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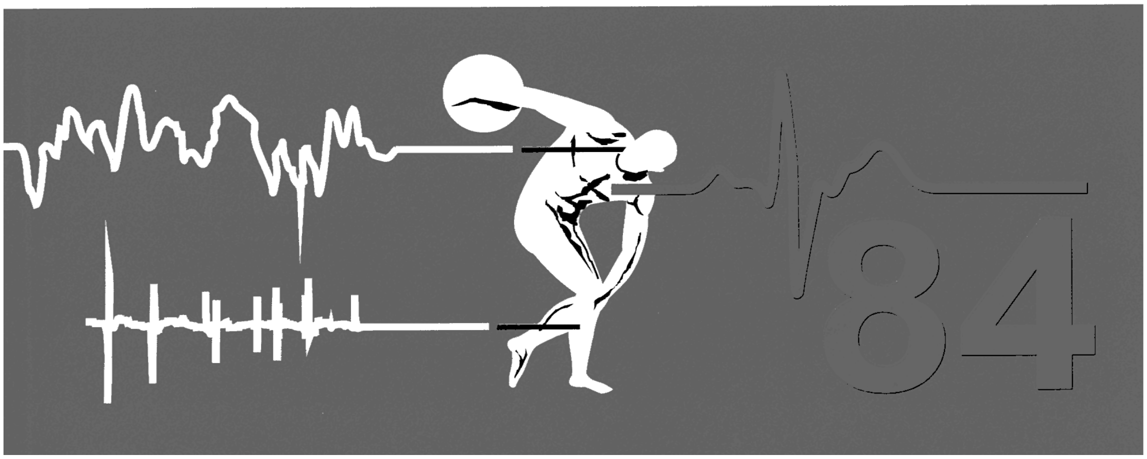

CONTROLLED ULTRASONIC DESTRUCTION OF THE POLYCAPROLACTONE SHELL MICROCAPSULES BASED ON RESONANCE SCATTERING THEORY

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Abstract

The use of the ultrasonically destructible microcapsules as local drug delivery systems continues to grow. Microbubble destruction requires correct ultrasonic frequency equal to its resonance. This frequency depends on the bubble size and polymer shell stiffness. Measurements of the ultrasonic signal, backscattered from microspheres gives practical information of the bubble resonance and nonlinearity. In experiment, the backscattered power spectrum of measured sample was recorded by an ultrasonic scanner. Radio frequency (RF) data was recorded at 2.0 – 6.6 MHz. The mean particle diameter in the measured sample was 21 μm. The resonance frequency, measured under the microscope, was 0.60 MHz for 43 μm diameter microsphere. The sample volume was 10cm^3 and the mean quantity of scatterers was $6{\cdot}10^3/\text{cm}^3$. The simulated power spectrum of the ultrasonic backscattered signal was calculated from the resonance scattering theory for the gas bubbles surrounded by elastic shell. In conclusion, the measured spectra matched those calculated from the theory. The use of the ultrasonic scanner with RF data output and the high sensitivity, wide bandwidth ultrasonic transducer allows to measure the backscattered signal from the very small quantity of resonance scatterers with satisfactory results at 40 dB signal to noise ratio.

1. Introduction

Gas filled lipid, protein or polymer microbubbles are used either as ultrasonic contrast agents [1] or controlled drug delivery microcapsules [2]. Nonlinear behaviour at resonance frequency and high backscattering cross section predisposes the microspheres to use as contrast particles for ultrasonic medical diagnostics. Combined with harmonic imaging, the microbubbles are used for the blood flow studies and tissue perfusion imaging. In other applications, the microcapsules are filled with drug. High-pressure ultrasonic wave is used for the polymer shell destruction and the controlled drug delivery into the tissue or blood. This technique allows healing the restricted space area like a tumour. The size of the spheres varies between 2 - 6 μm for the contrast agent particles and between 1 – 50 μm for the drug delivery microcapsules. The microbubble destruction requires a correct ultrasonic frequency equal to its resonance. This frequency depends on the bubble size and the polymer shell stiffness. Measurements of the ultrasonic signal, backscattered from the microspheres gives practical information of the bubble resonance and nonlinearity [3]. To obtain sufficient signal to noise ratio and wide bandwidth, either multiple transducers were used [4] or attenuation only was measured [5]. Authors propose a new technique of backscattered signal measurements, based on a commercial wide bandwidth ultrasonic transducer and RF data recording.

