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● *Technical Note*

INTERFACIAL RHEOLOGICAL PROPERTIES OF CONTRAST MICROBUBBLE TARGESTAR P AS A FUNCTION OF AMBIENT PRESSURE

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Abstract—In this Technical Note, we determine the interfacial rheological parameters of the encapsulation of the contrast agent Targestar P using ultrasound attenuation. The characteristic parameters are obtained according to two interfacial rheological models. The properties—surface dilatational elasticity (0.09 ± 0.01 N/m) and surface dilatational viscosity (8 ± 0.1*E*–9 N·s/m)—are found to be of similar magnitude for both models. Contrast microbubbles experience different ambient pressure in different organs. We also measure these parameters as functions of ambient pressure using attenuation measured at different overpressures (0, 100 and 200 mm Hg). For each value of ambient hydrostatic pressure, we determine the rheological properties, accounting for changes in the size distribution caused by the pressure change. We discuss different models of size distribution change under overpressure: pure adiabatic compression or gas exchange with surrounding medium. The dilatational surface elasticity and viscosity are found to increase with increasing ambient pressure. (E-mail: sarkar@gwu.edu) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Contrast agents, Interfacial rheology, Encapsulation, Shell, Pressure estimation, Bubble dynamics, Attenuation, Gas diffusion.**

INTRODUCTION

Use of lipid-, protein- or polymer-coated microbubbles, such as Optison (GE Healthcare, Oslo, Norway), Sonazoid (GE Healthcare), Definity (Lantheus Imaging, North Billerica, MA, USA), Sonovue (Bracco, Milan, Italy), Targestar (Targeson, San Diego, CA, USA), has led to significant enhancement of the quality of ultrasound imaging (Goldberg et al. 2001; Nahire et al. 2013; 2014; Paul et al. 2014). All these microbubbles differ in size and coating and require careful characterization. Unlike Targestar, the others mentioned have been approved for clinical use in the United States or Europe and have been characterized using controlled *in vitro* acoustic experiments determining the mechanical properties of the coating, for example, Definity (Goertz et al. 2007), Optison (Chatterjee and Sarkar 2003), Sonazoid (Hoff 2001; Paul et al. 2010; Sarkar et al. 2005) and Sonovue (Gorce et al. 2000). In contrast, Targestar has not been similarly characterized. Here, we measure the mechanical properties of Targestar contrast agent under different ambient hydrostatic pressures using *in vitro* broadband attenuation.

Targestar microbubbles have a perfluorobutane (PFB) gas core encapsulated by a layer of phospholipids (Shekhar et al. 2014) and have been investigated for applications in high frequency subharmonic imaging (Shekhar and Doyley 2011; 2012; 2013; Shekhar et al. 2013) and molecular imaging (Knowles et al. 2012; Saini et al. 2011; Wang et al. 2012; Warram et al. 2011). Targestar SA, Targestar P, Targestar HF and Visistar are a few available variants of this microbubble, each having different applications such as perfusion, labeling and targeting. Here, we describe our investigation of Targestar P agent, a non-targeted perfusion contrast agent designed to enhance and quantify blood flow.

Contrast agents experience widely different pressures in different organs: 5–10 mm Hg in portal vein (D'amico et al. 1995), 8–20 mm Hg in pulmonary artery (Simonneau et al. 2009) and 100–140 mm Hg in left ventricle (systolic) (Lawes et al. 2004). This motivates us to measure the properties of Targestar P under different ambient pressures in the range 0–200 mm Hg. Previously, Hoff (2001) investigated the stability of encapsulated microbubbles under enhanced ambient pressure through attenuation measurement. Recently, we performed a

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detailed characterization of Definity microbubbles, determining pressure-dependent shell properties using attenuation measured at different pressures (Kumar and Sarkar 2015). In this note, a similar procedure is followed for Targestar.

We used ultrasound attenuation through a suspension of contrast agent Targestar under different ambient pressures to determine the interfacial rheological properties of the encapsulation using two different models: the strain-softening exponential elasticity model (EEM) (Paul et al. 2010) and the Marmottant model (Marmottant et al. 2005).

