Determining Perfluorocarbon Particle Size Using Nuclear Magnetic Resonance

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Introduction:

Perfluorocarbon (PFC) particular contrast agents are used in different imaging modalities, including MRI and ultrasound. Particle size is important in determining the effects of these particles on image contrast. The primary objective of this study was to accurately determine the average size of perfluorocarbon particles using 19F Nuclear Magnetic Resonance (NMR), by measuring the restricted diffusion coefficient of the perfluorocarbon contained within the particles as a function of diffusion time Δ. In the short-time limit, which is determined by the particle radius and PFC viscosity, there is a measurable relationship between the apparent restricted diffusion coefficient and the particle size. It was shown by Latour et al. (1-2) that the relationship between the diffusion coefficient and the square root of diffusion time can be used to determine the size of the restricting environment.

Experimental Method:

There were two methods that were used to make the perfluorocarbon particles: the use of fluorosurfactant, or Lecithin to form the membrane of the particles. Initially, fluorosurfactant (FSO) was mixed with doubly distilled water and perfluorocarbon and subsequently passed through the emulsifier to form an emulsion of particles with a fairly small size distribution. For these particles, the size was limited by the amount of surfactant as the emulsifier supplied a surplus of energy to the system. By varying the concentration of the FSO, solutions of different particle diameters were made with an upper limit of approximately 8um and a lower limit of approximately 4um. All measurements were performed using a small-bore 1.5T system (SMIS, Surrey, England) with a custom 0.65T/cm gradient coil. Diffusion was measured using pulsed-field-gradient multi-spin-echo PFGMSE (3) technique. The diffusion gradients of 320μs duration were increased from 0 to 650Gs/cm in 20 uniform steps, the data was averaged 8 times and diffusion times were 1, 5, 9, 17 and 33ms To isolate the signal from perfluorocarbon, a radiofrequency copper coil was tuned to the resonant frequency for fluorine (40.06MHz. at 1.5T). We used the Latour (1-2) formula to evaluate average particle size:

$$\frac{ADC(\Delta)}{D_0} = 1 - \frac{4}{9\sqrt{\pi}}\sqrt{D_0\Delta}\,\frac{S}{V}$$

where D_0 denotes free diffusion coefficient of perfluorocarbon and S/V is a surface to volume ratio of the particle, which in the case of sphere is equal to 3r, where r is a sphere radius. D_0 was evaluated independently by measuring diffusion for pure perfluorocarbon. For comparison, the particles were also characterized using dynamic light scattering (DLS) and optical microscopy.

Results:

Figure 1 shows an image of the perfluorocarbon particles taken through an optical microscope at 40x magnification, from which the size was found to be in a range of 4 to 8μm. Figure 2 shows the experimental ADC's as a function of diffusion time, Δ. Solid line represents the Latour model, one parameter fit (2), from which the diameter of the perfluorocarbon particles was determined to be equal 6.8±0.7μm. Table 1 a presents comparison between different methods used in this study to evaluate particle size.

Conclusion:

A method of determining the size of perfluorocarbon particles was developed using 19F-NMR to determine the restricted diffusion coefficients in the short time limit, thus enabling the size to be determined. The size of the lecithin-based perfluorocarbon particles was found to be 6.8±0.7μm and comparable with other techniques, yet resulting in an improved accuracy of the average size. This study shows that size determination by 19F NMR is possible.

References:

1. PP Mitra et al. (1993). Physical Review B, **47** (14) 8565-8574. 2. LL Latour, PP Mitra, et al.(1993 Journal of Magnetic Resonance, Series A 101: 342-346 3. GJ Stanisz et al (1998) Magn Reson Med, **39**, 223-233

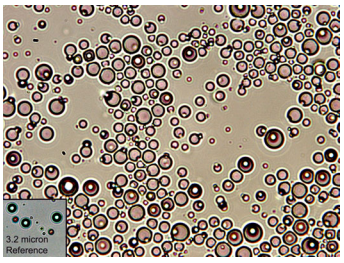

Figure 1: 40x optical image of perfluorocarbon particles, with polystyrene reference in corner

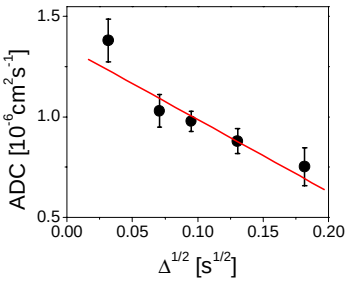

Figure 2: Fit of restricted diffusion coefficient versus square root of diffusion time

Method	Size	Error Estimate
NMR	6.8 μm	±0.7μm
DLS	5.3 μm	± 1.5 μm
OPTICAL	5.0μm	±2.5μm

Table 1: Comparisons of particle size determined using different methods