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Evaluation of magnetic heating of asymmetric magnetite particles

Xin Yao [a], Kairat Sabyrov [b], Todd Klein [c], R. Lee Penn [b], Timothy S. Wiedmann [d,*]

[a] School of Chemistry and Chemical Engineering, University of Chinese Academy of Sciences, Beijing, PR China
[b] Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, United States
[c] Department of Electrical Engineering, University of Minnesota, Minneapolis, MN 55455, United States
[d] Department of Pharmaceutics, University of Minnesota, Minneapolis, MN 55455, United States

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ABSTRACT

Characterization and theoretical description of relatively large (> 100 nm), asymmetric magnetic particles remain of interest particularly for applications to the mechanical damage of cells. In this work, we have examined the properties of three types of magnetite, Fe_3O_4, particles that were prepared by hydrogen reduction of hematite, α-Fe_2O_3. Transmission electron microscopy was used to measure the size and aspect ratio (AR), which were 1.8, 3.4 and 6.6, and all displayed magnetic hysteresis with corresponding saturation magnetization values of 65, 47, and 26 emu/g, respectively. With application of an alternating magnetic field to low concentrations, the temperature increased linearly with time, and the specific loss power (SLP) increased with increasing aspect ratio with values of 11.8, 24, and 26.8 W/g. The SLP increased linearly with the square of the applied magnetic field at low concentrations, but deviations were noted for high concentrations of the 2.4 and 6.6 AR particles. SLP was also dependent on frequency, but the functional relationship was not reliably determined. In consideration of the possible heating mechanisms, none provided a satisfactorily explanation for all types of particles. While these particles are not satisfactory for magnetic hyperthermia, they may have promise for causing cell death by magnetically inducing the particles to physically rotate or vibrate.

1. Introduction

The currently approved medical applications of magnetic nanoparticles (MNPs) include a contrast agent for MRI and induction of hyperthermia for the treatment of testicular cancer [1–5]. However, the potential of such particles is expansive, and most current efforts have been directed towards the use of iron oxide particles for site specific cancer detection and therapy [3]. MNPs are typically composed of small crystallites (< 100 nm), consisting of a single magnetic domain [6]. With an applied magnetic field, the induced magnetization is reversible, which is characteristic of superparamagnetic behavior [7, 8]. The small size and associated random diffusion also creates a fluctuating magnetic field [9]. This in turn can cause rapid relaxation in surrounding protons, which makes MNPs effective contrast agents for MRI. With the application of an alternating magnetic field, MNPs undergo heating through Brownian relaxation and/or Néel relaxation [1, 10]. Compared with larger sized magnetic particles, MNPs offer a greater potential for medical applications because of the high heat production per mass of particles [6, 7, 11]. This heat generation is sufficient to increase the temperature in vivo and thereby achieve cell death, which is referred to as magnetic hyperthermia and is exploited in the treatment of testicular cancer [2].

Recent studies with aggregates of iron oxide spherical and asymmetric shaped nanoparticles indicate that an alternative mechanism exists for inducing cell death [12, 13]. Here, physical rotation of the particles appears to cause mechanical disruption of the spatial distribution of biological molecules. This either results in catastrophic failure in the cell with either immediate death, presumed through cell membrane damage, or delayed death, through the process of apoptosis [12]. This mechanism offers a number of potential advantages over magnetic hyperthermia. In principle, it may be possible to induce cell death by introducing a single particle or aggregate into a cell, which would dramatically decrease the required mass of iron oxide to achieve therapeutic efficacy. In addition, inducing cell death with a single particle or aggregate overcomes the spatial limitation associated with magnetic hyperthermia, which requires a large number of particles distributed in a much larger tissue region [1]. That is, the effective hyperthermia requires introducing a sufficient concentration of particles in a sufficiently large volume, and failure to achieve these requirements results in heat input that is insufficient to increase in temperature.

* Correspondence to: Department of Pharmaceutics, University of Minnesota, 308 Harvard St. SE Minneapolis, MN 55455, United States. Fax: +1 612 626 2125.
E-mail address: wiedm001@umn.edu (T.S. Wiedmann).

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In characterizing the thermal response of magnetic particles, most have examined the nearly spherical shapes of magnetite that are obtained from the precipitation a 2:1 mol ratio of ferric and ferrous salts with base [14]. Rosenswieg [10] developed the theory for heat production where the particles are assumed to undergo Néel (τ_N) and Brownian relaxation (τ_B) in parallel; the magnitude of each contribution is a function of the particle size. This has been experimentally verified by a number of laboratories as reviewed by Deatsch and Evans [7]. While the properties of asymmetric particles have been explored to some extent, the complexity arising from the intrinsic heterogeneity of the larger sized particles precludes the assumption that they consist of a single magnetic domain [8, 15–17]. This in turn makes the magnetic susceptibility difficult to characterize as it theoretically depends on the orientation of the magnetic domains within the particle with respect to the applied magnetic field. The orientation in turn depends on the magnitude of the applied field as well as the frequency in the case of applying an alternating magnetic field. The larger sized particles are not strictly superparamagnetic as hysteresis becomes evident in the measured induced field as a function of the applied field. This also introduces another mechanism of heating referred to as hysteresis loss [1].

