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Sonic cracking at low acoustic amplitudes

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1. Introduction

Microbubbles encapsulated by thick, rigid shells were amongst the first to be considered as ultrasound contrast agents.[1)] They had been found to have limited scattering power at low acoustic amplitudes compared to microbubbles with thin, flexible shells. At higher amplitudes, though, sonic cracking had been observed. Sonic cracking is a term used for the ultrasound-assisted release of gas from rigid shell-encapsulated microbubbles.[2)] Sonic cracking has applications in noninvasive blood pressure measurements and in ultrasound-guided delivery.[3,4)]

Based on high-speed footage, it has been speculated that tiny flaws in the shell may contribute towards sonic cracking.[5,6)]

The purpose of this study was to evaluate this hypothesis by subjecting albumin-encapsulated microbubbles to simultaneous ultrasound and high-speed photography to trigger sonic cracking and collect qualitative evidence of any shell defects.

2. Materials and Methods

Quantison™ (Upperton Limited, Nottingham, UK) is a second-generation ultrasound contrast agent comprising human serum albumin-encapsulated air bubbles with, according to Coulter counter measurements published, a mean diameter of 3.2 μm and shell thicknesses between 0.2 μm and 0.3 μm.[7)]

Quantities of 5 mg of Quantison™ were stirred through 5 ml of degassed distilled water (FUJIFILM Wako Pure Chemical Corporation, Chuo-ku, Osaka, Japan). For each experiment, 200 µl of this dispersion was pipetted into a cylindrical compartment of 8-mm diameter and 2-mm height before being closed with an 18×18 mm Thickness No. 1 Micro Cover Glass (Matsunami Glass Ind.,Ltd., Kishiwada-shi, Osaka, Japan) and sealed with No.600M cloth tape (Sekisui Chemical Co., Ltd., Kita-ku, Osaka, Japan).

The compartment was part of a 244×145×76-mm^3 Perspex container that was positioned on top of an Eclipse Ti inverted microscope (Nikon Corporation, Minato-ku, Tokyo, Japan) with an S Plan Fluor ELWD 40×/0.60 objective lens (Nikon). The microscope was attached to an HPV-X2 high-speed camera (Shimadzu, Nakagyo-ku, Kyoto, Japan), operating at frame rates equal to ten million frames per second during sonication. The driving system was identical to the one previously described:[8)] a 3-cycle pulse at a 1-MHz centre frequency was generated by an AFG320 arbitrary function generator (Sony-Tektronix, Shinagawa-ku, Tokyo, Japan), amplified by a UOD-WB-1000 wide-band power amplifier (TOKIN Corporation, Shiroishi, Miyagi, Japan), and fed into a custom-built transducer.[9)] The signal amplitude of 0.5–1.0 V corresponded to a peak-negative pressure of 0.1–0.2 MPa. The acoustic pressure amplitudes used in this study were much less than the threshold for inertial cavitation to occur.[10)]

A total number of 51 high-speed videos was recorded, each consisting of 256 frames. These frames were imported into the matrix laboratory MATLAB® (The MathWorks, Inc., Natick, MA, USA) for further processing. For each particle, the

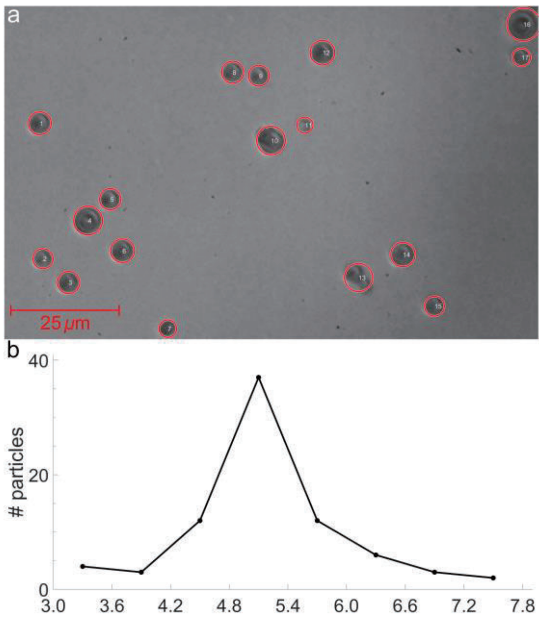

Fig. 1 Representative frame of a video with Quantison™ microbubbles indicated in red (a) and the total size distribution of Quantison™ microbubbles from all videos recorded (b).

