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Magnetic Phase-Change Nanodroplets for Magnetic Particle Imaging and Magnetic Vaporization

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Abstract

Phase-change nanodroplets (PCNs) are high-potent theranostic agents for efficient and targeted drug delivery. PCNs can be functionalized to accumulate in tumors and vaporized by external stimuli. Ultrasound (US) is the primary method for PCN vaporization and imaging. However, it has limitations due to wave propagation effects, a relatively high vaporization pressure, and a low scattering cross section of PCNs in the liquid phase. Here, we report magnetic phase-change nanodroplets (MPCNs) suitable for magnetic particle imaging (MPI) and vaporization with magnetic heating. MPCNs can enable quantitative monitoring of accumulation in the disease site using MPI, and vaporization with targeted magnetic heating, thereby improving the clinical potential of PCNs as a theranostic agent.

I. Introduction

Gas-filled micro-/nano bubbles have been developed as vascular contrast agents as they are highly responsive to ultrasound. They have also been used for therapeutic applications such as targeted drug delivery [1] and disruption of the blood-brain-barrier [2]. Micron-sized bubbles are highly responsive to ultrasound. However, they last only for seconds in the circulatory system and cannot extravasate to tumors. In contrast, nano-sized bubbles last much longer in the bloodstream and can accumulate inside tumors. However, they are less responsive to US than micron-sized bubbles. Phase change nanodroplets (PCNs) have been formulated as a new generation of nanodroplets [3] that can be turned into micron-sized bubbles through vaporization of their liquid core in a process called Acoustic Droplet Vaporization (ADV). However, vaporization pressure threshold and wave propagation effects prevent safe and effective use of ADV.

Being free of wave propagation effects, magnetic droplet vaporization has also been proposed to promote microbubble generation [4].

In this work, we have developed magnetic PCNs (MPCNs) that can be imaged using MPI, for the first time. The developed MPCNs were vaporized by magnetic heating. Magnetic particle spectroscopy (MPS) and US imaging results suggest that the developed MPCNs can be imaged with both MPI and US.

II. Methods and Materials

Oleic acid (OA) coated magnetic nanoparticles (MNPs) were synthesized using a two-step process. First, MNPs were produced via co-precipitation method [5]. Then, the MNPs were stabilized with OA coating. Subsequently, perfluorohexane (PFH) loaded magnetoliposomes were

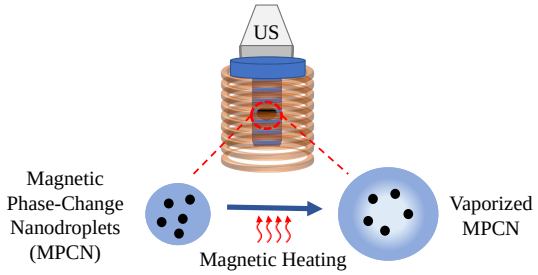

Figure 1: Schematic for the vaporization of the magnetic phase change nanodroplets (MPCN). MPCNs were vaporized by magnetic heating and imaged using ultrasound.

synthesized using the oil-in-water method [6]. The developed MPCNs consist of a PFH and OA-SPION core and a shell composed of saturated DPPC phospholipids.

MPS of MPCNs was measured using an in-house developed magnetic particle relaxometer. 20 μl MPCN solution was placed in a PCR tube, and measured with a sinusoidal field (7 mT-peak, 25 kHz). To observe the vaporization of the MPCNs, 1 ml of MPCN solution was placed in a cylindrical tube (16 mm length, 10 mm diameter). The tube was part of a 3D printed holder that was placed inside a 32 mm diameter solenoid heating coil. The holder allowed water coupling for US imaging. The magnetic field (631 kHz, 25 kA/m) was applied using a commercial hyperthermia system (nB Nanoscale, Spain), and US B-mode imaging was performed using Verasonics Vantage 256 (Verasonics Inc., USA) platform with a linear probe (IP-105). The measurement setup schematic is shown in Figure 1.

III. Results and Discussion

The MPS results of the MPCNs are shown in Figure 2 with the background signal, i.e., no particles present. It was observed that MPCNs generated harmonics up to the 15th order. Ultrasound imaging was performed while the MPCNs were magnetically heated. Figure 3 shows US images of the MPCNs taken at six different temperatures (25, 30, 35, 40, 45, and 48 °C). These images were obtained by subtracting the initial US image taken before the heating experiments. The results show that the brightness of the images increases substantially around 35 - 40° C, indicating that the vast majority of nanodroplets have been vaporized around these temperatures.

IV. Conclusion

The results obtained from the developed MPCNs demonstrate their potential use in both MPI and ultrasound imaging. Further studies will focus on improving the magnetization performance of the particles, optimizing the vaporization temperature threshold for *in vivo* applications, and MPS/MPI measurements before and after vaporization.

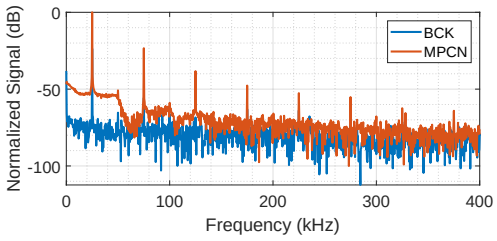

Figure 2: Normalized received signal of the developed MPCNs and background signal (BCK).

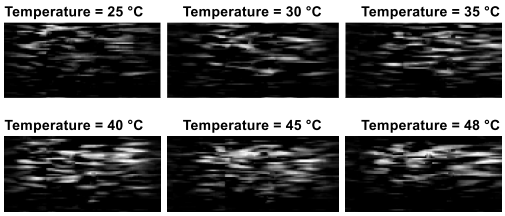

Figure 3: US images were obtained at different temperatures during magnetic heating of the MPCNs.

Author's statement

Authors state no conflict of interest.

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