Engineering Conferences International
ECI Digital Archives

Nanotechnology in Medicine: From Molecules to Humans

Proceedings

7-3-2016

Iron oxide nanoparticles with a variable size and an iron oxidation state for imaging applications

Vladimir Kolesnichenko
Xavier University, New Orleans, USA, vkolesni@xula.edu

Galina Goloverda
Xavier University, New Orleans, USA

Pavel Kucheryavy
Xavier University, New Orleans, USA

Leonard Spinu
University of New Orleans, USA

IRON OXIDE NANOPARTICLES WITH A VARIABLE SIZE AND AN IRON OXIDATION STATE FOR IMAGING APPLICATIONS

Vladimir Kolesnichenko, Galina Goloverda, Pavel Kucheryavy and Leonard Spinu
Xavier University, Chemistry Department, New Orleans, Louisiana, USA

Application of superparamagnetic iron oxide nanoparticles in biology and medicine finds its rapidly developing emphasis on contrast agents for MRI. Positive contrast imaging is frequently preferred in diagnostic practice, however the existing gadolinium-containing T_1 contrast agents raise substantial toxicity issues, and their high mobility shortens their presence in the vascular system. These drawbacks of gadolinium contrast agents motivate the researchers' effort on development of T_1 contrast agents based on ultrasmall superparamagnetic iron oxide particles.

Due to their high magnetic moment, superparamagnetic nanoparticles enhance proton relaxation predominantly via outer-sphere mechanism and therefore act as negative (T_2) contrast agents. In positive (T_1) contrast agents, the inner-sphere relaxation mechanism is utilized due to interaction of protons with the high-spin d^5 transition metal ions such as Mn^{II} and Fe^{III}, or more commonly, the f^7 Gd^{III} ions.

The best currently known blood pool MRI agents are based on iron oxides and considered non-toxic. Reducing the particle size below 5 nm can lower their magnetic moment, and therefore the outer-sphere relaxivity r_2. At the same time larger surface-to-volume ratio of these small particles can cause greater involvement of iron atoms in the spin-lattice relaxation process, which relies on direct water coordination and exchange at the metal sites. Consequently, particle size reduction can be the way to obtaining a better T_1 contrast agent. One of the goals of this work was to study how particle size affects the magnetic and relaxivity properties. We intentionally used no capping ligands or surfactants to make sure they would not interfere with water coordination and exchange at the particle's surface, which is important for accurate T_1 measurements.

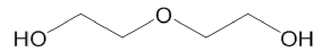
It is known that magnetite spontaneously oxidizes in the air yielding γ-iron(III) oxide with similar crystal structure. Similarity of their structures reflects on the magnetic properties being alike: maghemite (γ-Fe_2O_3) has saturation magnetization value ~80% of the value for magnetite. It could be expected that particles with the same size but different oxidation state of iron, would show similar r_2 relaxivity due to similarity of their magnetic moments. They might show very different r_1 relaxivities, however, due to their different surface chemistry and physics. Study on how iron oxidation state affects the magnetic and relaxivity properties of the nanoparticles, was another goal of this work.

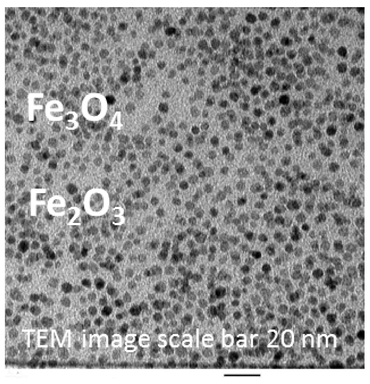
Materials and Methods

Magnetite nanoparticles in the size range of 3.2-7.5 nm were synthesized with high yields under variable reaction conditions using high temperature hydrolysis of the precursor iron(II) and iron(III) chelated alkoxide complexes in surfactant-free diethylene glycol solutions. The average sizes of the particles were adjusted by changing the reaction temperature and time, and by using sequential growth technique. Reaction products formed as shelf-stable colloids. In order to obtain γ-iron(III) oxide particles in the same range of sizes, diethylene glycol colloids of magnetite were oxygenated at room temperature. As-obtained colloids were characterized by DLS; powdery products obtained by coagulating them with oleic acid, were characterized by TEM, XRD, TGA, FTIR and magnetic measurements.

