Materials Science and Engineering C 58 (2016) 187–193

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Ferrimagnetic nanocrystal assemblies as versatile magnetic particle hyperthermia mediators

D. Sakellari [a,*], K. Brintakis [a,b], A. Kostopoulou [b], E. Myrovali [a], K. Simeonidis [a], A. Lappas [b], M. Angelakeris [a]

[a] Department of Physics, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece
[b] Institute of Electronic Structure & Laser, Foundation for Research & Technology, Hellas, Vassilika Vouton, 71110 Heraklion, Greece

ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form 14 June 2015
Accepted 12 August 2015
Available online 15 August 2015

Keywords:
Magnetic nanoparticles
Magnetic hyperthermia
Multi-core nanoclusters

ABSTRACT

Colloidal nanocrystal assemblies (nanoclusters), consisting of 13 nm iron oxide nanocrystals, were synthesized in various sizes (45–98 nm), and were investigated as heating mediators for magnetic particle hyperthermia. The colloidal nanocrystal clusters show enhanced heating efficiency in comparison with their constituent primary iron oxide nanocrystals due to collective magnetic features. The fine tuning of intra-cluster magnetic interactions results to the domination of the hysteresis losses mechanism over the relaxation loss heating contributions and eventually to a versatile magnetic particle hyperthermia mediator.

1. Introduction

Magnetic nanoparticles have attracted considerable attention in biomedical applications as Magnetic Resonance Imaging (MRI) contrast agents, drug delivery vehicles and heating mediators in Magnetic Particle Hyperthermia (MPH) [1–4]. The ease and cost efficiency of fabrication as well as their biocompatibility have established iron oxide nanoparticles as an important family of nanomaterials for biomedical applications [5,6]. Magnetic nanoparticles can be categorized by their size (total diameter D) and their blocking temperature (T_B), which is defined for a given measurement time and measuring technique, [7] as the characteristic temperature in which a magnetic transition from superparamagnetic (SPM) to ferro(i)magnetic (FM) state is observed. Up to date, numerous efforts on synthesis of novel superparamagnetic nanosystems have been extensively explored, while alternate routes for nanoparticles of ferro(i)magnetic state are also of growing interest [8,9].

When magnetic nanoparticles are exposed in an alternating magnetic field (AC), different mechanisms produce heat at the surrounding regions. In the SPM nanoparticles the heat is mainly generated from Néel (related to the fluctuation of magnetization through energy barrier) and Brown (related to the rotation of the entire nanoparticle in the fluid) relaxation mechanisms [10]. Within the ferro(i)magnetic regime the heat dissipation is mainly interconnected to the hysteresis losses [9]. In the multi-domain case, such an effect arises either from the domain wall motion or the reorientation in the presence of the externally applied field. Specifically, in the single domain state the main loss mechanism is due to the coherent rotation of all atomic magnetic moments [11].

Although various commercial ferrofluids exist already on the market of biomedicine, a worldwide scientific effort is going on further increasing the heating efficiency in nanosystems. Heating response of magnetic nanoparticles depends on intrinsic parameters like particle size, morphology and magnetic characteristics (saturation magnetization and coercivity) as well as on extrinsic parameters like the applied AC magnetic field (frequency and amplitude) [12,13]. Ideally, in order to maximize thermal response of SPM nanoparticles one should either utilize SPM nanoparticles with Néel relaxation time equal to the applied field period (1/f) or FM nanoparticles with anisotropy field matching the applied field amplitude [14]. The heating performance of a nanosystem is expressed by the specific loss power (SLP) value, a gauge of the heat conversion efficiency which has to be maximized. The strategy for enhancing SLP is crucial since higher SLP results in better efficiency with a lower dosage level of nanoparticles and milder magnetic field conditions. The side-effects expressed by the 3Ds (Dose, Dimensions and Durability) require carefully addressing during the design of an effective system for such applications. The SLP index is usually proportional to the saturation magnetization of nanoparticles (M_s) while inversely proportional to the size distribution of the nanoparticles (σ). In addition it exhibits a maximum value at a certain particle size (D) and magnetic anisotropy constant (K_{eff}) [15].

Despite the unceasing efforts to achieve the optimum parameters [13,14], such as their size and shape, [16,17] lately there is a tendency to enhance the magnetic profile of hyperthermia agents using other approaches. One such approach is the exploitation of the interparticle interactions of the material, like dipolar and/or exchange coupling

* Corresponding author.
E-mail address: dsakel@physics.auth.gr (D. Sakellari).

http://dx.doi.org/10.1016/j.msec.2015.08.023
0928-4931/

between or within nanoparticles [18,19] responsible for the enhanced heating response in hard–soft core–shell ferrite nanoparticles [20].

