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Research articles

Nano-sized ferrite particles for magnetic resonance imaging thermometry

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ABSTRACT

Recently, we reported the application of magnetic particles as temperature sensors for use in magnetic resonance imaging thermometry (tMRI). In this novel method, the brightness of the magnetic resonance (MR) image changes with temperature due to a temperature-dependent local magnetic field inhomogeneity caused by the dipolar field of the magnetic particles. Ferrites are new and promising compounds for tMRI applications because of their biocompatibility and because their magnetic properties can be varied by changing composition. Earlier studies used micrometer sized ferrite particles in a proof-of-concept demonstration. However, such large particles cannot be administered intravenously for *in-vivo* use. In this report, we establish the use of nanoscale ferrite particles as temperature sensors for tMRI. Scanning transmission electron microscopy and X-ray diffraction demonstrate the synthesis of 210 nm $Co_{0.3}Zn_{0.7}Fe_2O_4$ clusters comprised of 10–30 nm crystallites. Temperature-dependent magnetization measurements reveal a Curie temperature of around 275 K. We conducted nuclear magnetic resonance (NMR) and MRI studies of samples with different concentrations of ferrite nanoparticles suspended in agar gel. The relative MR image intensity shows a near-linear temperature dependence. At concentrations as low as 0.12 g/L these ferrite nanoparticles provide sufficient image contrast to determine temperature changes with accuracy of ± 1.0 K at 310 K, bolstering the potential viability of this material for biomedical applications.

1. Introduction

The magnetic resonance imaging thermometry technique (tMRI) promises to be a valuable tool for medical professionals due to its ability to noninvasively create a detailed overlaid map of both temperature and tissue water proton density [1–3]. One promising aspect of tMRI is the potential to utilize traditional, in-place magnetic resonance imaging (MRI) scanners to collect such information, lowering the clinical cost of obtaining spatio-thermal data.

Elevated physiological temperature has long been used as an indicator of disease as fever represents a universal immune response [4]. For example, temperature increases have been used to diagnose both potentially lethal tissue malperfusion following surgery and other maladies such as peripheral neuropathy [5]. Further, a localized increase in temperature of 1.5° has been observed in growing tumors [6,7], suggesting temperature-mapping as a potential diagnostic tool. Accurately monitoring temperature is also necessary for safety purposes in MRI guided thermal ablation procedures (radio-frequency, laser, or focused ultrasound) where there exists a need to deliver high energy to a treated area while simultaneously protecting adjacent healthy tissue [8–10].

Currently, the most common method of determining temperature via MRI is by the phase shift of proton resonance frequency (PRF). This method is based on an approximately −0.01 ppm/°C temperature dependence in water proton chemical shift [11]. However, PRF suffers several drawbacks, such as sensitivity to both physiological movement [12] and unstable magnetic fields [13,14]. In addition, PRF also becomes impractical in the presence of adipose tissue [15–17].

We have previously reported the method of using micrometer size magnetic particles as exogenous MRI temperature contrast agents that can make temperature measurements more robust [18–20]. These particles, suspended in tissue-mimicking agar gel phantoms, exhibit a strong change in magnetization over the physiologically relevant temperature range (290–330 K), and as a result, introduce a temperature-

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dependent inhomogeneity in the local magnetic field. This inhomogeneity can then be measured in T_2^* weighted gradient-echo MR images [21,22]. A decrease of magnetic moment with increasing temperature causes regions with a higher temperature to appear brighter, generating temperature dependent contrast. However, the size of these particles lay outside of the physiologically tolerable range for the proper biodistribution [23,24]. This work demonstrates that magnetic nanoparticles, with their Curie temperature below body temperature, can also be used as MRI temperature contrast agents.

While any magnetic particles with strong thermal dependence of magnetic moment can serve as temperature sensors for MRI thermometry, ferrites represent a uniquely versatile class of magnetic materials due to the strong effects of chemical composition, crystallographic structure, and morphology on their magnetic properties [25–28]. Ferrite nanoparticles have already been employed as MRI contrast agents targeting the liver and spleen [24,29,30] and are also widely studied for other medical applications, such as hyperthermia therapy [30–34]. Cobalt ferrites have garnered attention due to their relatively high saturation magnetization [35,36]. In particular, the composition $Co_{0.3}Zn_{0.7}Fe_2O_4$ was chosen for this study due to an observed steep decline in magnetic moment near body temperature, which permitted accurate temperature measurement based on changes of brightness in T_2^* weighted MR images [37].

In this work, the initial results of employing $Co_{0.3}Zn_{0.7}Fe_2O_4$ ferrite nanoparticles as MRI contrast agents are presented. The nanoparticles were synthesized by hydrolysis of metallic salts in an aqueous solution. Scanning transmission electron microscopy (STEM), scanning electron microscopy (SEM) and X-ray diffraction (XRD) were used to determine size and the structural properties of the synthesized nanoparticles, while a Superconductive Quantum Interference Device (SQUID) magnetometer was used to perform non-spatial magnetic characterization over a wide temperature range. Nuclear Magnetic Resonance (NMR) and MRI systems were used to gather spatio-thermal data relevant to the influence of ferrite nanoparticles within tissue-mimicking phantoms. Collectively, these studies demonstrate that a low nanoparticle concentration produces the contrast in MRI images necessary for temperature determination with resolution higher than ± 1.0 K at 310 K.

