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First-cycle oscillation excursions of Pickering-stabilised microbubbles subjected to a high-amplitude ultrasound pulse

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Abstract: Pickering stabilisation is a manufacturing process involving the adsorption of colloidal particles at gas–liquid interfaces. It is used to create the shells of stable, long-lived ultrasound contrast agent microbubbles. The purpose of the present study is to determine whether high-amplitude sonication influences the integrity of Pickering-stabilised shells. To this purpose, Pickering-stabilised microbubbles were subjected to high-speed photography at 10 million frames per second during 1-MHz, 1-MPa sonication. In addition, radial excursions as a function of time were simulated using the Rayleigh-Plesset equation for free gas microbubbles and microbubbles encapsulated by Pickering-stabilised shells of 7.6-N m^{-1} stiffness. The maximum expansions observed from camera recordings were either agreeing with those computed for Pickering-stabilised microbubbles or corresponding to greater values. The results indicate that optically identical microbubbles may undergo shell disruption of different severity. We conclude that the disruption occurs during sonication and not prior to it. These findings may aid in the development of Pickering-stabilised agents that facilitate ultrasound-triggered release.

Keywords: Acoustic cavitation, ultrasound contrast agent, shell stiffness, microbubble oscillation modelling, high-speed photography.

1 Introduction

Ultrasound contrast agents comprising gas microbubbles surrounded by stabilising elastic or viscoelastic shells are commonly used in diagnosis [1, 2]. Their highly nonlinear oscillation behaviour makes them suitable aides for harmonic ultrasonic imaging [3]. The dynamics of individual ultrasound contrast agent microbubbles under sonication has traditionally been studied with high-speed photography setups [4, 5]. The manufacturing process of more stable, very long-lived microbubbles involves the adsorption of colloidal particles at the interfaces, a process which is called Pickering stabilisation [6]. This process has been extensively used to stabilise emulsions, albeit rarely in combination with acoustics [7–9]. Pickering-stabilised microbubbles and antibubbles have been observed to generate a harmonic acoustic response, even at modest transmission amplitudes [10]. Therefore, Pickering-stabilised ultrasound contrast agents may be of interest in contrast-enhanced ultrasonic imaging [10, 11]. In a previous study, we determined the shell stiffness of Pickering-stabilised microbubbles from oscillation excursion data using low-amplitude sonication [11]. The stiffness was found to be 7.6 N m^{-1} [11]. The purpose of the present study is to determine whether high-amplitude sonication influences the integrity of the Pickering-stabilised shell.

2 Materials and methods

Pickering-stabilised microbubbles were produced with Aerosil® R972 hydrophobised silica particles (Evonik Industries AG, Essen, Germany) as a stabilising agent, identical to the procedure in our previous studies [10, 11]. A 0.2-ml volume of microbubble suspension was pipetted into the observation chamber of a high-speed observation system, which was placed under an Eclipse Ti inverted microscope (Nikon Corporation, Minato-ku, Tokyo, Japan) with a Plan Apo LWD 40× WI (N.A. 0.8) objective lens. The microscope was coupled to an HPV-X2 high-speed camera (Shimadzu, Nakagyo-ku, Kyoto, Japan), operating at a recording speed of 10 million

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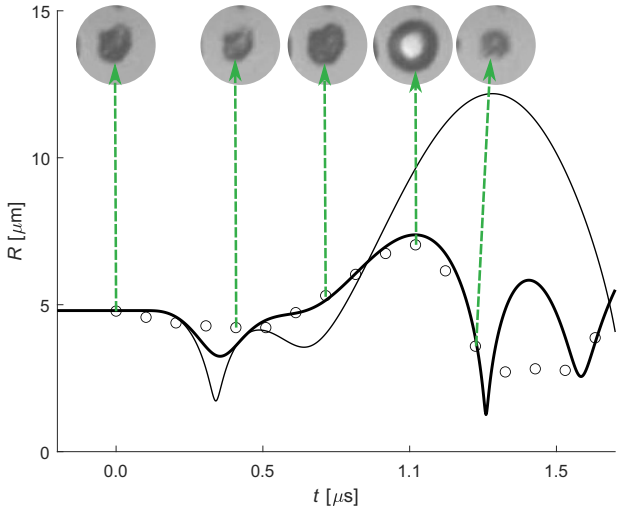

Fig. 1: Radius measured as a function of time for a Pickering-stabilised microbubble (○), simulated $R(t)$ curves of a free (—) and a shell-stabilised (—) microbubble of R_0=4.8 μm, and inlays extracted from high-speed video footage. Each inlay corresponds to a 22-μm diameter.

