A Highly Sensitive MR Contrast Agent Based on Liposomal Nanocarrier Containing Superparamagnetic Iron-oxide

K. Ghaghada[1], K. Hagen[2], and S. Mukundan[1,3]

[1]Radiology, Duke University Medical Center, Durham, NC, United States, [2]Chemistry, Emory University, Atlanta, Georgia, United States, [3]Biomedical Engineering, Duke University, Durham, NC, United States

Introduction: The rapid growth in cellular and molecular MR imaging is driving the development of novel contrast agents that demonstrate high sensitivity and specificity [1, 2]. The majority of the MR contrast agents utilized for molecular imaging are based on iron oxide particles because of its high T2 relaxivity. We have developed a magnetic resonance (MR) contrast agent by encapsulating highly soluble superparamagnetic iron-oxide nanoparticles within long circulating PEGylated liposomes (liposomal-Fe). In this work, the synthesis and characterization of the agent is described.

Materials and Methods: Water soluble iron oxide crystals were dissolved in de-ionized water to prepare iron oxide solution of desired iron concentration. To prepare liposomal-Fe, lipids were dissolved in ethanol and then mixed with iron oxide solution and stirred for 2 hr. The solution was sequentially extruded at 60°C with four passes through a 400 nm filter membrane, and ten passes through a 200 nm filter membrane. The size of the resultant liposomal-Fe formulations was determined by dynamic light scattering (DLS) using a Brookhaven Zeta Potential Instrument. The concentration of iron in the liposomal-Fe formulation was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The structure of liposomal-Fe nanoparticle was determined using transmission electron microscopy. The T2 molar relaxivities of liposomal-Fe and native iron oxide samples were determined on a 2 Tesla MR scanner using a multi-spin multi-echo (MSME) sequence using the following parameters: TR = 3000 ms, TE was varied from 10 – 200 ms; Bandwidth = 31.25 KHz, Slice thickness = 4 mm. Similar T2 measurements were also performed on a 7 T MR scanner with the following parameters: TR = 3000 ms, TE was varied from 8 – 170 ms; Bandwidth = 31.25 KHz, Slice thickness = 5 mm.

Results: The mean diameter of liposomal-Fe was 142.3 nm with polydispersity of 0.12. The molar iron:phospholipid ratio as determined using ICP-AES was 1.4:1. Transmission electron microscopy images of the native iron oxide solution showed single 5-10 nm iron oxide crystals. In the case of liposomal-Fe, the iron oxide crystals were sequestered inside liposomes (Figure 1). At 2 Tesla, the T2 relaxivity of liposomal-Fe was 300 $(mM.sec)^{-1}$ and that of the native iron oxide solution was 175 $(mM.sec)^{-1}$. At 7 Tesla, the T2 relaxivity of liposomal-Fe was 311 $(mM.sec)^{-1}$ and that of the native iron oxide solution was 186 $(mM.sec)^{-1}$ (Figure 2).

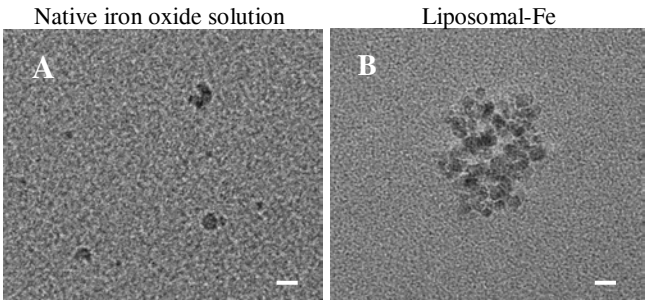

Figure 1. Transmission electron microscope images of native iron oxide solution (A) and liposomal-Fe solution (B). Bar represents 20 nm.

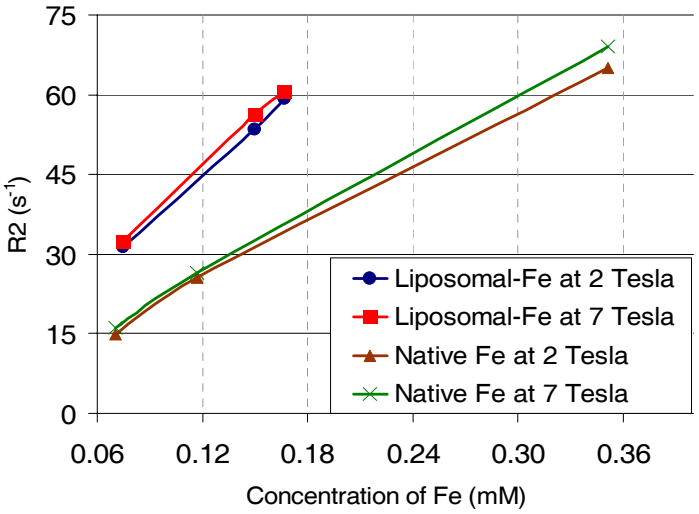

Figure 2. T2 molar relaxivity plot for liposomal-Fe and native iron oxide agents.

Discussion: The majority of the iron oxide-based MR contrast agents have a T2 relaxivity of about 60 $(mM.sec)^{-1}$. The liposomal nanocarrier encapsulating superparamagnetic iron oxide synthesized in this work has a 5 fold higher T2 relaxivity than commercially available agents. The liposomal envelope used to prepare the agent can be easily modified to present ligands for targeting specific receptors over-expressed on pathological tissues. The ability to target the liposomal-Fe would therefore enable imaging of targets with very high sensitivity.

References: 1. Brindle KM. Br J Radiol. 2003;76 (2):S111-7.
2. Bulte JW, Kraitchman DL. NMR Biomed. 2004;17(7):484-99.