Characterization of Fe-Co ferrite nanoparticles for contrast generation and heat therapy in cancer

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INTRODUCTION.

Superparamagnetic iron oxide nanoparticles are widely used for generating tissue contrast with MRI because they are found to be less deterrent for organs in the human body [1,2]. Biocompatibility can be achieved further by appropriate coating (or encapsulation). The magnetic susceptibility of ferrite nanoparticles is much higher due to their novel magnetic property – i.e., their higher magnetic moment in the state of superparamagnetism – which increases water relaxivity significantly. Ferrite nanoparticles also have potential for cancer therapy because they can be heated by alternating RF fields [1,2]. Since diamagnetic resonances (e.g., water for ^{1}H MRI in temperature mapping or high energy phosphates for ^{31}P MRS in pH mapping) are susceptibility-shifted with ferrite nanoparticles, temperature and/or pH mapping with typical MRI/MRS methods become quite challenging. The goals of this investigation were to observe enhancement of the relaxivity by increasing the magnetic moment of Fe-Co mixed ferrites for their application as MRI contrast agents and then use a novel ultra-high speed 3D chemical shift imaging (CSI) method called **B**iosensor **I**maging of **R**edundant **D**eviation in **S**hifts (BIRDS), which requires that we detect protons emanating from a highly sensitive temperature/pH probe (e.g., $TmDOTP^{5-}$) itself, instead of the agent's effect on water proton relaxation times. We show encouraging in vitro results from a family of Fe-Co mixed ferrite systems which allow both temperature and pH mapping in the presence of these ferrite nanoparticles.

MATERIALS AND METHODS.

Nanaoparticles of Fe-Co mixed spinel ferrite with the composition of $Fe_{1-x}Co_xFe_2O_4$ in the range of $0 \le x \le 1$ (x = 0.2) were synthesized by using chemical co-precipitation with various agents. Nanoparticles were coated with biocompatible chitosan. In vitro characterization was achieved by X-ray diffractometer (XRD), superconducting quantum interference device (SQUID), and 9.4T MRI. Temperature and pH mapping was achieved with $TmDOTP^{5-}$ in conjunction with BIRDS at 9.4T [3].

Table 1. Characterization of Fe-Co nanoparticles.

Composition	Coprec. agent	g.s. (nm)	M_s (emu/g)	r_2 ($mM^{-1}s^{-1}$)
Fe_3O_4	NH_4OH	5.2	71.7	365
$Fe_{2.8}Co_{0.2}O_4$	NH_4OH	4.0	59.3	528
$Fe_{2.6}Co_{0.4}O_4$	NH_4OH	4.5	55.3	509
$Fe_{2.4}Co_{0.6}O_4$	NH_4OH	2.8	43.6	326
$Fe_{2.2}Co_{0.8}O_4$	NaOH	4.9	73.1	769
$CoFe_2O_4$	NaOH	5.7	65.0	353

RESULTS.

Material characterization of Fe-Co mixed spinel ferrite with the composition of $Fe_{1-x}Co_xFe_2O_4$ in the range of $0 \le x \le 1$ (x = 0.2) were carried out by XRD (using Mo Kα radiation), SQUID, and NMR, where an example for Fe_3O_4 is shown in Fig. 1. Grain size (g.s), magnetic moment (M_s), and water relaxivities (r_2) for all Fe-Co systems are presented in Tab. 1. Relaxivities of all the compositions were quite strong, although the grain size could be an important consideration with different co-precipitation methods utilized in nanoparticle synthesis. We then used $TmDOTP^{5-}$ in mixtures of Fe_3O_4 nanoparticles to see if BIRDS could be used to map both pH and temperature. Fig. 2 shows that accurate pH and temperature could be reported from the same compartments in which Fe_3O_4 nanoparticles were present.

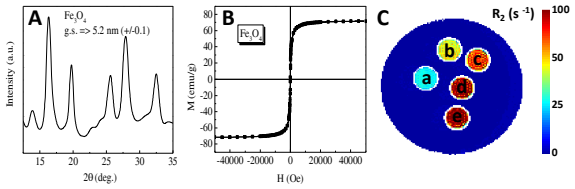

Figure 1. Characterization of Fe_3O_4 nanoparticles with (A) XRD, (B) SQUID, and (C) R_2 map by MRI image where (a) 0.055 (b) 0.11 (c) 0.16 (d) 0.22 (e) 0.27 mM.

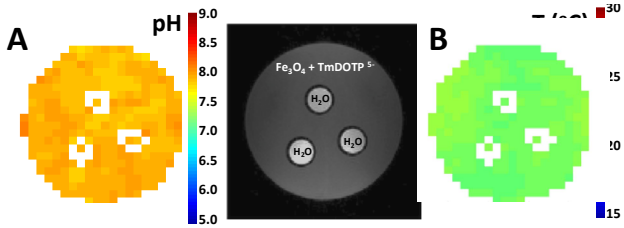

Figure 2. Ability to map (A) pH and (B) temperature in presence of Fe_3O_4 with $TmDOTP^{5-}$ as an agent for BIRDS.

DISCUSSION.

We characterized Fe-Co systems for MRI contrast and molecular imaging. XRD patterns demonstrated single-phase formation of spinel ferrite characterized by broadened peaks, which depicted ultra-small scale structure with grain sizes of ~5 nm. SQUID measurements of magnetization values were higher than 50 emu/g, thereby enabling high relaxivities which were confirmed by MRI measurements. Finally, we found that BIRDS in conjunction with temperature and pH probes like $TmDOTP^{5-}$ may allow molecular imaging of the MRI contrasted tissue, which is a significant step towards cancer theragnostics [4].

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