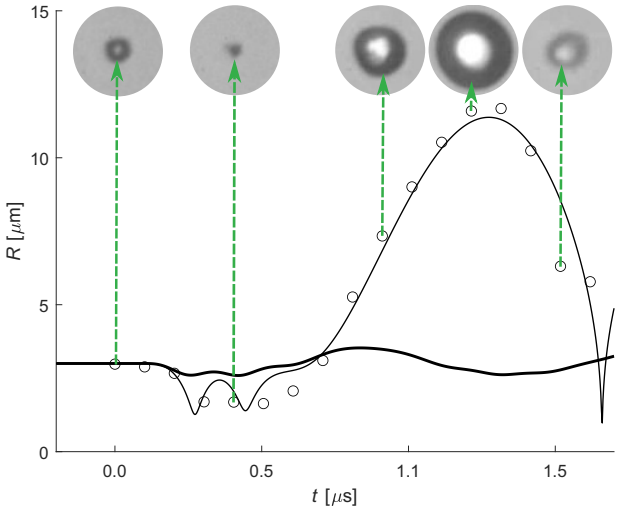

Fig. 2: Radius measured as a function of time for a Pickering-stabilised microbubble (○), simulated $R(t)$ curves of a free (—) and a shell-stabilised (—) microbubble of R_0=3.0 μm, and inlays extracted from high-speed video footage. Each inlay corresponds to a 22-μm diameter.

frames per second with exposure times of 100 ns per frame. High-speed videos were recorded during sonication. A burst comprised a 3-cycle sine pulse with a centre frequency of 1 MHz and a peak-negative pressure of 1.0 MPa, which corresponds to a high mechanical index of 1.0. The frames were clipped, segmented, and analysed using MATLAB® (The MathWorks, Inc., Natick, MA, USA). A total number of one hundred different microbubbles was included in this study. In addition, radius as a function of time, $R(t)$, curves were computed from the Rayleigh-Plesset equation [12], using the ode45 differential equation solver of MATLAB®, for free gas microbubbles and for microbubbles encapsulated by shells with a 7.6-N m^{-1} stiffness [11]. The latter can be explained if shell disruption took place during the first oscillation cycle.

3 Results and discussion

Figure 1 shows the radial dynamics during the first oscillation cycle of a Pickering-stabilised microbubble of 4.8-μm initial radius. The measured data correspond to the first cycle of the simulated $R(t)$ curve of a microbubble with shell stiffness of 7.6 N m^{-1} and clearly do not correspond to the much greater expansion of a free microbubble. The microbubble did not appear to have undergone disruption during its first expansion. Figure 2 shows the radial dynamics during the first oscillation cycle of a Pickering-stabilised microbubble of 3.0-μm initial radius. The measured data correspond to the first cycle of the simulated $R(t)$ curve of a free microbubble and clearly do not correspond to the almost negligible expansion of a microbubble with shell stiffness 7.6 N m^{-1}. The microbubble whose dynamics are shown in Figure 2 did not appear to have undergone gas release. From this observation, we deduct, that stabilising particles must have been present on the interface during expansion. From the large expansion, however, we conclude that, if indeed stabilising particles were present on the interface, these did not form a uniform stabilising shell.

Figure 3 shows an overview of measured first-cycle oscillation amplitudes, $R_{\max}$, as a function of initial radius, R_0. Some 40% of the microbubbles had expanded to excursions computed for microbubbles with a shell stiffness of 7.6 N m^{-1}. The remaining microbubbles had expanded to greater excursions, with only three microbubbles reaching free-gas bubble excursions. Microbubbles of the same initial radius were observed to expand to different maxima. This could indicate that optically identical microbubbles may have different shell properties. However, that would also mean that maximum excursions at lower acoustic amplitudes should be different for optically identical bubbles, which they are not [11]. A different explanation for the observed excursion amplitudes is that optically identical microbubbles may undergo shell disruption of different severity. Although disruption prior to sonication might be possible, we rule it out for an explanation based on the consistency of excursion observations at low acoustic amplitudes [11]. In the absence of other mechanisms observed, we hold the explanation that the disruption occurs during first expansion for most plausible.

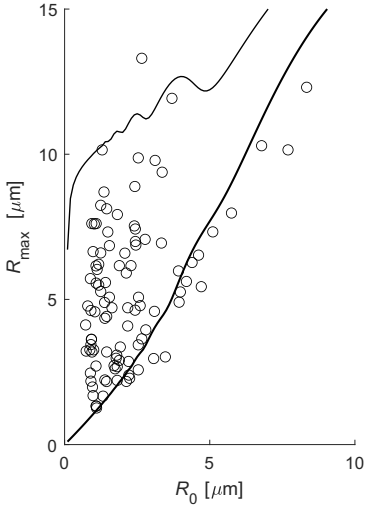

Fig. 3: Scatter plot of maximum microbubble expansion measured as a function of initial radius (○), overlain with simulated $R_{max}(R_0)$ curves of free (—) and Pickering-stabilised (—) microbubbles.

4 Conclusions

In summary, the maximum radial expansions observed were either agreeing with the maxima predicted by the model of Pickering-stabilised microbubbles or corresponding to greater values. These observations support the hypothesis that the rigidity of Pickering-stabilised shells is affected by sonication. Nevertheless, gas release from these disrupted microbubbles was not observed, indicating that the particle structuring remained on the interface during radial oscillation. The results indicate that optically identical microbubbles may undergo shell disruption of different severity. We conclude that the disruption occurs during sonication and not prior to it.

These findings may aid in the development of Pickering-stabilised agents that facilitate ultrasound-triggered release.

Author statement

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