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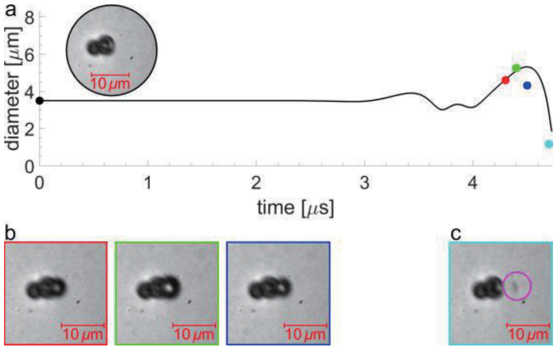

Fig. 2 Diameter as a function of time, simulated for a free gas bubble of initial diameter 3.5 μm (a) and selected video frames (b), whose timestamps are indicated in red, green, blue, cyan, and black, respectively. A cup-shaped fragment is circled in magenta (c).

visible particle surface area was measured, after which the effective diameter was computed.

In addition, radial pulsations of released gas were computed using the Rayleigh-Plesset equation for a forced damped free microbubble containing compressible gas only.[8)]

3. Results and Discussion

Fig. 1 shows a representative still frame of 17 Quantison™ ultrasound contrast agent microbubbles under a calibrated brightfield microscope and the total size distribution of the Quantison™ microbubbles observed in all experiments. The diameter were measured to vary from 2.8 μm to 7.6 μm. The median diameter was 5.2 μm and the mean was 5.2±0.9 μm. These values are greater than those published.[7)]

Fig. 2 shows selected highspeed video frames of an example of sonic cracking during sonication at a signal amplitude of 0.5 V. Both Quantison™ microbubbles appeared to be intact before sonication. During sonication, a pulsating bubble was seen inside the encapsulating shell of the right-hand-side microbubble. During the second ultrasound cycle, gas was observed to escape from the shell, with what appeared to be part of the shell. In subsequent cycles, a shape in the form of a cup was seen to pulsate.

Fig. 3 shows selected highspeed video frames of an example of sonic cracking with clearly visible gas release during sonication at a signal amplitude of 1.0 V. The Quantison™ microbubble appeared to have a flaw in the shell before sonication. The gas bubble inside the encapsulating shell was measured to have a 2.2-μm initial diameter. The simulated pulsation of a free microbubble of this initial diameter was computed to coincide with the excursion of the released gas in the highspeed video footage.

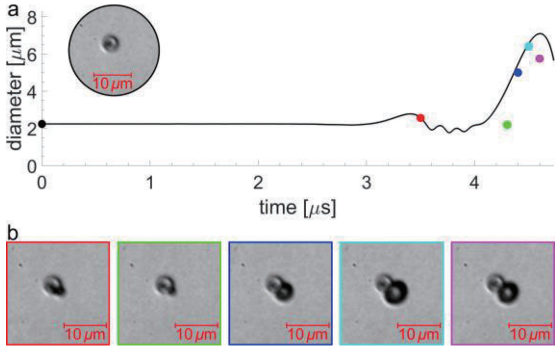

Fig. 3 Diameter as a function of time, simulated for a free gas bubble of initial diameter 2.2 μm (a) and selected video frames (b), whose timestamps are indicated in red, green, blue, cyan, magenta, and black, respectively.

4. Conclusions

Although some highspeed photography footage showed release from microbubble with apparent flaws, gas release from apparently intact bubbles was also observed. Therefore, the hypothesis that sonic cracking of ultrasound contrast agent microbubbles is associated with the pre-existence of such flaws in the microbubble shells has not been confirmed.

Acknowledgements

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