



Research articles

One-step microwave-assisted synthesis of water-dispersible Fe₃O₄ magnetic nanoclusters for hyperthermia applications



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ABSTRACT

To realize magnetic hyperthermia as an alternate stand-alone therapeutic procedure for cancer treatment, magnetic nanoparticles with optimal performance, within the biologically safe limits, are to be produced using simple, reproducible and scalable techniques. Herein, we present a simple, one-step approach for synthesis of water-dispersible magnetic nanoclusters (MNCs) of superparamagnetic iron oxide by reducing of Fe₂(SO₄)₃ in sodium acetate (alkali), poly ethylene glycol (capping ligand), and ethylene glycol (solvent and reductant) in a microwave reactor. The average size and saturation magnetization of the MNC's are tuned from 27 to 52 nm and 32 to 58 emu/g by increasing the reaction time from 10 to 600 s. Transmission electron microscopy images reveal that each MNC composed of large number of primary Fe₃O₄ nanoparticles. The synthesised MNCs show excellent colloidal stability in aqueous phase due to the adsorbed PEG layer. The highest SAR value of 215 ± 10 W/g_{Fe} observed in 52 nm size MNC at a frequency of 126 kHz and field of 63 kA/m suggest the potential use of these MNC in hyperthermia applications. This study further opens up the possibilities to develop metal ion-doped MNCs with tunable sizes suitable for various biomedical applications using microwave assisted synthesis.

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1. Introduction

Colloidal magnetic nanostructures have applications in photonics, Li-ion battery, catalysis, chemical sensors, and various biomedical applications including drug delivery, magnetic separation, contrast agents in magnetic resonance imaging, drug delivery, cellular imaging, and hyperthermia [1–11]. Among different magnetic nanostructures, iron oxide, particularly Fe₃O₄ and γ-Fe₂O₃, has been considered as a model system in hyperthermia because of their superior properties such as superparamagnetism, chemical stability, and biocompatibility [8]. Magnetic fluid hyperthermia is a promising alternate cancer therapy to the existing chemotherapy and radiotherapy [9,12]. In hyperthermia, magnetic nanocrystals acts as heat generators by Néel (spin flip) or Brownian (particle rotation) relaxation or both under the rapid changes in the external alternating current (AC) magnetic field [12–14]. The heat generation is assessed in terms of specific absorption rate (SAR), which depends strictly on the quality of the nanocrystals, the specific heat capacity of the base fluid, strength of the applied magnetic field and frequency [15–18]. Indeed, biological safety limit, i.e., 4.8 × 10⁹ A m⁻¹ s⁻¹, restricts the upper range of frequency and

magnetic fields [14]. Thus, researchers have been in pursuit of magnetic nanostructures with superior properties to achieve the desired heating ability even at lower fields and frequencies.

In recent years, advances in colloidal nanoparticle syntheses have opened up new possibilities to tailor the nanomaterials of different morphologies either by a direct one-pot [19,20] or a secondary growth process [21]. For biomedical applications such as drug delivery and cellular imaging, bigger sized iron oxide nanoparticles of comparable sizes of biological entities are essential. Particles with lower surface spin disorder, higher crystallinity, and higher magnetic moments are essential in achieving superior heating abilities. The other factors affecting the heating efficiency are the surface anisotropy, shape anisotropy, polydispersity, remnant magnetization, susceptibility and coercivity. In fact, a major hurdle in utilizing discrete nanoparticles of bigger size (>28 nm for Fe₃O₄) nanoparticles is that they become ferromagnetic where magnetic agglomeration is significant and the particles are prone to settling. To circumvent these issues, magnetic nanoclusters made-up of discrete smaller sized nanoparticles are desirable because of their ability to act as multifunctional surfaces and their soft magnetic nature. Considering the above aspects, efforts were made to prepare magnetic nanoclusters (MNCs) with good control over the size and composition [22–26]. Discrete magnetic nanocrystals were obtained by thermal decomposition methods

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and later, they were forced to aggregate in a controlled manner and embedded in polymer matrix also known as multi-core nanoparticles with suitable surface modification for different payloads [27]. For example, Teresa et al. successfully developed the colloidal methods to prepare roughly 200 nm size spherical magnetic nanobeads by using individual iron oxide nanoparticles with different shapes (spherical and highly interacting cubic-shaped nanocrystals) and studied their heating ability and relaxivity relevant for magnetic hyperthermia and magnetic resonance imaging applications [27–29]. Instead of two step approach, several research groups have focussed on the synthesis of magnetic nanoclusters which consist of oriented aggregates of nanoparticles with tunable sizes, without compromising superparamagnetic behaviour by the one-step polyol synthesis using autoclave [1,23,30,31]. For example, Li's group developed a solvothermal reduction method to obtain hydrophilic and single crystalline MFe_2O_4 , (where M could be Mn, Co or Zn) magnetic microspheres of size 200–800 nm that are similar to protein molecules [32]. Similarly, Yin et al. designed a chemical method to synthesize colloidal clusters size ranging from 30 to 180 nm, which was composed of many single magnetite crystallites approximately 10 nm in size [33,34]. Recently, Wang et al. prepared Fe_3O_4 nanoclusters of 168 nm size with spherical shape using sodium citrate in a mixed solvent of diethylene glycol and ethylene glycol [30]. The quantity of water and the solvothermal reaction temperature, and exposure time seems to play vital role in the formation of the iron oxide phase and shape [35,36]. Gazeau group used mixed polyols to produce maghemite nanoflowers with tunable size (20 to 55 nm) by changing the reaction time (0.5 to 24 h) at 220 °C [37]. Interestingly these nanoflowers show very high heating ability ($1992 \pm 34 \text{ W}\cdot\text{g}^{-1}$) among the nanoclusters reported so far. The polyol synthesis method often involves extreme reaction conditions such as a long reaction time (nearly 6–48 h), and high pressure to obtain ~ 100 nm size MNC [32,33]. Furthermore, there are very few reports on microwave-assisted polyol synthesis to obtain MNCs of less than 100 nm size [35,38–40]. Herein, we present an improved synthesis method to produce water-soluble Fe_3O_4 nanoclusters with tunable sizes less than 100 nm using cost-effective ferric sulfate with ethylene glycol (EG) as a solvent in the presence of anhydrous sodium acetate and polyethylene glycol (PEG) as capping agent. Further, the water-dispersible Fe_3O_4 nanoclusters are characterised and examined for their performance in magnetic fluid hyperthermia application.