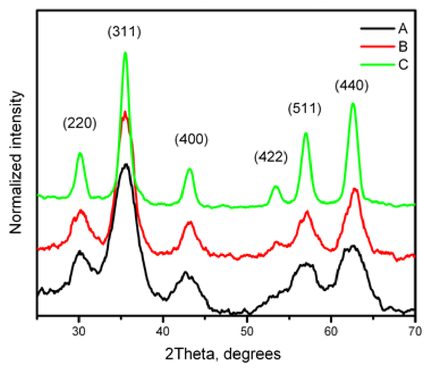
$$[Fe(Hdeg)_2] + 2[Fe(Hdeg)(deg)] + 4H_2O \rightarrow Fe_3O_4$$

$$Fe_3O_4 + O_2 \rightarrow Fe_2O_3$$

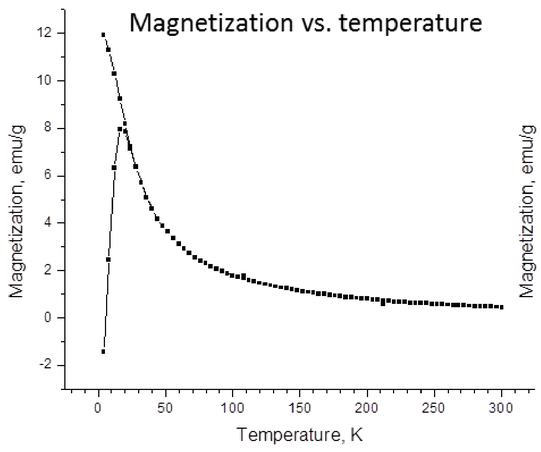
H_2deg = 



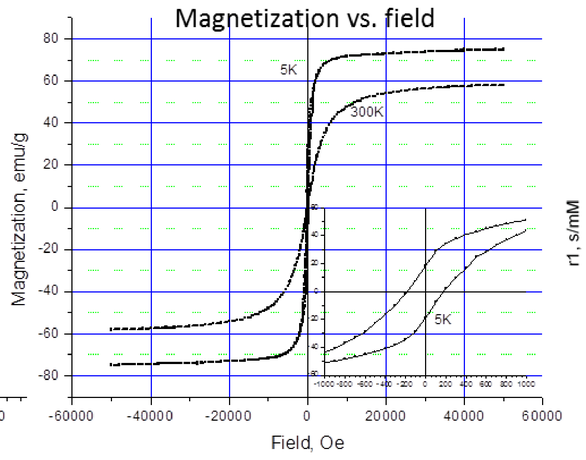
Powder X-ray diffractograms



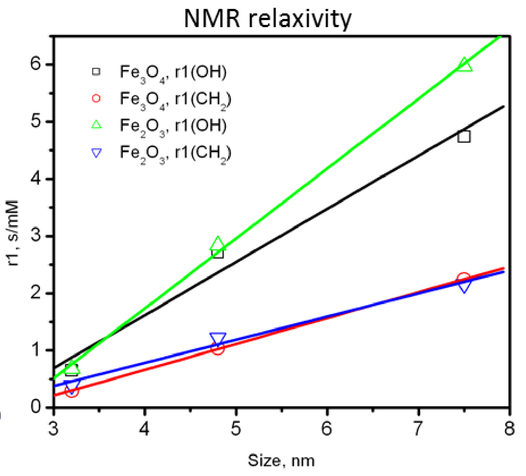
Magnetization vs. temperature



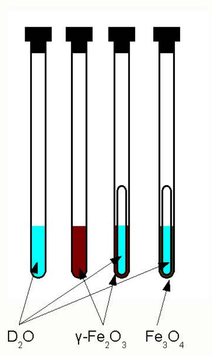
Magnetization vs. field



NMR relaxivity

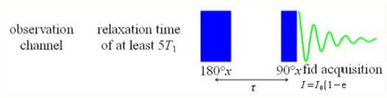


Relaxivity studies for synthesized nanoparticles



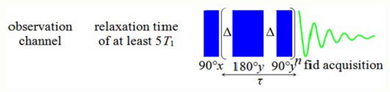
- In relaxivity measurements we are looking for solvent signal. In our case it is either water or DEG signals.
- We need deuterated solvents in order to lock spectrometers
- Spectrometers are very sensitive so we need limited amount of sample
- Coaxial tube is a solution for this purpose

Experiments for determination of *T1* amd *T2* relaxation times



$I = I_0(1 - e^{-\frac{\tau}{T1}})$

TRIR pulse sequence for determination of T1 relaxation time



$M = M_0(\frac{-\tau}{T2})$

CPMG (Carr-Purcell-Meiboom-Gil) experiment for determination of T2 relaxation time

http://chem.ch.huji.ac.il/nmr/techniques/other/t1t2/t1t2.html

Typical experiment in determining the relaxivity by measuring the relaxation time for signals of the solvent at a presence of variable amounts of magnetic material.