Characterization and theoretical description of relatively large (>100 nm), asymmetric magnetic particles remain of interest particularly for applications to the mechanical damage of cells. For these goals, achieving uniformity is important, particularly in a scaled manufacturing setting, which would be required in preparing materials for clinical applications. In this work, we have examined the properties of magnetite particles, Fe_3O_4, that were prepared from reduction of hematite, α-Fe_2O_3. The advantage of this approach is that hematite is the most stable state of iron oxide at STP and therefore amenable to shape altering additives during crystal growth [18]. In this way, extremely uniform particle distributions can be produced on a large scale with an equally elegant means available for the controlled hydrogen reduction to magnetite. Here, three sets of uniform particles were prepared and characterized; thereafter, the heat generation was measured as a first step to characterize these systems. Ultimately, it is hoped that such particles can be used to induce cell death by simple rotation or vibration rather than through the mechanism of hyperthermia.

2. Materials and methods

2.1. Materials

Iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) was purchased from Fluka, and sodium phosphate monobasic was purchased from Maillinckrodt. Water used in these experiments was deionized and distilled.

2.2. Synthesis of asymmetric αFe_2O_3 nanoparticles

For the nanoparticle synthesis, 0.271 g $FeCl_3$ was placed into a 100 mL round bottom flask, and 50 mL H_2O was added. After $FeCl_3$ dissolved completely, 50, 100 or 200 μL of 0.1125 M NaH_2PO_4 was added into the flask [18]. The flask was placed into the pre-heated glycerol bath, and the temperature was adjusted to keep the solution at just above the boiling point, which fell in the range of 100 °C to 105 °C. The reaction was continued for 2–7 days with longer times required for the larger particles and completion evident by the formation of an opaque, loose precipitate.

2.3. Reduction of αFe_2O_3 to Fe_3O_4

A 50 ml volume of the above hematite particle dispersion was centrifuged, and the pellet was washed three times with water. The final pellet volume was adjusted to 5 mL and 100 mg of 50 nm silica particles was added. The dispersion was quantitatively transferred to a 7 mL Coors reaction boat with water and dried in a convection oven at about 110 °C. The reduction was carried out at 340 °C with a hydrogen gas flow rate of 1 mL/min, which resulted in a gray-black powder. The silica was removed from the Fe_3O_4 nanoparticles by dispersing the powder in a solution of 10 mL concentrated aqueous potassium hydroxide and 1 mL ethanol and sonicating for 5 min in a bath sonicator. Following magnetic separation, the nanoparticles were washed twice more with the same solution and then equilibrated overnight at room temperature. After pelleting and washing with water, the jet-black dispersion of nanoparticles was suspended in water.

2.4. Magnetic particle characterization

The hydrodynamic particle size distribution in water was determined by dynamic light scattering using a Delsa™ Nano C Particle Analyzer (Beckman, Brea, CA). The measurement was performed at 25 °C and the mean hydrodynamic diameter was calculated based on size distribution by weight, assuming a log-normal distribution.

The phenanthroline iron assay was used to determine the iron content of the particles [19]. The nanoparticles were first dissolved in 12 N hydrochloric acid and then diluted with distilled water to obtain a final acid concentration of 0.2 N HCl. To the acid solution of nanoparticles, 200 μl of each of the following was added sequentially: 10 mg/ml ascorbic acid, 1.2 mg/ml 1,10 phenanthroline, 22.4 mg/ml potassium hydroxide, 123 mg/ml sodium acetate and water. The absorbance was measured at 490 nm using a microplate reader (EL × 800 Absorbance Microplate Reader, Biotek, Winooski, VT). Ferric chloride (hexahydrate) and ferrous chloride solutions in 0.2 N hydrochloric acid were used as standards with a 0.2 N HCL blank.

Transmission electron microscopy (TEM) of the NPs was performed on a JEOL JEM-1210 transmission electron microscope (Peabody, MA). A drop of an aqueous dispersion of the particles was placed on a Formvar 200 mesh copper grid (Ted Pella Inc. Redding, CA) and allowed to air-dry before imaging. Diameters were measured from different TEM images using ImageJ software.

The magnetic properties were determined by placing a known volume of the particle dispersion on a Kimwipe, which was inserted into a plastic straw. The sample was placed in a vibrating sample magnetometer (Micromod Model 3900, Princeton, NJ) operating at room temperature. Magnetization curves were recorded in magnetic fields ranging from -1 T to 1 T, at increments of 0.005 T. The remanence and coercivity were instrumentally provided parameters. The saturation magnetization was estimated from the plateau value measured at high field and normalized to obtain the saturation magnetization per gram of magnetite. The energy density per gram was estimated from the area within the hysteresis loops applying the trapezoidal rule and normalizing by the mass.

2.5. Heating measurements

For the heating experiments, various amounts of MNPs were dispersed in 1 ml water and placed at the center of a three turn radiofrequency coil (41.5 mm diameter) that generated the AC magnetic field (1 kW Hotshot, Ameritherm Inc., NY). The temperature of the suspending media was measured using a fluoro-optic thermometry system (Luxtron 3100 thermometer, Luxtron Inc., CA). Experiments were carried out at room temperature in triplicate with varying concentration, magnetic field strength and frequency.