Modeling Phase Transitions of Nanoemulsion for Ultrasonic Gene Delivery

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During the bubble expansion phase, and then returned to the initial temperature 4
5

**INTRODUCTION:**

Ultrasound gene delivery is enhanced by the presence of microbubbles (MBs) that create cavitation events leading to the transient permeabilization of cell membranes, thus allowing the diffusion of DNA or other oligonucleotides into the cell. However, the size of microbubbles, usually 2-5 microns, restricts them to the circulatory system; thus gene transfection is limited to the endothelial cell layer, or perhaps 1 cell layer beyond if the cavitation disrupts the endothelium. Microbubbles cannot pass through the intima to enhance gene transfection further into a tissue system.

However, in some tumors, the capillary vasculature has much larger gaps and fenestrations which allow passage of much larger particles, sometimes up to 600 nm in diameter. This is called "enhanced permeation and retention" (EPR). Thus, sufficiently small nanoemulsion particles could escape from the capillaries. Our concept is to generate cavitation gas bubbles in "leaky" tumor tissues beyond the endothelium by creating submicron nanoemulsions containing perfluorohexane, a liquid (at body temperature) that boils at 5°C. But even at 37°C, the liquid will transform to gas as the surrounding pressure is reduced, such as during the rarefaction phase of the ultrasonic cycle. Experiments in vitro have shown that 20 kHz and 500 kHz ultrasound (US) can produce cavitation gas bubbles from perfluorohexane emulsions (250 nm and 550 nm diameter) stabilized by perfluorocarboxylic acids.

In order to better understand the physics that govern the ultrasonic-induced phase transition of perfluorocarbon emulsions, and exploit them for gene delivery, we created a mathematical model and computer program of this phenomenon.

**MATHEMATICAL AND COMPUTER MODEL:**

We employ a model of a sphere of liquid with a surfactant layer producing a given surface tension. The ultrasonic wave model is defined as a sine wave oscillating around the local hydrostatic pressure. The pressure inside the emulsion liquid is the external pressure plus the Laplace pressure. As the US pressure decreases, the pressure inside the nanoemulsion eventually drops below the vapor pressure of the liquid at its local temperature. We assume the liquid boils to form a gas phase beyond the endpoint of the liquid-vapor phase diagram. The computer model was written that simulates the transformation of a perfluorocarbon emulsion, and exploit these for gene delivery, we created a mathematical model and computer program of this phenomenon.

**RESULTS AND DISCUSSION:**

The most significant parameter affecting maximum bubble diameter and collapse velocity is the ultrasonic frequency. At 40 kHz (compared to 500 kHz) there is much more time available for the expansion phase of bubble growth, and there is a significant surfluent momentum that allows the bubble to keep expanding even after the pressure is no longer large enough to sustain bubble growth. This leads to more than one bubble being created at low frequencies, as has been observed experimentally.

Figs. 1-8 show the behavior of gas phase radius, gas/water interface velocity, and gas phase pressure as a function of the acoustic pressure and frequency, surface tension, bubble diameter, and initial temperature. The authors thank the National Institutes of Health CA-08133 for funding.

**REFERENCES:**


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**RESULTS AND DISCUSSION:**

Figure 1 shows an example of the bubble radius, gas-water interface velocity, and gas phase temperature as a function of time at 500 kHz. The gas phase temperature is the same as that of the surface of the liquid droplet that cools during evaporation. The computer code appeared to run properly in that the gas phase formed only after the external pressure plus the Laplace pressure dropped below the vapor pressure of the perfluorocarbon. Larger emulsions nanoemulsions formed larger bubbles than smaller ones because the decreased Laplace pressure allowed gas phase incipient to occur sooner and there was a longer time for bubble growth. At low acoustic pressures the gas phase condenses back into liquid phase as the acoustic pressure reversed. At some higher acoustic pressures, the gas phase is large enough to persist through several cycles, and then finally collapsed. The results of the gas-water interface upon bubble collapse generally increased as the maximum diameter of the gas bubble increased. This is significant because higher collapse velocities produce higher shear stresses and more powerful shock waves.

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The pressure inside the gas phase (and liquid surface) dropped by as much as 40°C during the bubble expansion phase, and then returned to the initial temperature before injection so the DNA is present when the liquid transforms to gas and stresses the local cell membranes. The model gives guidance as to which parameters most affect the transfection efficiency and interact with their neighbors and coalesce into larger bubbles. We have some confidence in the computer model because the thermal balance appears to be correct, within the numerical precision of the computer. As for applications in drug and gene delivery, this model shows that nano-sized perfluorocarbon emulsions can be activated into oscillating gas bubbles that can create shear stress on surrounding cells. DNA in the form of plasmids could be attached to the nanoemulsion surface or free (unattached) DNA could be mixed with the nanoemulsion before injection as the DNA is present when the liquid transforms to gas and stresses the local cell membranes. The model gives guidance as to which parameters most affect the interaction of oscillating gas bubbles with nanoemulsions.

**CONCLUSION:**

We have successfully developed a mathematical model and computer program that simulates the generation of gas bubbles from perfluorocarbon nanoemulsion droplets. The model qualitatively matches experimental data of the onset of collapse cavitation in this system. The advantage of using nanoemulsions in gene delivery is that the nanoemulsions droplets can pass through the leaky capillaries of tumors exhibiting EPR, and then application of US gas bubbles will be formed that will permeabilized the cells towards gene delivery.

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