$I = I_0(1 - 2e^{(t/T1)})$

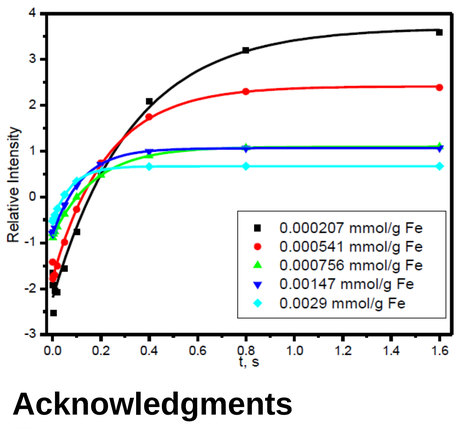
I – signal intensity

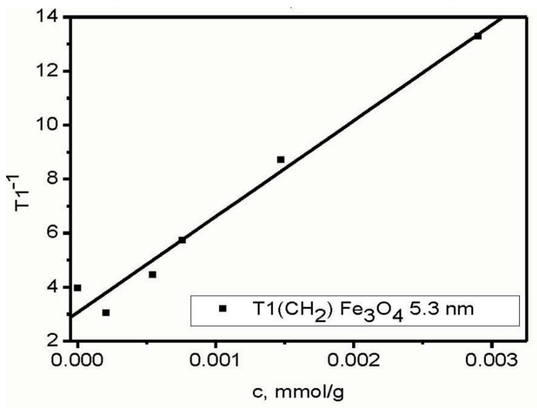
t – time

$1/T = 1/T_0 + r[Fe]$

T_0 – relaxation time for pure solvent ([Fe] = 0)

Slope determines the relaxivity r





Acknowledgments

The authors acknowledge the support by Louisiana Cancer Research Consortium and XU Cell and Molecular Biology Core for biological screening, and by the following grants:
National Institutes of Health: NIGMS-BUILD 8UL1GM118967-02, RCMI 2G12MD007595-06 and SC3GM088042 and National Science Foundation: LA-SIGMA EPS-1003897

Magnetization and relaxivity data in diethylene glycol

Sample	Magnetization, emu/g		r_1(OH)	r_1(CH_2)
	15 kOe	50kOe		
Fe_3O_4 3.2 nm	30	49	0.65	0.29
Fe_3O_4 4.8 nm	52	58	2.72	1.04
Fe_3O_4 7.5 nm	66	70	4.74	2.24
Fe_2O_3 3.2 nm	-	-	0.68	0.39
Fe_2O_3 4.8 nm	41	46	2.84	1.22
Fe_2O_3 7.5 nm	-	-	5.97	2.16

Relaxivity of γ-iron(III) oxide nanoparticles and magnevist in deuterium oxide

Sample	r_1	r_2	r_2/r_1
GdDTPA	4.81	3.84	0.80
Fe_2O_3 3.2 nm	3.00	23.75	7.92
Fe_2O_3 4.8 nm	3.52	28.26	8.03
Fe_2O_3 7.5 nm	10.8	204.2	18.91

The Results

The notable finding about magnetic properties of the synthesized nanoparticles was that γ-iron(III) oxide particles had ~ 20 % lower saturation magnetization than the magnetite particles of the same size. The NMR relaxivity studies revealed similar longitudinal (r_1) relaxivity values for magnetite and γ-iron(III) oxide and have shown that there is a linear relationship between r_1 values and particle size for both types of particles with the slope greater for OH-protons. The r_2 values are more strongly affected by the particle size than the r_1 values, and consequently, the r_2/r_1 ratios decrease with the particle size reduction. This makes smaller particles suitable candidates for positive contrast enhancing MRI agents. Based on magnetic and relaxivity properties, the γ-iron(III) oxide particles would be even better candidates for this role than the magnetite particles, as they are chemically more stable and consequently less toxic.