



---

All Faculty Publications

---

2005-10-03

# The Role of Cavitation in Acoustically Activated Drug Delivery

Mario A. Diaz

Ghaleb A. Hussein

ghaleb\_hussein@hotmail.com

*See next page for additional authors*

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

 Part of the [Chemical Engineering Commons](#)

## Original Publication Citation

Hussein, G.H., Diaz, M.A., Christensen, D.A., Richardson, E. S., and Pitt, W.G., "The Role of Cavitation in Ultrasonic Release of Doxorubicin from Pluronic (P15) Micelles", *Trans. Soc. for Biomaterials*, 3, 584, Memphis, Tennessee, April 27-3, 25

---

## BYU ScholarsArchive Citation

Diaz, Mario A.; Hussein, Ghaleb A.; Pitt, William G.; Richardson, Eric S.; and Christensen, Douglas A., "The Role of Cavitation in Acoustically Activated Drug Delivery" (2005). *All Faculty Publications*. 64.  
<https://scholarsarchive.byu.edu/facpub/64>

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](mailto:scholarsarchive@byu.edu), [ellen\\_amatangelo@byu.edu](mailto:ellen_amatangelo@byu.edu).

---

**Authors**

Mario A. Diaz, Ghaleb A. Hussein, William G. Pitt, Eric S. Richardson, and Douglas A. Christensen

# The Role of Cavitation in Acoustically Activated Drug Delivery

## Introduction

The triblock copolymer, Pluronic P105, has been found to be an ideal ultrasonically activated drug delivery vehicle because it forms micelles with hydrophobic polypropylene oxide cores that sequester hydrophobic drugs (Fig. 1). These micelles release their contents upon the application of low frequency ultrasound [1] such that drugs can be released specifically at the ultrasonicated region (Fig. 2). Such ultrasonically controlled release has been effective against cancer cells in vitro [2] and in vivo [3].

This poster presents our results showing that collapse cavitation is associated with drug release. Cavitation is generally divided into two types of behavior. Stable cavitation is the stable oscillation of a bubble without collapse, and it occurs at lower acoustic intensities (Fig. 3). Collapse cavitation occurs at higher acoustic intensity when ultrasonic pressure oscillations greatly expand and then quickly collapse a gas bubble to a fraction of its volume (Fig. 3). This creates high shear stresses and a shock wave. Collapse cavitation is evidenced by the appearance of a subharmonic at one half of the ultrasonic frequency.

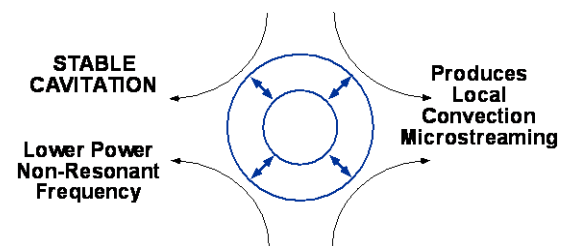


Figure 3. Stable cavitation in the left drawing produces local microstreaming. Transient or collapse cavitation is the rapid collapse to a small point that produces high convection and a shock wave.

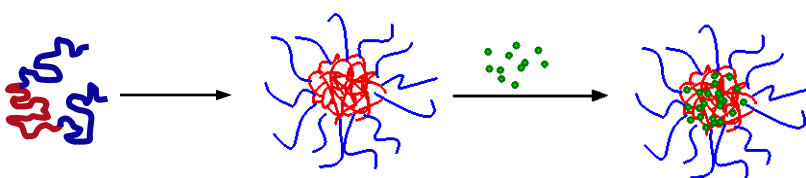


Figure 1. Pluronic P105 forms dense micelles whose hydrophobic core readily sequesters hydrophobic chemotherapeutic drugs.

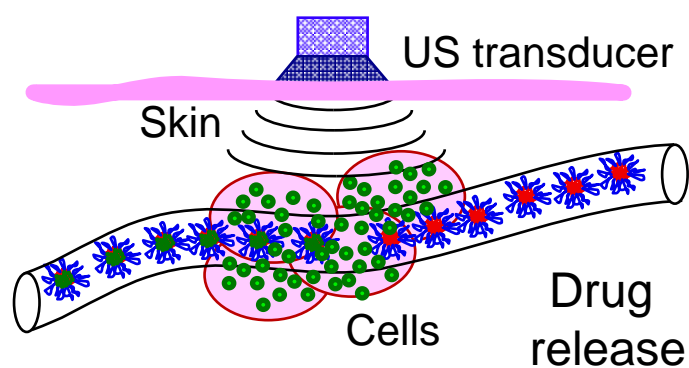
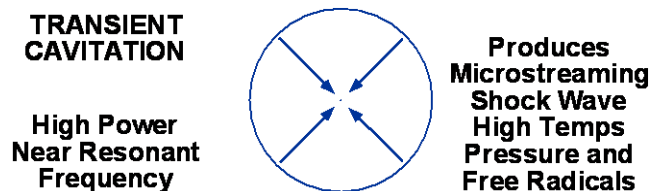


Figure 2. Micelles release the encapsulated drug at the targeted tissue upon application of ultrasound then quickly reform.



