Modeling Phase Transitions of Nanoemulsion for Ultrasonic Gene Delivery

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ABSTRACT SUMMARY: A computer model was written that simulates the transformation of a nanoemulsion droplet to a gas bubble by the application of ultrasound. Experimentally such a technique could be used to enhance non-viral gene transfection beyond the boundary of the endothelial lining of the circulatory system, particularly in tumors exhibiting enhanced permeation and retention of nanoparticles.

MATERIALS AND COMPUTER MODEL: We employ a model of a sphere of liquid with a surfactant layer producing a given surface tension. The ultrasonic wave is modeled as a sine wave traveling through the liquid. In order to better understand the physics that govern the ultrasonic-induced phase transition of perfluorocarbon emulsion, and exploit them for gene delivery, we created a mathematical model and computer program for this phenomenon.

DISCUSSION: We were successful in generating a mathematical model and computer program that described the behavior of high-voltage pressure nanoemulsions in the presence of an ultrasonic field. The results of the calculation qualitatively matched previous experimental data from our laboratory regarding the thresholds and intensity of collapse cavitation of perfluorohexane emulsions subjected to 20 and 500 kHz ultrasound.

The first-order model in that many of the more detailed physics were not included, such as the change in surface tension with expansion of the gas-water interface, and the evaporation (and condensation) of water at the (water) interface. The model also only considered an isolated emulsion droplet, whereas in reality, the gas bubbles may 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.

RESULTS AND DISCUSSION: Figure 1 shows an example of the bubble radius, gas-water interface velocity, and gas temperature as a function of time at 500 kHz. The gas-phase temperature is the same as that of the surface of the liquid interior drop 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 perfluorocarbons. Larger nanoemulsions formed larger bubbles than smaller ones because the decreased Laplace pressure allowed gas phase formation to occur sooner and there was a longer time for bubble growth. At low acoustic pressures the gas phase condensed back into liquid phase as the acoustic pressure reversed. At some higher acoustic pressures, the gas phase was 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 duration of the gas bubble increased. This is significant because higher collapse velocities produce higher shear stresses and more powerful shock waves. The most significant parameter affecting maximum bubble diameter and collapse velocity is the ultrasonic frequency. At 20 kHz (compared to 500 kHz) there is much more time available for the expansion phase of bubble growth, and there is a significant subsonic momentum that allows the bubble to keep expanding even after the pressure is no longer favorable for bubble growth. This leads to more energetic behavior at low frequencies, as has been observed experimentally.

We have successfully produced a mathematical model and computer program that simulate the generation of gas bubbles from perfluorocarbon nanoemulsions at acoustic pressures. The results qualitatively match experimental data of the onset of collapse cavitation in this system. The advantage of using nanoemulsions in gene delivery is that the nanoemulsion droplets can pass through the leaky capillaries of tumors exhibiting EPR, and then by injection of US, gas bubbles will be formed that will permeabilize the cells towards gene delivery.

REFERENCES:

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