasound field is shown in Fig.3(b).



(a) Captured by micropipette (b) Breakup by Ultrasound

Fig.3 Microbubbles-endohedral vesicles

SHAPE INSTABILITY OF ENCAPSULATED MICROBUBBLES

Microbubbles for medical use have surface coating to sustain the long life time in the human body. Those surface coating is often modeled as hyper-elastic membrane and called as encapsulated bubbles. Related to the deformation of these bubbles, we conducted numerical simulations using boundary-fitted grid system[5] and the theoretical analysis using Toroidal-Poloidal field theory [6]. Both results indicated that shape instability is triggered after the resonant volume oscillation. And it is more easily triggered by choosing the bubble size which has shape instability integer-multiplication to the radial bubble volume oscillation. More detail discussion of the numerical and theoretical results is given in the talk.

CONCLUSION

In this paper, we have introduced various topics related to the functional microbubbles toward the future application in the field of ultrasound therapy. Ultrasound contrast agent itself has already many possibility of utilization. Adding more functions on bubble surfaces through the well-controlled system gives further possibility of application, especially in the drug delivery systems. The generation of sub-micron size bubbles and the measurement system of those bubbles will be an important issue for the future applications.

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