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Lifetime Control of Vaporized Nano Droplets Using Ambient Temperature Conditioning

ナノ液滴相変化時の周囲温度調節による生成気泡寿命制御

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1. Introduction

Phase change nano droplets (PCND), whose diameters are 200-400 nm, are droplets of perfluorocarbon (PFC) covered with phospholipid layers. They are promising candidate for targeted drugs, because they are small enough to permeate through the tumor vessel wall and reach the tumor site by enhanced permeability and retention (EPR) effect. They can be vaporized by ultrasound and transformed to microbubbles at the accumulated site [1]. They will be utilized as ultrasound contrast agents and ultrasound therapy sensitizers. There are several types of PCND which are often used in research, whose internal compositions are different, such as perfluoropentane (PFP: C_5F_{12}) and perfluorohexane (PFH: C_6F_{14}) [2].

The lifetimes of generated microbubbles changed from PCND are different from type to type. The short lifetimes are suitable for contrast agents, and the long lifetimes are suitable for therapy sensitizers. Therefore, if the lifetimes of generated microbubbles can be controlled in some way after the accumulation at the tumor site, they can be used for both purposes.

The purpose of this study is to investigate the physical behaviors of PCND through phase changes and to find the key to control these behaviors.

2. Materials and Methods

Experimental setup for ultrasound exposure and high-speed imaging are shown in **Fig. 1**.

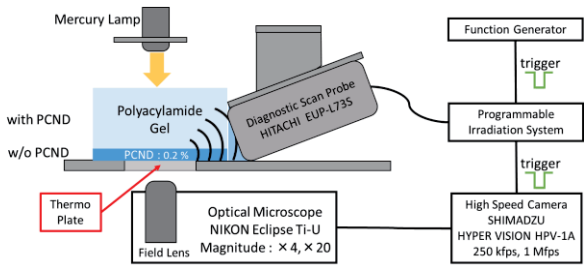

Fig. 1 Experimental setup

2.1. Preparation of PCND and gel phantom

In this study, we used the three types of PCND, whose internal compositions were PFP, PFH, and the mixture (MIX; PFP: PFH = 1:1), respectively. They were purchased from Central Research Lab., Hitachi. Their main differences are boiling points (PFP: 29 ℃, PFH: 57 ℃, MIX: 40 ℃), and the boiling point of MIX is estimated by thermodynamic calculation. For the observation of the vaporization of PCND, we used two-layer structure of polyacrylamide gel phantom (layer with PCND and layer without PCND), and set the layer with PCND at the focal point of the transducer.

2.2. Experimental setup for ultrasound exposure and high speed imaging

PCND were vaporized by ultrasound (5 MHz center frequency, 5 cycle bursts, Peak Negative Pressure = 3.5 MPa), which were irradiated with an arbitrary ultrasound beam controller (Verasonics) and a linear array transducer (EUP-L73S, Hitachi Aloka Medical). Time-lapse behaviors of PCND through phase changes were recorded with the high-speed camera (HPV-1A, SHIMADZU), coupled with inverted microscope (NIKON Eclipse Ti-U). The ambient temperature (gel phantom temperature) conditions were controlled with a hot water bath and thermo plate (TOKAI HIT) on the stage of the microscope.

3. Results

First, we observed the vaporization of the three types of PCND at 37 ℃. The high-speed images of vaporization at 37 ℃ are shown in **Fig. 2**, and the time-lapse change of vaporized area with the integrated brightness value at 37 ℃ are shown in **Fig. 3**. As to PFH (B.P.=57 ℃) and MIX (B.P.=40 ℃), generated microbubbles disappeared soon (within 10 μs) after the ultrasound exposure.

On the other hand, as to PFP (B.P.=29 ℃), generated microbubbles remained for a while (more than thirty seconds).

