Nonlinear dynamics of polymer shell ultrasound contrast agents at 8-32 MHz ultrasonic excitations

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Abstract—The response of polymer shell ultrasound contrast agents (PSUCAs) at frequencies < 5 MHz has been shown to be associated with shell rupture and the formation of free gas bubbles. Recently, it was shown that PSUCAs produce significant subharmonic (SH) response at higher frequencies (20-40 MHz) which is not consistent with the formation of free bubbles. Despite the high control over the manufacture of PSUCAs, there is limited knowledge on the response of PSUCAs to ultrasonic excitation, especially at higher excitation frequencies. In this work, the dynamics of individual PSUCAs in response to 30 cycle 8-32 MHz excitations with pressure amplitudes ranging ~70 kPa - 2.5MPa was studied by experimental observations using a Vevo 770 ultrasonics imaging instrument. In each case a very dilute solution of PSUCAs were used to minimize the interaction between the PSUCAs. The RF signal of the individual UCA oscillations were extracted and analyzed. The results of this study show that PSUCAs can undergo stable linear and nonlinear oscillations with substantial amplitude. 2nd and 3rd order super harmonic (SUH) oscillations excitations and 1/2, 1/3, 1/4 and 1/5 order SHs were detected for the investigated frequencies. Compression only behaviors were also detected mainly resulting in linear oscillations. The generation of the compression only behavior and SH oscillations in thick shell PSUCAs may only be explainable by the Marmottant model. Results of this study show the feasibility of the substantial nonlinear oscillations in the oscillations of the PSUCAs. Further investigations are needed to be carried out to fully realize the potential of the application of PSUCAs within the field of medical ultrasound.

Keywords—Polymer Shell Ultrasound Contrast Agents; Nonlinear Oscillations; Buckling; Rupture;

I. INTRODUCTION

Optimization of imaging and therapeutic applications of ultrasound contrast agents (UCAs) in medical ultrasound strongly depends on a solid understanding of their acoustic behaviour. UCA dynamics depend on ultrasound exposure parameters such as the acoustic pressure and pulse frequency, and the UCA characteristics such as the UCA shell composition and UCA size. The characterization of UCAs non-linear dynamics may potentially allow improvements in ultrasound imaging and therapeutic applications [1]. In this regard several studies have investigated the dynamics of lipid shell contrast agents [2,3].

Polymer shell UCAs (PSUCAs) can also be employed as UCAs both in diagnostic and therapeutic ultrasound. The manufacture of PSUCAs allows maximum control of the diameter and shell thickness [4,5]. The response of PSUCAs at frequencies < 5 MHz has been shown to be associated with shell rupture and escape of free gas bubbles [6,7]. However, recently, it was shown that PSUCAs produce significant subharmonic (SH) response at higher frequencies (20-40 MHz) which is not consistent with the formation of free bubbles [5,8].

Despite being able to control polymer contrast agent physical parameters (e.g. shell thickness to radius ratio), there is limited knowledge on the response of PSUCAs to ultrasonic excitation, especially at higher excitation frequencies.

Better understanding the behavior of PSUCAs can help optimize their application in contrast enhanced ultrasound and drug delivery. In this study the behaviors of individual thick shell PSUCAs (~100nm) are studied over a large range of acoustic pressure (0.07-2.5 MPa) and insonation frequency (8-32 MHz). This investigation was guided by the classification of the nonlinear dynamics and bifurcation structure of the UCA oscillation [1,9,10].

II. METHODS

A. UCA preparation

The method of preparation is similar to the one discussed in [6]. The two immiscible liquids, perfluorohexane (PFH) and Polymethylsilsequioxane (PMSQ) solution, were subject to coaxial electrohydrodynamic atomization at flow rates of 650 μl/min and 150 μl/min, respectively. Once a stable jet was formed at an applied electrical potential difference of 4.8 kV, droplets of PFH surrounded by PMSQ were generated by jet breakup and then neutralized by a grounded electrode [3].

The relevant physical properties of the liquids used in the experimental work are given in table 1. The resulting polymer spheres were stable and sedimented in water due to their relatively high density. In this work, the measured size distribution of the PSUCAs had a peak at ~1 μm and a shell thickness of ~100 nm. The shell elasticity is approximately 100 MPa. The estimation of the shell properties is based on bulk polymer properties under quasi static testing.
Table 1: Relevant physical properties of the liquids used in the experimental work.

<table>
<thead>
<tr>
<th>Material</th>
<th>Density kg/m³</th>
<th>Viscosity mPa s</th>
<th>Surface tension mN/m</th>
<th>Electrical conductivity Sm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluorohexane</td>
<td>1710</td>
<td>1.1</td>
<td>12</td>
<td>&lt; 1 × 10⁻¹²</td>
</tr>
<tr>
<td>PMSQ 18 wt%</td>
<td>805</td>
<td>1.8</td>
<td>23</td>
<td>9 × 10⁻⁵</td>
</tr>
</tbody>
</table>

B. Acoustical measurements of single UCA backscatter

Dilute solutions of PSUCAs were sonicated at 8-32 MHz with 30 cycle train pulses with pressures which were varied over a range of ~0.1-2.5 MPa using a Vevo 770 ultrasound imaging system (Visualsonics Inc. Toronto, Ontario). The signals of single PSUCAs oscillations were extracted and their nonlinear behavior were investigated in a method similar to [11]. Figure 1, shows the process of extracting the signal from a single UCA oscillations.

