Bubble Dynamics of Ultrasonic Drug Release from Polymeric Micelles

Mario A. Diaz

William G. Pitt
pitt@byu.edu

Follow this and additional works at: https://scholarsarchive.byu.edu/facpub

Part of the Chemical Engineering Commons

Original Publication Citation

BYU ScholarsArchive Citation
https://scholarsarchive.byu.edu/facpub/59

This Poster is brought to you for free and open access by BYU ScholarsArchive. It has been accepted for inclusion in All Faculty Publications by an authorized administrator of BYU ScholarsArchive. For more information, please contact scholarsarchive@byu.edu, ellen_amatangelo@byu.edu.
Introduction

We have reported the ability of Pluronic P-105 micelles to sequester anthracycline drugs and release their contents upon application of 70 kHz ultrasound (US) (Figure 1). Optimal targeting to tumors depends on focus and control of US. This work, which is better achieved at higher frequencies. While no evidence of in vitro drug release was found at 500 kHz, drug release at 70 kHz correlates with the intensity of the subharmonic signal in the acoustic spectrum generated by the insonated bubbles (Figure 2).

Having established that bubble oscillations (cavitation) are directly related to drug release at 70 kHz, we now investigate the differences in the dynamic of oscillating bubbles at both frequencies.

Figure 1 (above). Micelles release the encapsulated drug at the targeted tissue upon application of ultrasound then quickly return.

Figure 2 (right). Drug release correlates with subharmonic intensity at 70 kHz.

Methods:

For this study we followed the bubble dynamics treatment of Parlitz et al. by using a modification to the Keller-Miksis model:

\[ p_{\text{stat}} - p_R + \frac{2S}{R} \left( \frac{R_0}{R} \right)^3 - \frac{2S}{R} \left( \frac{R_0}{R} \right) - p_{\text{stat}} = \sin(2\pi ft) \]

where \( p_R \) is the static pressure, \( p_R(T) \) is the vapor pressure far from the bubble, \( S \) is the surface tension, \( R_0 \) is the equilibrium radius, \( k \) is the polytropic constant, \( p_R \) is the viscosity of the liquid, and \( f \) is time. The last term represents a sinusoidal driving pressure of frequency \( f \) and amplitude \( A \).

\[ \frac{d^2 R}{dt^2} + \frac{4A}{c^2} \frac{R}{R_0} - \frac{2S}{R} \frac{R_0}{R} = \sin(2\pi ft) \]

Results: Figure 3 shows that the bubble undergoes the classic period-doubling route to chaos at 500 kHz, shown by the appearance of all periods after MI=0.4. This is peculiar since no subharmonics were seen during experiments for this frequency. It also shows that at 70 kHz the bubble instead first period-doubles near MI=0.32, in agreement with the experimental subharmonic (and drug release) threshold of 0.35, and then goes back to a single period oscillation, only to suddenly burst into chaos (intermittent route to chaos). In general, bubble behavior at 70 kHz is more erratic and violent than at 500 kHz (expected due to resonance) and is reflected in the "quasi-stable" subharmonic oscillations that accompany the intermittent route to chaos as opposed to the more deliberate and repeating subharmonics expected of the latter. If drug release is to be seen at 500 kHz, the same geometry seen at 70 kHz must first be identified in parameter space and then reproduced experimentally. These results also suggest the need to update the current categorization of cavitation phenomena (Figure 4).

Conclusions: Bubble oscillations under US at 70 kHz and 500 kHz are fundamentally different as the bubble exhibits an intermittent route to chaos in the former and a period-doubling one in the latter. Drug release from Pluronic micelles at high frequencies is expected to occur under parameter values that reproduce the intermittent type of cavitation seen at 70 kHz.