Novel Nanoparticle Formulations with Enhanced ^{19}F Relaxation

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Introduction

Fluorine MRI is receiving increasing attention, primarily due to the high NMR sensitivity of ^{19}F nuclei, the physiological absence of fluorine containing substances and the availability of contrast materials based on bio-compatible perfluorinated carbon (PFC) nanostructures. The applicability of ^{19}F MR as a molecular and cellular imaging technique has been demonstrated in a number of studies ranging from in vivo cell tracking[1] to detection and imaging of tumors in small animals[2]. Besides applications, developing new contrast materials with improved relaxation properties has also been a core research topic in the field, since the inherently low longitudinal relaxation rates of PFC compounds result in to relatively low imaging efficiencies. Borrowed from ^{1}H MRI, the incorporation of Lanthanides, specifically Gd(III)-complexes, as signal modulating ingredients into the nanoparticle formulation has emerged as a promising approach towards improvement of the Fluorine signal[3]. In this paper we present three different ^{19}F nanoparticle formulations where perfluoro-15-crown-5-ether has been used as the core material and Gd(III)-DOTA-DSPE, Gd(III)-DOTA-C6-DSPE and Gd(III)-DTPA-BSA (Figure 1) as the relaxation altering components. Single voxel spectroscopy based T_1 measurements conducted at 3.0T revealed enhanced relaxation in all three compositions with respect to a reference sample consisting of Gadolinum-free PFCE nanoparticles.

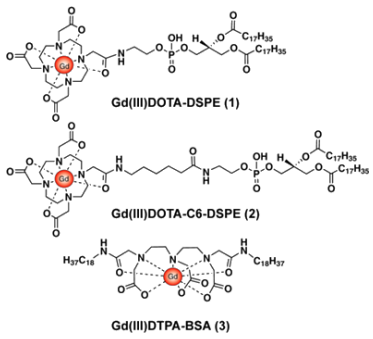

Figure 1 Gd(III)-lipid complexes used in NP formulations.

Materials and Methods

Perfluoro nanoparticles were composed of 20% (w/v) perfluoro-15-crown-5-ether, 2% (w/v) surfactant in physiological salt. The surfactant comprised DSPC, DSPE-PEG-2000, Gd-DOTA-DSPE/Gd-DOTA-C6-DSPE/Gd-DTPA-BSA, Rhodamine-PE and cholesterol in a molar ratio of 1.55:0.15:0.3:0.003:1 while the composition of Gadolinum-free nanoparticles consisted of DSPC, DSPE-PEG-2000, Rhodamine-PE and cholesterol in a molar ratio of 1.85:0.15:0.003:1. The mixtures were emulsified at 20,000 PSI using a microfluidizer (prewarmed to 70°C) for 3 min in an ice bath. Subsequently, samples were cooled for 5 minutes in an ice bath. Particle sized were determined at 25°C by dynamic light scattering whereas the concentrations of gadolinium and fluorine in the samples were determined by Inductively Couple Plasma (ICP) analysis and high field NMR spectroscopy, respectively,. T_1 measurements were conducted in a 3.0T Philips Achieva clinical scanner (Philips Healthcare, Best, The Netherlands) equipped with a special design ^{1}H/^{19}F small bore coil[4]. Longitudinal relaxation was measured by means of a single voxel spectroscopy sequence consisting of a 180° inversion pulse and a 90° excitation pulse, both wideband and tuned to the NMR offset of PFCE, and a sampling phase where the free induction decay (FID) signal generated by the fluorine nuclei was acquired. The time interval between inversion and excitation was altered over a range from 1.5 ms to 15 s with 44 time points. The repetition time of the measurements was kept long, i.e. 20s, in order to ensure complete relaxation after each acquisition. The effect of nanoparticle concentration was assessed by evaluating a concentration-series of each emulsion formulation for their T_1 values, in a similar manner. The gain in SNR was evaluated by performing a F-uTSI[5] measurement acquiring 32 echoes per imaging cycle with a repetition time of 378 ms, echo time and echo spacing of 5.75 ms.

Results and Discussions

Preliminary results indicate that all three compositions increase the relaxation rate of ^{19}F nuclei more than twofold in comparison to the Gd(III)-free reference sample at a magnetic field strength of 3.0T. When the number of Gd molecules per particle, which is determined to be 10.000-12.000, is taken in consideration, it can be concluded that the results comply with findings reported in the literature[3]. While Gd-DOTA-C6-DSPE and Gd(III)-DTPA-BSA containing samples showed no significant dependence on particle concentration, the relaxation rate of Gd-DOTA- DSPE was found to be increasing as the concentration decreased. Further investigation of this behavior is of vital importance in developing a better understanding of the relaxation dynamics of such nanostructures. The reduction of T_1 from 2.1 seconds to under a second is expected to provide a significant gain in MR signal within similar measurement times. In case of a F-uTSI acquisition, for instance, the gain in SNR was found to be about 1.5- fold (Figure 4).

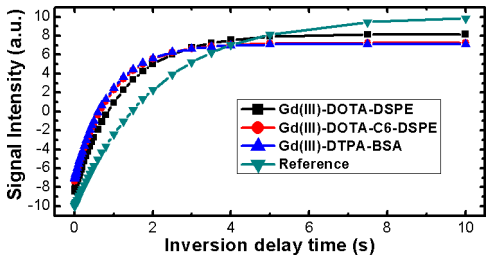

Figure 2 Inversion recovery curves obtained on the highest concentrated samples of NP formulations.

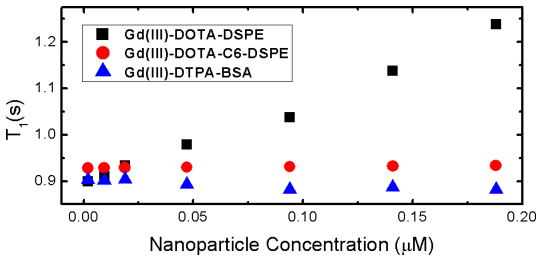

Figure 3 Concentration dependency of measured T_1 values

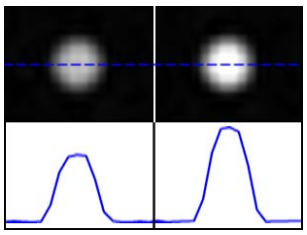

Figure 4 Signal gain obtained with Gd-DOTA-C6-DSPE (right) w.r.t. a reference sample (left)

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