METHODS

Contrast agent

Targestar P agent was procured from Targeson, delivered in suspension form in glass vials with a perfluorobutane headspace. The agent was stored at 4°C in accordance with the product specification. Before use, the vial was shaken very gently two or three times to mix the contents, and then 10 μL was extracted from the vial using a syringe and mixed in 100 mL of standard phosphate-buffered saline (PBS) solution. The resulting dispersion has 2.54×10^5/mL bubbles (according to the information supplied by the vendor).

Estimation of encapsulation parameters using attenuation

In our earlier publications (Chatterjee and Sarkar 2003; Kumar and Sarkar 2015; Paul et al. 2010; 2013; Sarkar et al. 2005), we described in detail the procedure for determining the encapsulation properties of an encapsulation based on different models using attenuation data. Here, attenuation was measured in an airtight setup that can control the ambient pressure with an accuracy of 0.07 kPa (Fig. 1a, b) using an unfocused broadband transducer (Olympus NDT, Waltham, MA, USA) with a central frequency of 3.5 MHz (6-dB bandwidth: 2.5–4.99 MHz). It was excited by a pulser/receiver (Model 5800, Panametrics-NDT, Waltham, MA, USA) to produce a broadband pulse with a pulse repetition frequency of 100 Hz with a peak amplitude of 35 kPa at 3.5 MHz, low enough so that the acoustic propagation through the microbubble suspension remains linear (Chatterjee et al. 2005a; 2005b). The pulse traveled a total distance of 10 cm through the contrast agent suspension before being received and fed to the digital oscilloscope (Model TDS 2012; Tektronix, Beaverton, OR, USA) to observe the signal in real time. A pressure gauge (SSI Technologies, Janesville, WI, USA) was used to measure the static pressure of the chamber. Signals were acquired from the oscilloscope using LabView (National Instruments, Austin, TX, USA) software. Fifty voltage–time radiofrequency traces were acquired in an averaging mode (64 sequences are used for averaging) and saved. They were transformed to frequency domain and averaged for 50 acquisitions. The frequency-dependent attenuation coefficient was calculated using the expression

$$\alpha(\omega) = 20 \log\left(\frac{\overline{V}_{\mathrm{ref}}(\omega)}{\overline{V}_{\mathrm{sig}}(\omega)}\right)\Big/ d, \tag{1}$$

where $\overline{V}_{\mathrm{ref}}(\omega)$ is the averaged response in the frequency domain without any contrast agent in the medium, $\overline{V}_{\mathrm{sig}}(\omega)$ is the averaged response in the frequency domain microbubbles suspended in the medium and $d = 10$ cm is the total path traveled by the pulse before it is being received by the transducer. Theoretically an expression for attenuation is obtained using a linearized version of the modified Rayleigh–Plesset equation with an effective surface tension $\gamma(R)$ and interfacial dilatational viscosity $\kappa^s(R)$ (Paul et al. 2010) for bubble radius $R(t)$:

$$\rho\left(R\ddot{R}+\frac{3}{2}\dot{R}^2\right) = P_g\left(1-3\kappa\frac{\dot{R}}{c}\right)-4\mu\frac{\dot{R}}{R}-\frac{4\kappa_s(R)\dot{R}}{R^2}-\frac{2\gamma(R)}{R} -P_0+P_A\sin\omega t. \tag{2}$$

here, ρ is the density of the liquid; P_g is the gas pressure inside the bubble, which expands with a polytropic coefficient κ; c is the speed of sound in the liquid, μ is its viscosity; and P_0 is the ambient pressure. Since with oscillations at megahertz frequency Peclet number $\mathrm{Pe} = R_0^2\omega/D_g \sim 1$ (D_g is the thermal diffusivity; for C_4F_{10} 2.57×10^{-6} m^2/s), we assume an adiabatic behavior for the gas inside ($\kappa=\kappa_{\mathrm{ad}}=1.07$ for C_4F_{10}). The bubble is responding to an ultrasound wave with amplitude P_A and circular frequency ω. The EEM uses

$$\gamma(R) = \gamma_0+E^s\beta,\ \ \beta=(R/R_E)^2-1,\ \ E^s=E_0^s\exp(-\alpha^s\beta),\ \text{and}\ \ \kappa^s(R)=\kappa^s\ \ (\text{constant}), \tag{3}$$

characterizing the encapsulation with a reference surface tension γ_0, reference dilatational elasticity E_0^s and coefficient α^s. R_E is the stress-free radius. The Marmottant model uses

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