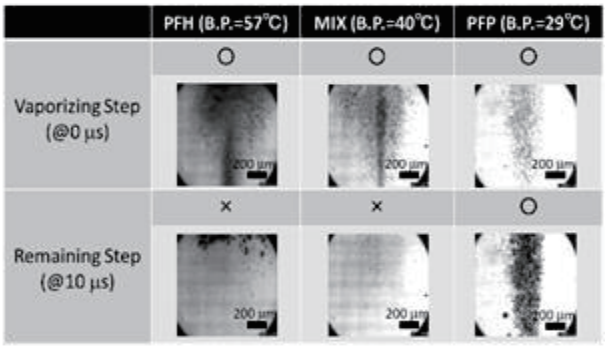

Fig. 2 High speed images of vaporization at 37 ℃

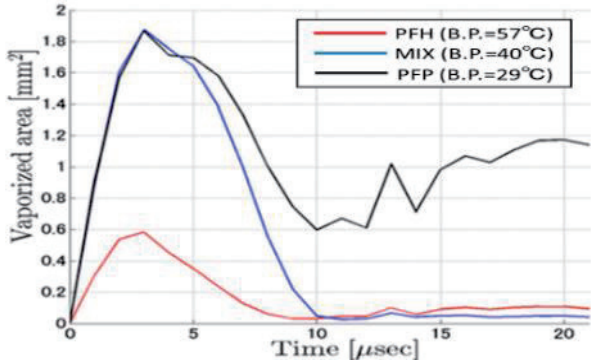

Fig. 3 Time lapsed vaporized area at 37 ℃

Phase change process can be divided into two steps: the first one is vaporizing step and the second one is remaining step. When considering the application of PCND, it is remaining step that matters. Therefore, we focused attention on the remaining step, and investigated the key factor that affects the lifetimes of generated microbubbles.

Because the main difference of these three types of PCND are the boiling point, we assumed that temperature is the key factor, and tried to control the difference between the boiling point and the ambient temperature. Then, we did some vaporization experiment at various temperatures. Some of the high-speed images of vaporization at 26 ℃, 48 ℃ are shown in **Fig. 4**.

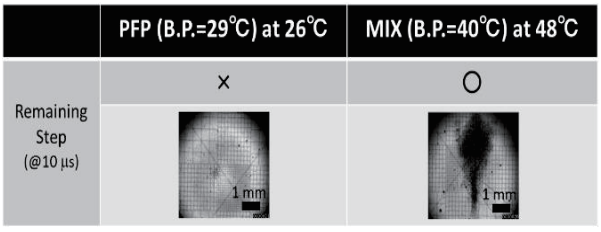

Fig. 4 High speed images of vaporization at 26, 48 ℃

As to PFP (B.P.=29 ℃), generated microbubbles disappeared soon after the sonication at 26 ℃, although they remained for some time at 37 ℃. As to MIX (B.P.=40 ℃), generated microbubbles had long lifetimes at 48 ℃, although they had very short lifetimes at 37 ℃. It can be considered that the lifetimes of generated microbubbles are greatly affected by not only the internal composition, but also the ambient temperature. Besides, behaviors after vaporization at 26~48 ℃ are shown in **Fig. 5**. Whether generated microbubbles will remain or disappear was switched around the boiling point.

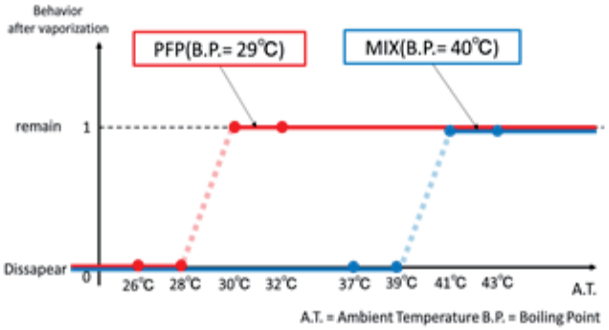

Fig. 5 Behaviors after vaporization at 26~48 ℃

4. Discussions

From these results, considering the application, even with one kind of PCND, we can control the lifetimes of microbubbles by switching the ambient temperature according to the intended use. Therefore, the combination of diagnosis and therapy will be possible with one kind of PCND. For example, generated microbubbles at lower temperature can be used as contrast agents because of their short lifetimes, on the other hand, generated microbubbles at higher temperature can be used as therapy sensitizers because of their long lifetimes. Moreover, the temperature difference between both cases was only 2, 3 ℃, so, if we prepare PCND with the boiling point around the body temperature, we can check first the accumulation of PCND at the tumor site as contrast agents at lower temperature, and, subsequently, use as therapy sensitizers at higher temperature.

Acknowledgment

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References

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2. R.Asami: Jpn. J. Appl. Phys. **49** (2010) 07HF16