Impact of agglomeration on the relaxometric properties of gadolinium oxide nanoparticles as a contrast agent for MRI

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Context: Magnetic resonance imaging (MRI) is a non invasive biomedical imaging modality that allows high resolution diagnostics. The signal in MRI is provided by relaxing ^{1}H protons. In order to increase the efficiency of tissue differentiation, it is often necessary to increase the signal in specific organs or tissues. To date, contrast agents are used in 30% of all clinical scans and the most used are gadolinium chelates [1]. These chelates are referred to as "positive-T_1" contrast agents since they enhance the signal from relaxing ^{1}H protons. In the context of cellular imaging however, those chelates do not allow the study of cell migration in vivo since they are not efficiently retained within the cells. This is a niche application for which ultra-small gadolinium oxide nanoparticles (US-Gd_2O_3, ∅ core = 3 nm) have been considered [2, 3]. Nanoparticles can be efficiently ingested and retained by cells, leading to improved contrast with T_1-weighted MRI sequences [4, 5]. However, once internalised by the cells, the nanoparticles tend to agglomerate in endosomes [4]. The present study aimed at evaluating the impact of agglomeration on the relaxometric properties of Gd_2O_3 nanoparticles. In order to avoid interference with organic materials, here only aqueous suspensions of nanoparticles were characterized (without cells).

Materials and Methods: US-Gd_2O_3 were synthesized by hydrolysis in a polyol solvent [6, 7]. As-synthesized nanoparticles are covered with diethylene glycol (DEG-Gd_2O_3). Then, they were dialyzed against water. Due to the presence of contaminating DEG, the resulting nanoparticle suspensions tend to form nanoagglomerates of hydrodynamic size ranging from 3 nm (individual nanoparticles) to about 105 nm. The hydrodynamic radius of agglomerates was studied by dynamic light scattering (DLS), while longitudinal relaxivities (r_1) were measured on a Stelar field cycling relaxometer (NMRD) from 0.01 to 10 MHz. The relaxometric study was completed by using dedicated relaxometers (Bruker Minispec, 10, 20, 60 MHz) to measure ^{1}H longitudinal and transversal relaxation times (T_1 and T_2) at clinical fields. High resolution NMR spectrometers were used to characterize the suspensions at 300 and 500 MHz (high-field MRI). Gd concentration was measured by ICP-MS.

Results and conclusions: Agglomeration of DEG-Gd_2O_3 results in a slight decrease of both r_1 and r_2. However, even 105 nm agglomerates still perform well as "positive-T_1" contrast agents, as suggested by r_2/r_1 ratios close to 1.5 at 60 MHz, compared to 1.3 for individual nanoparticles. The simulated signal intensity is 10.5% higher for individual nanoparticles. At clinical fields (~1.5 T, 60 MHz), NMRD curves indicate a promising maximum in r_1 relaxivity. This maximum occurs at magnetic fields six times higher than for individual ultra-small iron oxide nanoparticles (USPIOs). This result suggests that Gd_2O_3 nanoparticles are more suitable than USPIOs to provide positive contrast in clinical 1.5 to 3 T MRI [8, 9]. DEG-Gd_2O_3 could also be used in high-field pre-clinical MRI (at 4-7 T), a range of magnetic fields for which USPIOs cannot be used to provide positive contrast because the T_2^* effects become too important [8].

References:

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Figures:

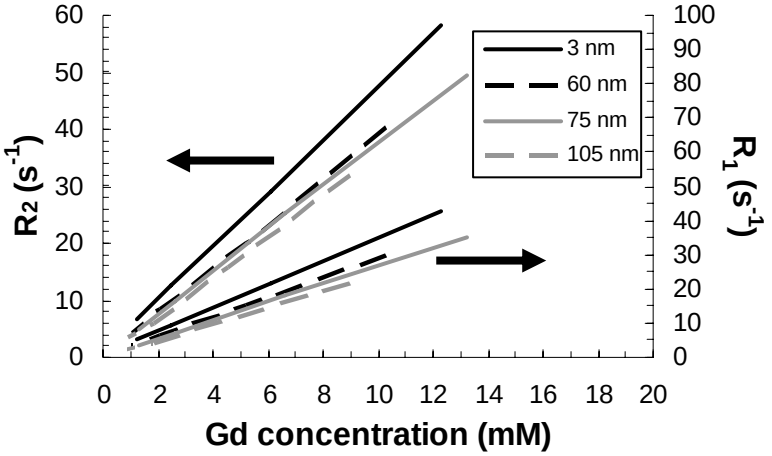

Figure 1: Longitudinal (R_1) and transversal (R_2) relaxation rates of DEG-Gd_2O_3 agglomerates

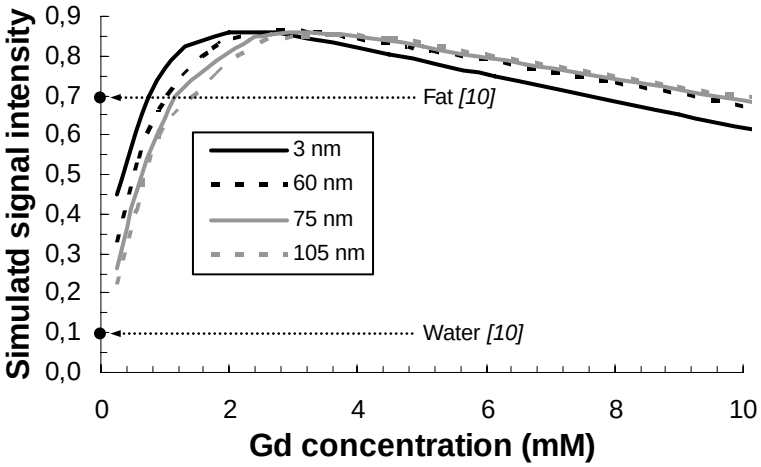

Figure 2: Simulated signal intensity for suspensions of Gd_2O_3-containing nanoagglomerates (based on measured T_1 and T_2, and a spin-echo sequence with TE 10 ms, TR 400 ms)

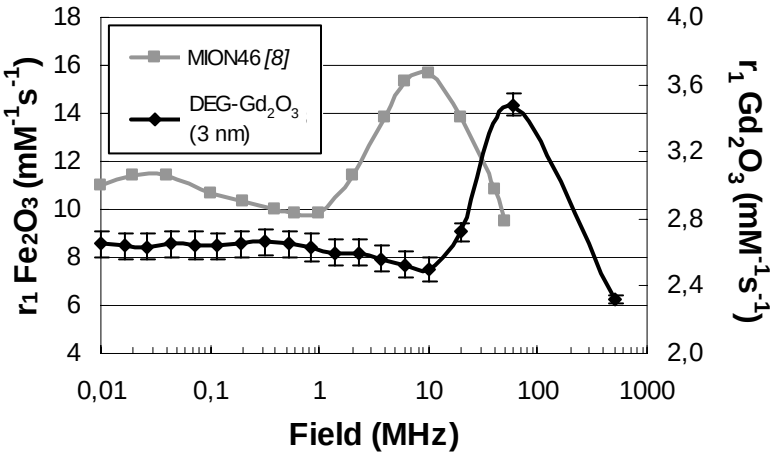

Figure 3: NMRD curves of Fe_2O_3 and DEG-Gd_2O_3 nanoparticles