## Methods

Dox was dissolved in 10 wt% P105 solutions at 10 mg/ml. Because Dox fluorescence is quenched by water, the amount of Dox release is quantified by measuring the decrease in fluorescence as ultrasound is applied. Laser excitation at 488 nm is brought to the Dox solution through a fiber optic bundle, and the emission at 530 nm is carried by another fiber optic bundle to a detector (Fig. 4). Dox fluorescence was measured with and without ultrasound applied at various power densities.

Ultrasound at 70 kHz was applied in an ultrasonic bath, and the power density was measured with a hydrophone and oscilloscope. After measurements of Dox fluorescence, the fiber optic was replaced with the hydrophone in the same location. The hydrophone signal was Fourier transformed to obtain the spectra of the vibrations of the cavitating bubbles in the ultrasonic field (Fig. 5).

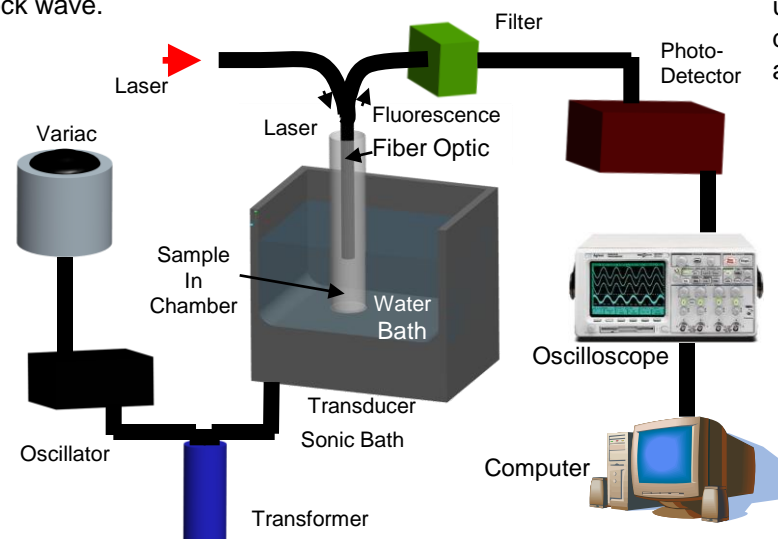


Figure 4. Fluorescence of Dox is excited by a laser through a fiber optic, and then collected by a fiber optic and recorded on a computer. Ultrasonic intensity is controlled by a variac.

## Results

Figure 6 shows the percent of doxorubicin release from micelles as a function of the acoustic power density delivered. No significant ( $p > 0.05$ ) change in fluorescent intensity is seen below approximately  $0.28 \text{ W/cm}^2$ . Above this power density the drug release increases and then levels off.

The three inserts in Fig. 6 show examples of the frequency spectra. The spectrum on the lower left (at  $0.25 \text{ W/cm}^2$ ) contains no subharmonic peak (in the vicinity of 35 kHz) and was collected at an intensity where no Dox was released. The insert on the right shows the development of a subharmonic peak (at approximately 35 kHz) at  $0.28 \text{ W/cm}^2$ , where the Dox release was first measured. The top inset shows that with increasing intensity, the subharmonic peak increases in magnitude.

The onset of ultrasonically released Dox corresponds to the emergence of a subharmonic peak. Figure 7 shows the acoustic intensity of the subharmonic signal correlated with the drug release.

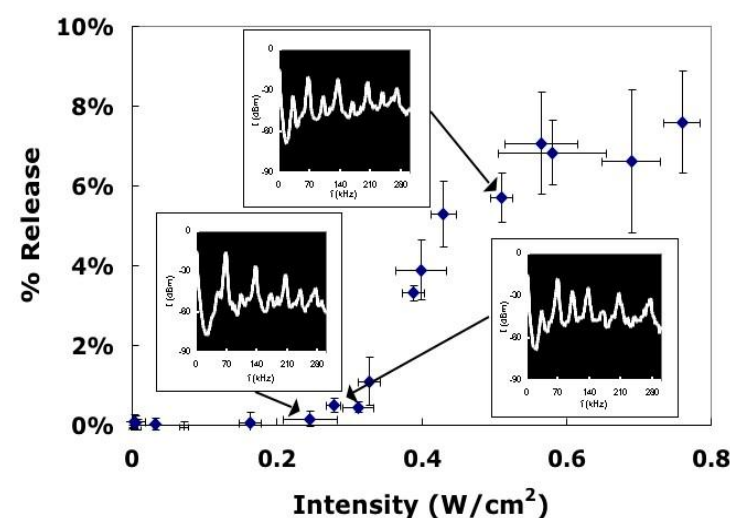


Figure 6. Average percent release of Dox as a function of ultrasonic intensity at 70 kHz. Error bars represent standard deviations ( $n \geq 4$ ) of the mean. Inserts show the acoustic spectra at 0.25, 0.28, and  $0.52 \text{ W/cm}^2$ .