2. Theory

The ultrasonic properties of the gas filled microspheres were derived from the resonance scattering theory. Total scattering cross section of a single bubble can be expressed as follows [6]:

$$\sigma_s = \frac{4\pi R^2}{\left(\frac{f_r^2}{f^2} - 1\right)^2 + \delta^2} \tag{1}$$

where R = bubble radius, f_r = bubble resonance frequency, f = frequency of the incident ultrasonic wave, δ = total damping constant caused by the surrounding liquid medium. When a gas bubble is surrounded by a shell, the shell causes an additional restoring force. The resonance frequency is [1]:

$$f_{rs} = \sqrt{f_r^2 + \frac{S_{shell}}{4\pi^2 m}} \tag{2}$$

where f_{rs} = resonance frequency of the gas filled microcapsules with shell, f_r = resonance frequency of a gas bubble without a shell, S_{shell} = stiffness of the shell, m = effective mass of the system. If the shell mass $m_{shell} \gg m_{gas}$ and h_{shell} = shell thickness has the constant value, then equation (2) can be modified [7]:

$$f_{rs} = \frac{1}{2\pi R} \cdot A \tag{3}$$

where A = constant value.

3. Materials and methods

Sample of air filled microspheres with the polycaprolactone shell was used in the experiment. The diameter of the bubble was 21 μm mean ± 12 μm standard deviation.

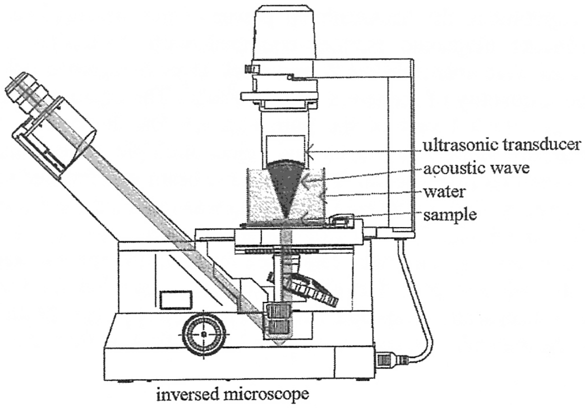

Fig.1. Microscope setup for the measurement of the microbubble resonance frequency

The resonance frequency was measured using Nikon Eclipse 100 inverted microscope with Nikon LU Plan 10x/0.30 lens. The sample was illuminated by Schott KL 200 light source with goose neck fiber light guide. The microcapsules were suspended in 1 mm thick layer of agarose gel. The sample was sonified by a custom made 50 mm diameter ultrasonic transducer focused at 75 mm. The -3 dB frequency range was 0.4 – 0.9 MHz, measured by hydrophone. The transducer was excited by 20 period sine burst generated by Ritec RAM 10000 power generator. The maximum negative pressure was $P_- = 3$ MPa. The acoustical pressure was sufficient for destructing the microbubble at its resonance frequency. Diagram of the microscope setup is presented on Fig.1, and the microscope image of the destructed microcapsule is presented on Fig.2. The experiment was repeated to measure resonance frequency of the different size microbubbles.

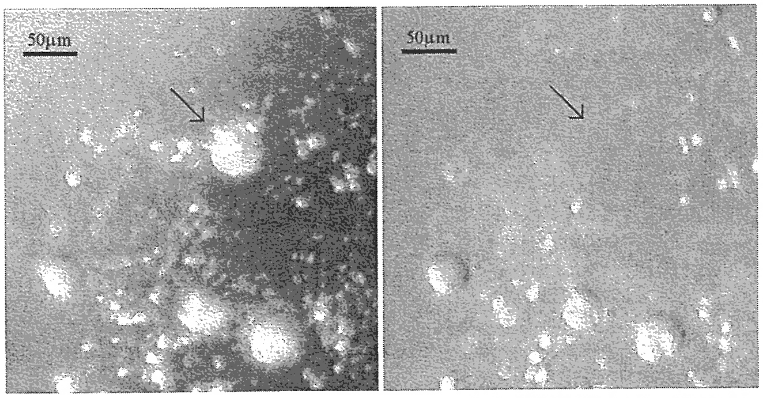

Fig.2. Microscope image of 43 µm microbubble with resonance frequency fr = 0.60 MHz (left). Microbubble disappeared after the destruction caused by ultrasonic wave (right)

