

Lanthanide Trifluoride Nanoparticles for Dynamic Contrast Enhanced MRI

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Introduction: Positive contrast agents currently used for MR imaging are currently limited to low-molecular weight gadolinium compounds. While these agents are very useful for highlighting cancerous tumors and providing dynamic contrast enhanced MR data, they are inherently limited. Because of their small size, they leak outside of the vasculature, making blood volume measurements difficult and requiring very fast imaging to obtain good quality dynamic contrast enhanced data.

Here we present a new class of gadolinium-based contrast agents for MR imaging based on earlier work [1]. The contrast agent consists of nanoparticles (NPs) with a lanthanide fluoride core (GdF₃ and CeF₃) surrounded by a coating of polyacrylic acid (PAA). Because of the chemical similarity of the elements in the lanthanide series it is relatively straightforward to use a combination of several different lanthanide fluoride species. This versatility allows the NPs to be tailored for particular applications: Gd for MRI contrast, Eu or Tb for fluorescence, and ¹⁷⁷Lu for PET or SPECT. Because of their relatively high atomic numbers, they are all reasonable X-ray attenuators and provide CT contrast. The PAA coating serves several purposes: it renders the NPs soluble in water, minimizes toxicity, and provides scaffolding to which cell-targeting species can be attached. Changes to the percentages of the particular lanthanides used in the core of the nanoparticle can affect the size and the relaxivity of the nanoparticle.

Methods: The relaxivity of the nanoparticles was evaluated using a spin echo inversion recovery experiments on a GE Signa 1.5T MRI scanner (General Electric, Milwaukee, USA) and GE Signa 3T MRI scanner (General Electric, Milwaukee, USA), FOV 14 cm, 5mm slice thickness, 128x128 matrix, 1 NEX, 15.63 Hz bandwidth, TE 9ms, TR 2500ms, with 9 inversion times evenly spaced between 50ms and 2500ms. Nanoparticle size was determined using a scanning transmission electron microscope. Dynamic contrast enhanced MRI was done in rat brain on at 3T, using a fast SPGR sequence, FOV 4cm, 2mm slice thickness, 128x128 matrix, 20 NEX, 122 Hz bandwidth, TE 3ms, TR 8ms, 20s time resolution, 36 min total scan time. A bolus of 0.4ml nanoparticles at a concentration of 18.6 mg/ml was injected 1 minute after the start of DCE image acquisition, into the cannulated tail vein.

Results:

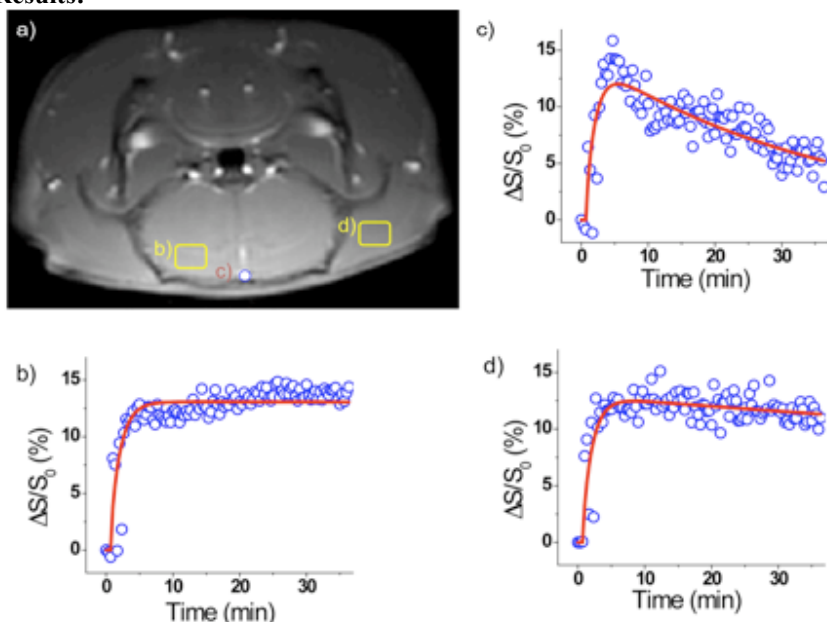


Figure 1. DCE-MRI of supine rat brain with enhancement curves shown for b) brain, c) blood vessel, and d) muscle.

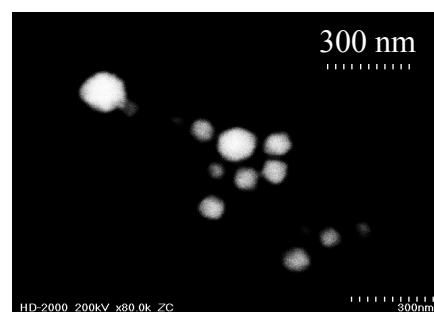


Figure 2. STEM image of nanoparticles

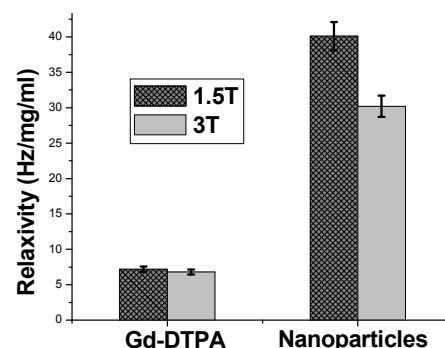


Figure 3. Relaxivity of nanoparticles.

Discussion: STEM images show that the nanoparticles are approximately 70nm in diameter. Mass relaxivity of the nanoparticles is significantly higher than that of Gd-DTPA, allowing this contrast agent to be used at much lower concentrations. Dynamic contrast enhanced MRI with a concentration of 18.6 mg/ml nanoparticles was similar to that obtained with 287mg/ml Gd-DTPA.

Conclusion: Lanthanide-fluoride nanoparticles can be used for dynamic contrast enhanced MR imaging. They provide a very flexible platform for modifications including targeting to particular cell types, fluorescence imaging, and variability in size.

[1] Evanics, F.; Diamente, P. R.; van Veggel, F.; Stanisz, G. J.; Prosser, R. S. *Chemistry of Materials* **2006**, *18*, 2499-2505.