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# Nanoscale assembly of amine-functionalized colloidal iron oxide

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## ABSTRACT

We demonstrate a single-step facile approach for highly water-stable assembly of amine-functionalized $Fe_3O_4$ nanoparticles using thermal decomposition of Fe-chloride precursors in ethylene glycol medium in the presence of ethylenediamine. The average size of nanoassemblies is $40\pm1$ nm, wherein the individual nanoparticles are about 6 nm. Amine-functionalized properties are evident from Fourier transform infrared spectrometer (FTIR), thermal and elemental analyses. The saturation magnetization and spin-echo $r_2$ of the nanoassemblies were measured to be 64.3 emu/g and 314.6 $mM^{-1}\,s^{-1}$, respectively. The higher value of relaxivity ratio ($r_2/r_1 = 143$) indicates that nanoassemblies are a promising high-efficiency T2 contrast agent platform.

## 1. Introduction

Magnetic resonance imaging (MRI) is a powerful clinical tool for the non-invasive diagnosis and post-therapy assessment of variety of diseases. The MRI technique relies upon the relaxation of water protons that depends on the magnetic field, pulse sequence, heterogeneous distribution and surrounding environment of water in the organism [1,2]. The interpretation of the resulting MR image helps demarcate and identify most of the tissues. The contrast can be improved by using positive or negative contrast enhancers [3]; negative contrast agents induce a large shortening of the transverse relaxation time (T2) leading to a darkening of MR images, wherein the close contact of water molecules with positive contrast agent is reflected by a brightness that echoes the shortening of longitudinal relaxation time (T1).

Superparamagnetic iron oxide nanoparticles are the most promising T2 contrast agents for non-invasive *in vivo* monitoring of molecular and cellular events [4–6]. Most of the work in this area has been focused on multi-step surface functionalization of superparamagnetic iron oxide nanoparticles for MRI applications [5–8]. Recently, monodispersed magnetic nanoparticles, nanoassemblies (MNNA) made up of numerous superparamagnetic nanoparticles are attracting considerable interest because of their potential applications in MRI; iron oxide core of individual superparamagnetic nanoparticles in the nanoassembly becomes more efficient at dephasing the spins of surrounding water protons and hence enhances T2 relaxation time [9–11]. Of late, advances in chemical synthesis have enabled the preparation of high-quality functionalized nanoassemblies of tunable (size and shape) nanoparticles. This can lead to artificially enhanced relaxation properties generated by the accumulative interparticles interaction. Thus, self-aggregation or self-assembly through spatial arrangement of nanoparticles as building blocks is the fundamental mechanism by which different nanoparticle assembly motifs or even closed packed ordered structures are formed in materials. The forces that controlled the assembly are determined by competing noncovalent intramolecular or intraparticulate interactions such as electrostatic interaction [12], hydrogen bonding [13], van der Waals [14] and dipole–dipole interactions [15]. Thus, well-defined ordered structures obtained through the assembly of nanocrystalline building blocks provide new opportunities for optimizing, tuning and/or enhancing the properties and performance of the materials.

Here, we demonstrate an environmentally and economically preferable one-step green chemistry approach for synthesizing highly water-stable $Fe_3O_4$ nano-colloidal assemblies with enhanced T2 contrast properties as compared to commercially available contrast agent. Specifically, superparamagnetic amine-functionalized $Fe_3O_4$ MNNA were produced by thermal decomposition of the Fe-chloride precursors in biocompatible

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ethylene glycol medium in the presence of ethylenediamine (EDA) molecules.

## 2. Materials and methods

All chemicals are of analytical grade and used as received. In a typical synthesis of amine-functionalized $Fe_3O_4$ nanoassemblies, 1 g of Fe-chloride precursors ($Fe^{2+}/Fe^{3+} = 1{:}2$), 2 g of sodium acetate and 7 ml ethylenediamine were added to ethylene glycol (30 ml), and stirred vigorously by a magnetic stirrer at 70 °C to obtain a clear homogeneous golden yellow coloured mixture. This reaction mixture was transferred into a round bottom flask and temperature was slowly increased to 197 °C under reflux, and reacted for another 6 h. The black-coloured precipitates were obtained by cooling the reaction mixture to room temperature and then thoroughly rinsed with water to remove the solvent and by-products. During each rinsing step, samples were separated from the supernatant using a permanent magnet.

X-ray diffraction (XRD) pattern was recorded on a Philips powder diffractometer PW3040/60 with Cu K$\alpha$ radiation. The electron micrographs were taken by Hitachi HF 2000 transmission electron microscope (TEM) for particle size determination. The infrared spectra were recorded in the range 2000–400 $cm^{-1}$ on a Fourier transform infrared spectrometer (FTIR, Magna 550 and Nicolet Instruments Corporation, USA). The thermogravimetric analysis (TGA) was performed by TA Instruments SDT Q600 analyzer. The elemental analysis was carried out by FLASH EA 1112 series CHNS (O) analyzer (Thermo Finnigan, Italy). The concentration of metal ions in the samples was obtained by ICP–AES (8440 Plasmalab; Labtam, Australia). The field-dependence magnetization ($M$ vs. $H$), and temperature-dependence magnetization under zero-field cooled (ZFC) and field-cooled (FC) conditions in an applied field of 500 Oe were measured by Quantum Design PPMS. The Curie temperature ($T_C$) was determined in an applied field of 100 Oe using vibrating sample magnetometer (VSM, Model 7410; Lake Shore).