In the second experiment, the backscattered power of the measured sample was recorded by Siemens Antares ultrasonic scanner equipped with 2 – 6 MHz convex transducer. The microcapsules were suspended in 5 mm thick layer of agarose gel with 10 cm^3 total volume. The mean quantity of scatterers was $6 \cdot 10^3/cm^3$. The agarose sample was positioned between two 2 cm thick layers of the pure agarose. On the bottom there was a layer of silicone to absorb ultrasonic waves and reject multiple reflections in the phantom. The sample was sonified from the top. The ultrasonic beam was focused at 4 cm, at the layer with the microcapsules. Radio frequency (RF) data was recorded for 5 transmitted ultrasonic frequencies 2.0 – 6.6 MHz. 300 lines of RF signal were recorded at 40 MHz sampling frequency. The frequency spectra were calculated for each line and averaged. As a reference, ultrasonic signals reflected from the plastic ball were recorded for the same transmitter frequencies. The backscatterd spectra were calculated by the Matlab® software and subtracted from the transmitter spectrum, recorded as a reflection from the perfect reflector.

4. Results

The resonance frequency of a polymer coated gas bubble from the measured sample and calculated from the equation (3) is:

$$f_{rs} = \frac{25.8}{R} \tag{4}$$

where f_{rs} = resonance frequency in MHz and R = bubble radius in μm.

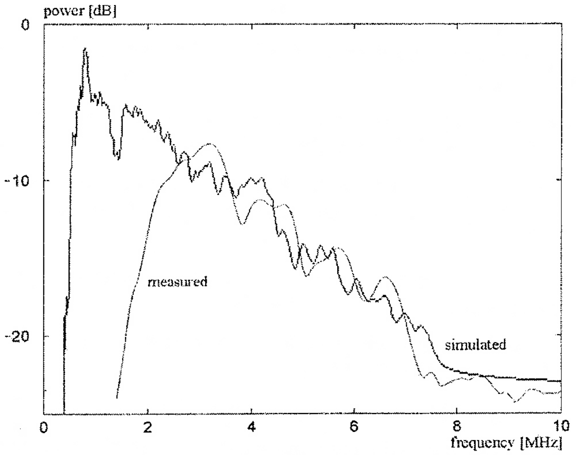

Fig.3. a.) Computer simulated backscattered frequency spectrum of the microbubbles with polymer shell. b.) The measured frequency spectrum of the microbubbles with polymer shell, corrected by the reference spectrum

The backscattered power was estimated as a sum of scattered cross sections of the microbubbles used in the experiment. Based on equation (1), measured histogram of the size distribution and resonance frequency measured under the microscope, the frequency spectra of backscattered signal were calculated for 6000 scatterers. The calculated frequency spectrum of backscattered signal for the measured sample is presented on Fig.3a.

The measured frequency spectrum, backscattered on the agarose sample of microbubbles with the polymer shell, corrected by reference spectrum is presented on Fig.3b. The signal to noise ratio of the recorded signal was $S/N \geq 40$ dB.

5. Conclusions

The technique proposed by authors allowed to measure power of ultrasonic signal backscattered on polymer shell microcapsules in low concentration $6 \cdot 10^3$ particles/cm^3. In 2 - 6 MHz frequency range, the signal to noise ratio was $S/N \geq 40$ dB. Those results were obtained using single probe and direct measurements of ultrasonic scattering signal, which is an improvement, compared to the multi transducer ant attenuation only measurements [4, 5].

The measured frequency spectrum of the backscattered signal matches those calculated from the resonance scattering theory based on equation (1) and the measured particle resonance frequency given by equation (4) and the size distribution of measured scatterers. The microsphere resonance frequency, measured under the microscope, was 0.60 MHz for 43 μm diameter.

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