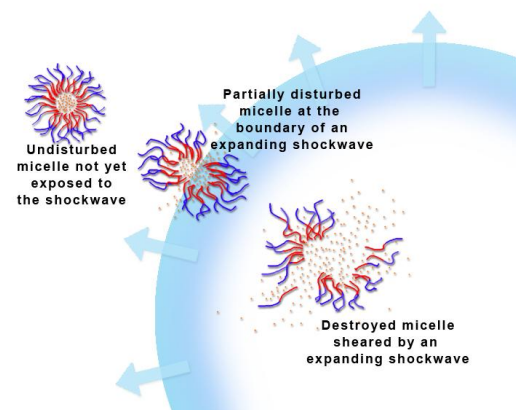


Figure 8. The expanding shockwave generated by a collapsing bubble shears micelles apart, causing them to release their contents.



Figure 5. Hydrophone readings of fluorescence experiments were converted from time to frequency domain (Fourier Transform), thus generating acoustic spectra that describe the bubble vibrations at individual frequencies.

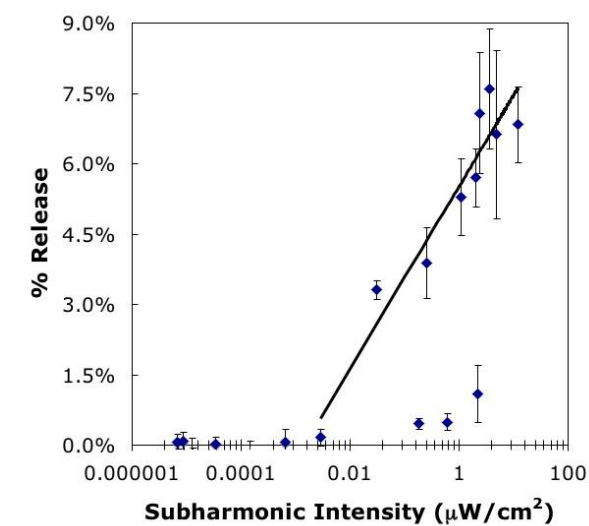


Figure 7. Percent Dox release from Pluronic micelles correlated with the acoustic intensity of the subharmonic peak. Error bars represent the standard deviations of the mean.

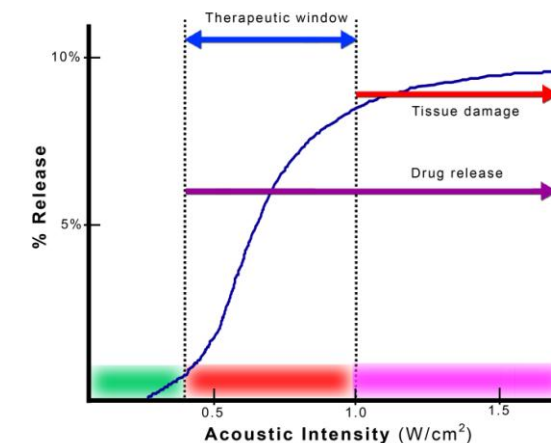


Figure 9. Results suggest a possible therapeutic window where collapse cavitation is strong enough to release drug but mild enough to spare tissue damage.

## Discussion

Two features of these results show that Dox release from Pluronic micelles is strongly correlated with collapse cavitation. First, drug release has an obvious threshold near  $0.3 \text{ W/cm}^2$ , and the onset of collapse cavitation occurs in this region. Secondly, the subharmonic peak appears at the same intensities as drug release starts, and the subharmonic intensity correlates with drug release, with the exception of a few outliers. We hypothesize that the high shear stresses associated with the collapse of the cavitating bubble and subsequent shock wave shears micelles, disrupting their structure and releasing a portion of sequestered drug before the micelle reforms and the drug is re-encapsulated (Fig. 8). The boundary of the shock wave consists of highly compressed gas followed by rarefied gas that creates high shear displacement sufficient to rupture lipid layers [1].

These data show that drug can be released by ultrasound that causes collapse cavitation. The threshold for tissue damage by ultrasound is usually above 1 or 2  $\text{W/cm}^2$ . This provides a therapeutic window as Fig. 9 shows.

## References

- G.A. Hussein, G.D. Myrup, W.G. Pitt, D.A. Christensen, N.Y. Rapoport, Factors Affecting Acoustically-Triggered Release of Drugs from Polymeric Micelles, *J. Contr. Release* **69** (2000) 43-52.
- G.A. Hussein, R.I. El-Fayoumi, K.L. O'Neill, N.Y. Rapoport, W.G. Pitt, DNA damage induced by micellar-delivered doxorubicin and ultrasound: comet assay study, *Cancer Lett.* **154** (2000) 211-216.
- J.L. Nelson, B.L. Roeder, J.C. Carmen, F. Roloff, W.G. Pitt, Ultrasonically Activated Chemotherapeutic Drug Delivery in a Rat Model, *Cancer Res* **62** (2002) 7280-7283.
- H.R. Guzman, A.J. McNamara, D.X. Nguyen, M.R. Prausnitz, Bioeffects caused by changes in acoustic cavitation bubble density and cell concentration: A unified explanation based on cell-to-bubble ratio and blast radius, *Ultrasound in Medicine and Biology* **29**(8) (2003) 1211-1222.