2. Experimental method

2.1. Materials

Ethylene glycol (EG) (Merck, 99%), ferric sulphate (Loba chemie, 98%), sodium acetate (NaAc) (Sigma Aldrich, 99%), polyethylene glycol (PEG) (Fulka Analytical, molecular weight: 5000–6000 Da), Milli-Q water (with resistivity of 18.2 $M\Omega\cdot\text{cm}$; Millipore), and acetone (Merck, AR grade) were used. All the chemicals were used as purchased without further purification.

2.2. Synthetic procedure

MNCs were prepared by following the previous method with suitable modifications [41]. In a standard flask, ferric sulfate (1 M) was dissolved in 100 mL of EG and sonicated for few minutes to get a clear, deep-brown solution that was kept separately. 5 mL of 1 M Fe^{3+} stock solution, 5 g (0.4 M) of NaAc, 1.25 g of PEG, and 45 mL of EG were mixed together in a 100-mL beaker. This mixture was sonicated using horn sonication (Vibra Cell, Sonics) for 15 min, operated at 130 Watt and 120-kHz frequency setting at 30% amplitude to get a clear-brown solution. Nearly 10 mL of this stock solu-

tion was transferred into a glass reaction flask with magnetic stirring, pressure cap and placed in a microwave digestion system (Monowave 300 from Anton-Paar). The microwave digestion system was equipped with an automatic temperature control system, which allowed continuous monitoring and control of the internal temperature and pressure of the reaction systems. The temperature of the system was raised rapidly (10 s) to 200 °C and incubated at different reaction times (10 to 600 s.) and cooled down to room temperature. The black colloidal suspension was washed couple of times with excess amount of water and acetone mixture. At each cycle of cleaning, particles were collected using a permanent magnet and redispersed in water and sonicated for 10 min.

2.2.1. X-ray diffraction

Powder X-ray diffraction (XRD) pattern of the MNCs was collected using a Rigaku Ultima IV diffractometer equipped with $Cu K\alpha$ radiation source operating at 40 kV/30 mA. The measurements were collected in the range of 25–65° (2θ) with a scan rate of 2° per minute and a step size of 0.02°. The crystallite size (d) was estimated using the Scherer's equation: $d = k\lambda/\beta\cos\theta$, where $k = 0.89$ and β is the full width at half maximum of the highest peak in the XRD pattern.

2.2.2. Vibrating sample magnetometer

Hysteresis loop was recorded at room temperature in the applied field range of ± 15 kOe using a vibrating sample magnetometer (Lakeshore VSM 7410).

2.2.3. Hydrodynamic size

Dynamic light scattering measurements were done using Malvern nano ZS equipped with a 4-mW He–Ne laser operating at 632 nm. Hydrodynamic size and zeta potential were performed on optically clear samples filled with disposable, folded capillary cells (DTS-1070), setting the refractive index (1.33) and viscosity as 0.8869 cP at 25 °C. Three independent measurements were made with automatic duration at each time.

2.2.4. Thermogravimetric analysis–differential scanning calorimetry

Thermal stability of the nanoclusters was studied by simultaneous thermogravimetric analysis–differential scanning calorimetry (TGA–DSC) using TGA–DSC-1, 1100 LF (Mettler Toledo). The empty reference pan and sample pan were placed on top of the microbalance and heat treatment was carried out in the temperature range of 30–1000 °C at the rate of 10 °C/min under the mixture of argon and oxygen with a continuous flow rate of 30 mL/min.

2.2.5. Fourier transform infrared spectroscopy

ABB Bomem MB 3000 Fourier transform infrared spectroscopy (FTIR) spectrometer was used to probe the surface fictionalization of MNCs in the wave number range of 480–3600 cm^{-1} . For each scan, transparent pellets were prepared by grinding few milligrams of sample along with KBr powder (1.5 wt%) followed by hard pressing.

2.2.6. Transmission electron microscopy

Transmission electron microscopy (TEM) was carried out to study the morphology and size distribution of MNCs using JEOL 2011. TEM instrument operated at an accelerating voltage of 200 kV. Dilute MNCs in ethanol medium were drop-casted on top of the carbon-coated copper grid and dried at room temperature before analysis.

2.2.7. Hyperthermia measurements

High-frequency induction heating system (Fives Celes, France) equipped with water-cooled electrolytic copper heating coils of 50 mm diameter and 6 turns was used for hyperthermia measure-

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