Figure 1: The process of extracting the signal from single UCA oscillations. Left, the B-Mode image of the dilute solution of the UCA where the selected RF line belongs to a single scattering event. Right, the detected signal in red and the corresponding frequency spectrum in blue.

III. RESULTS

Figure 2a shows a sample of compression only signals from single PSUCAs at 8 MHz and acoustic pressure of ~2 MPa. The backscattered signal compresses more than it expands which is the characteristic of shell buckling. The frequency spectrum is shown in fig. 3a.

Figure 2b shows a period 4 (P4) backscattered signal from a single PSUCA at 8 MHz and ~2 MPa of pressure. The frequency spectrum in fig. 3b has sub harmonic (SH) frequencies at 2, 4 and 6 MHz and ultraharmonic (UH) frequencies at 10, 12 and 14 MHz.

Figure 2c illustrates the case of 2nd order superharmonic oscillations of a single PSUCA at 16 MHz and acoustic pressure of ~2 MPa. The signal has 2 maxima and 60 peaks for the 30 cycle acoustic driving force. The superharmonic oscillation is characterized by a very strong 2nd harmonic component at 32 MHz in fig. 3c.

Figure 2d shows the SH backscattered signal from a single PSUCA at 16 MHz and acoustic pressure of ~2 MPa. The frequency spectrum in fig. 3d has a SH component at 8 MHz and an UH component at 24 MHz.

Figure 2e shows the P3 oscillations of a single PSUCA at 16 MHz and acoustic pressure of ~2 MPa. The RF signal has 3 distinct maxima. The frequency spectrum in fig. 3e has 2 SH components at 5.33 and 10.66 MHz.

Figure 2f shows a P5 oscillations of a single PSUCA at 18 MHz and acoustic pressure of ~2 MPa. The backscattered signal has

Figure 2: The RF signal of single PSUCA backscatter at ~2 MPa of acoustic pressure when the sononation frequency is: (a) 8 MHz (compression only), (b) 8 MHz (P4 oscillations), (c) 16 MHz (2nd order superharmonic oscillations), (d) 16 MHz (1/2 order SH oscillations), (e) 16 MHz (P3 oscillations), (f) 18 MHz (P5 oscillations, (g) 24 MHz (1/2 order SH oscillations), and (h) 24 MHz (P3 oscillations)
5 distinct maxima. The corresponding frequency spectrum in fig. 3f has 4 SH components at 3.6, 7.2, 10.8, 14.4 MHz and UH components at 21.6, 25.2, 28.8 and 32.4 MHz.

Figure 2g shows the SH backscattered signal at 24 MHz and acoustic pressure of ~2MPa. The corresponding frequency spectrum in fig. 3g has a SH component at 12 and an UH component at 32 MHz.

Figure 2h shows a P3 backscattered signal from a single PSUC at 24 MHz and ~2 MPa of acoustic pressure. The signal has 3 distinct maxima and the corresponding frequency spectrum in fig. 3h has 2 SH components at 8 and 16 MHz.

IV. DISCUSSION

The acoustical behavior of thick shell PSUCAs was investigated over a range of (8-32 MHz) sonication frequencies and driving acoustic pressures (-0.07-2.5 MPa). The average size and shell thickness of the PCUCAs were 1 μm and 100nm respectively. It was shown that the PCUCAs exhibit considerable SH activity when sonicated with frequencies over the range of 8-32 MHz and acoustic pressures of >-1.5 MPa. We have observed ½ order SH activity for all the insonation frequency range. Recent experimental investigations on the behavior of PSUCAs at 40 and 20 MHz [6,7] have shown that PSUCAs can exhibit SH oscillations at acoustic pressures >1 MPa.

It was also seen that PCUCAs can undergo compression dominated behavior which is the signature of the shell buckling. This is in line with recent experimental observations by Chitnis et al [6] at high frequencies. The compression dominated behavior can be explained by Marmottant model for solid shell bubbles [11] undergoing buckling. The compression dominated behavior has also been observed in high speed optical investigation of PSUCAs at 1.7 MHz [7]. In their study, the PSUC was fragmented after a few cycles of compression dominated behavior.

It was shown for the first time that in addition to conventional SH oscillations of ½ order, PCUCAs can also undergo higher order SH oscillations of 1/3, 1/4 and 1/5 order. These results contradict the predictions by viscoelastic models (e.g. Hoff model) which require very high acoustic pressures for the generation of higher order SHs in case of microbubbles with solid and thick shells. The nonlinear surface tension in the Marmottant model for solid shell bubbles [11] which takes in to account the phenomena of buckling and rupture can be used to explain the experimental observations. Another explanation for the enhancement in the generation of SHs in this study is due to imperfections in the thick shell. As discussed in [12], the integrity of the shell is weakened by the imperfections in the shell and this reduces the effective shell thickness. This phenomenon is used to explain the generation of SHs in thick shell PSUCAs in [6].

V. CONCLUSION

It was experimentally observed that solid thick shell polymer UCAs can exhibit substantial nonlinear oscillations and SH behavior at high frequencies and acoustic pressures. The results were based on limited experimental observation of a one type of PSUCA. Further investigations are needed to be carried out to fully realize the potential of the application of PSUCAs within the field of medical ultrasound.

REFERENCES