2. Material and methods

Nanoparticles with the composition $Co_{0.3}Zn_{0.7}Fe_2O_4$ were synthesized based on a previously reported colloidal method [38,39]. Cobalt chloride hexahydrate ($CoCl_2{\cdot}6H_2O$, 98%), ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$, 97%), and anhydrous zinc chloride ($ZnCl_2$, 98%) were dissolved in 18 MΩ deionized water to make an amber-colored solution of 4.95 mM $CoCl_2{\cdot}6H_2O$, 11.6 mM $ZnCl_2$, and 33.0 mM $FeCl_3{\cdot}6H_2O$ with a pH of 2.1. Each synthesis was performed by heating 50 mL of a 0.25 M 1,6-hexanediamine (HMDA, 98%) solution of pH 11.9 to 353 K while stirring at 800 RPM using a magnetic stir bar. A 50 mL volume of the metal ion solution was added to the stirring HDMA solution using a syringe pump set to dispense at a rate of 2 mL/min, immediately precipitating dark-brown particles upon addition. The solution was stirred at 353 K for 4 h at a rate of 800 RPM (ending pH 11.0). Particles were isolated through retention of the pellet following centrifugation at $4800 \times g$ for 10 min. Washing was performed through iterative addition, mixing, and subsequent centrifugation ($4800 \times g$, 10 min) of 20 mL volumes of 0.25 M HMDA solution. To thermally degrade the remaining HMDA, the nanoparticles were dried and annealed at 1070 K under ambient atmosphere for 15 min.

Nanoparticle stoichiometric composition was verified using flame atomic absorption and energy dispersive x-ray spectroscopy (data not shown). X-ray diffraction measurements were carried out using Kα-Cu radiation in parallel beam configuration with a graphite diffraction grating monochromator. The average ferrite cluster size and distribution were determined using scanning electron microscopy. Scanning transmission electron microscopy was used for analysis of sizes of individual crystallites. Samples for STEM imaging were prepared by dispersing the ferrite particles in isopropanol and drop casting onto lacey carbon coated copper grids, which were subsequently dried at 150 °C for 1 h under ambient conditions. Imaging was performed at an electron acceleration of 200 kV.

The magnetic properties of the ferrite nanoparticles were studied using a SQUID magnetometer. Two samples were used for the measurements of the temperature dependence of magnetization; a 1.0 mg sample for measurements in an applied field of 3 T, and an 8.4 mg sample for low-field measurements (2–20 mT). The magnetic moment of the nanoparticles was measured in low fields using both zero field cooling (ZFC) and field cooling (FC) modes in the 4–350 K temperature range.

Measurements of the water proton NMR linewidth and relaxation times T_1 and T_2 were taken in a 3 T magnetic field as a function of temperature. Both reference (2% agar solution in deionized water) and sensitized (the same agar gel with embedded ferrite nanoparticles of 0.12 g/L concentration) phantoms were prepared. The inversion recovery and Carr Purcell Meiboom Gill (CPMG) methods were used to determine the relaxation times T_1 and T_2, respectively [40].

For each MRI temperature measurement, two phantoms (cylindrical tubes 10 mm in diameter and 80 mm long) were imaged; the first containing the reference sample of pure agar gel and the second contained agar gel with embedded ferrite nanoparticles. The bottom half of the second cylinder was filled with agar gel containing particles at concentration 0.24 g/L. After solidifying gel in ice water, the remaining space in the cylinder was filled with the gel having particle concentration of 0.12 g/L. The details of thermal control during MRI imaging are described in our previous paper [20].The gradient echo method (GEM, sensitive to the inhomogeneity of local magnetic fields) [41] was used with: axial slice orientation, 3 cm × 3 cm field of view, 0.47 mm/pixel in-plane resolution, 6 mm slice thickness, 100 ms repetition time (TR), 2.676 ms echo time (TE), and a radio-frequency flip-angle of 20°. Images were acquired in a research MR scanner with a 30 cm bore at an applied static field (B_o) of 3 T.

Particles were checked 12 months after the fabrication for stability. Dry particles were tested using SQUID for mass magnetization changes after storage at room temperature. Aqueous solution of particles in 0.12 g/L concentration was tested after storage at 4 °C by measurement of R_2^* relaxivity using pulse NMR.

3. Results and discussion

3.1. Structural characterization

The formation of a single crystal phase of inverse spinel ferrites was confirmed by XRD analysis, Fig. 1. The measured lattice constant a = 0.8419 nm agrees with values reported in the literature [42]. The observed Full Width at Half Maximum (FWHM) of the XRD peaks (see Fig. 1) allowed the determination of the average crystallite size of 13.2 nm using the Scherrer formula [43]. Ferrite nanoparticle crystallinity and size were further probed with STEM. Fig. 2**a and b** show STEM bright field images of ferrite nanoparticles at different magnifications. The images show agglomerates consisting of crystallites ranging in size from 10 to 30 nm. All the acquired STEM images allowed us to determine the crystallites size distribution, which can be fit with log-normal functions (see Fig. 2**c**). The acquired data indicates a trinomial distribution of crystallite sizes, with average crystallite sizes of 10.4 (± 1.0), 16.5 (± 3.4) and 27.3 (± 2.3) nm, where the number in brackets is the standard deviation for each population. The percentage of particles in each population is 24, 66 and 10, respectively. Such a size distribution will have a detrimental effect on magnetic behavior and clearly indicates that sample preparation needs further improvements to obtain monodisperse nanoparticle distribution. The analysis of STEM images, however, agrees with XRD analysis that predicted crystallite of 13.2 nm average size.