The T1 and T2 relaxation times (s) of the samples were measured for different concentrations of $Fe_3O_4$ nanoassemblies using a 3 T clinical MRI scanner (General Electric Healthcare, USA). The different concentrations of amine-functionalized $Fe_3O_4$ samples were prepared by diluting them with milli-Q water (resistance 18.2 M$\Omega$). T1-weighted images were obtained with a multiple inversion recovery SE sequence (TR 2200 ms; TI 2100, 800, 400, 200 and 50 ms; matrix 512 × 512) and T2-weighted images were obtained with an FSE sequence. The $r_1$ and $r_2$ relaxivities ($mM^{-1}\,s^{-1}$) were calculated from the slope of the linear plots of 1/T1 and 1/T2 vs. Fe ion concentrations.

## 3. Results and discussion

The XRD pattern of amine-functionalized $Fe_3O_4$ MNNA samples (Fig. 1a) reveal single-phase $Fe_3O_4$ inverse spinel structure. The presence of sharp and intense peaks confirmed the formation of highly crystalline nanoparticles. Fig. 1b shows the TEM image of amine-functionalized $Fe_3O_4$ MNNA (inset: magnified TEM image of a single $Fe_3O_4$ MNNA). The electron micrographs show that spherical nanoassemblies are well defined, discrete and porous in nature. Each 'nanosized sphere' of an average size 40 ± 1 nm is made up of three-dimensional (3-D) spatially connected nanoparticles of average diameter of about 6 nm. These fine nanoparticles are presumably assembled spontaneously into porous spherical superstructure to minimize their surface energy. The formation of such spherical nanoassemblies may be dependent on the collective behavior of nanoparticles and the intermolecular forces existing between them.

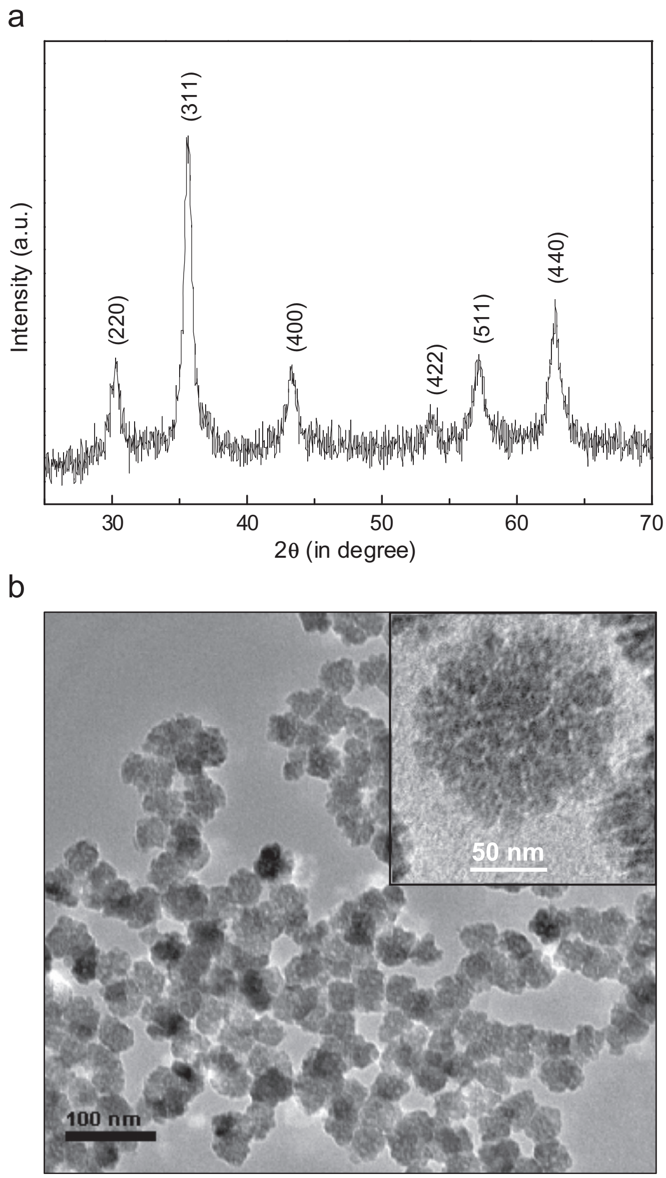

**Fig. 1.** (a) XRD pattern of amine-functionalized $Fe_3O_4$ MNNA samples (position and relative intensities of all diffraction peaks well matched with those from the Joint Committee on Powder Diffraction Standard (JCPDS) card 75-1609 of magnetite) and (b) TEM micrographs of amine-functionalized $Fe_3O_4$ MNNA samples (inset: magnified TEM image of a single $Fe_3O_4$ MNNA).

Fig. 2 shows the FTIR spectra of (a) ethylenediamine and (b) amine-functionalized $Fe_3O_4$ MNNA samples. The IR bands observed at around 588 $cm^{-1}$ can be ascribed to the Fe–O vibrational mode of $Fe_3O_4$. The vibrational modes attributed to the free amine group such as $NH_2$ scissoring at 1595 $cm^{-1}$, C–N stretching at 1320 $cm^{-1}$ and NH wagging at 932 $cm^{-1}$ are clearly observed in the FTIR spectrum of amine-functionalized $Fe_3O_4$ nanoassemblies with a slight shift in their band positions.

Fig. 3 shows the TGA plot of amine-functionalized $Fe_3O_4$ MNNA samples. A weight loss of about 2.9% below 230 °C can be ascribed to the removal of diamine-modified glycol molecules attached to the surface of $Fe_3O_4$ MNNA and entrapped solvent from the porous network of nanoassemblies. The weight loss of about 2.3% between 230 and 310 °C may be associated with the transformation of $Fe_3O_4$ to $\gamma$-$Fe_2O_3$ phase upon thermal treatment [16].