When nanoparticles assemble in secondary structures, the particles interact with each other and collective magnetic features become pronounced. The study of the physical properties of such cluster-like assemblies is very important in order to unravel interconnections between the heating response mechanisms and particle interactions. Enhanced coercivity is observed in the case of a pomegranate-like assembly of hematite particles as its magnetic response is governed by intra-cluster interactions [21]. Meanwhile, in maghemite multi-core nanoparticles, the crystallographic orientation of the consisting particles gives an enhanced magnetization and heating efficiency keeping their SPM character [22]. The assembly of interacting magnetic nanoparticles in controllable cluster-like formation may provide a novel roadmap in enhanced heat-triggered biomedical modalities [23].

In the present work we report on the thermal efficiency of maghemite nanocrystal assemblies named hereafter colloidal nanocrystal clusters (CNCs) comprised of primary iron oxide nanocrystals (PNCs). These assemblies have already shown a remarkable improvement (4–5 times comparing the commercial product Endorem®) of the image contrast in Magnetic Resonance Imaging [24]. Thus, by a careful engineering of dipolar interactions through the nanocrystals' cluster-packing together with the emerging collective properties and the occurrence of FM, an enhanced heating response may be achieved. Eventually, such systems may be further exploited for combinatory diagnosis and therapy schemes, classifying them into the group of theranostic agents [15].

2. Materials and methods

2.1. Materials

All reagents were used as received without further purification. Anhydrous iron chloride ($FeCl_3$, 98%), was purchased from Alfa Aesar. Anhydrous sodium hydroxide (NaOH, 98%), polyacrylic acid (PAA, $M_w = 1800$), were purchased from Sigma Aldrich, while diethylene glycol (DEG, $(HOCH_2CH_2)_2O$) of reagent (<99.7%) and laboratory (<99.5%) grades were purchased from Fisher. The absolute Ethanol was purchased from Sigma Aldrich.

2.2. Synthesis

The primary iron oxide nanocrystals and the colloidal nanocrystal clusters of γ-Fe_2O_3 were synthesized using a high-temperature polyol-based chemical protocol with iron chloride ($FeCl_3$) as precursor, sodium hydroxide (NaOH) as reductive medium and polyacrylic acid (PAA) as capping agent. Details of the synthetic procedure may be sought in Ref. 25. The diameter of the colloidal nanocrystal clusters varies from 45 to 98 nm while the diameter of the primary iron oxide nanocrystals is 13 nm. Sample notation hereafter is S-XX, where XX refers to the average diameter in nm as calculated from TEM images.

2.3. Characterization

2.3.1. Structure and morphology characterization

The shape, morphology and size of colloidal nanocrystal clusters were investigated with conventional and high resolution Transmission Electron Microscopy (TEM) images, using a LaB_6 JEOL 2100 electron microscope operating at an accelerating voltage of 200 kV. All the images were captured by the Gatan ORIUS™ SC 1000 CCD camera. For the purposes of the TEM analysis, a drop of a diluted colloidal nanoparticle aqueous solution was deposited onto a carbon-coated copper TEM grid and then the water was allowed to evaporate. In order to estimate the average size, statistical analysis was carried out on several low-magnification TEM images, with the help of specific software (ImageJ) [26].

2.3.2. Determination of iron concentration

Iron concentration was determined by graphite furnace atomic absorption spectrophotometry using a Perkin Elmer AAnalyst 800 instrument. Prior to analysis, the samples were completely dissolved in HCl.

2.3.3. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was carried out by a SDT Q600 V8.3 Build 101 TG–DTA (TA Instruments) from 20 to 600 °C with a heating rate of 10 °C/min under Ar flow. The volume fraction (φ) of the inorganic (magnetic) phase has been calculated from the weighted fraction according to the formula:

$$\frac{\rho_{\gamma-Fe_2O_3}\cdot\left(1-f_{\gamma-Fe_2O_3}\right)}{\rho_{PAA}\cdot f_{\gamma-Fe_2O_3}}=\frac{1-\varphi_{\gamma-Fe_2O_3}}{\varphi_{\gamma-Fe_2O_3}}$$

where $\rho_{\gamma-Fe_2O_3}$, $f_{\gamma-Fe_2O_3}$ and $\varphi_{\gamma-Fe_2O_3}$ (denoted as φ hereafter) are the crystal density, the weight fraction and volume fraction of γ-Fe_2O_3 nanoparticles respectively and ρ_{PAA} is the average density of the organic component [27].

2.3.4. Magnetic characterization

Magnetic measurements were carried out with a Superconducting Quantum Interference Device (SQUID) magnetometer — MPMS, at 5 and 300 K. The measurements have been performed in powder samples inside gelatin capsules. Minor hysteresis loops of the same samples were recorded with Vibrating Sample Magnetometer (VSM) at room temperature, under a maximum applied field equal to the applied field strength of hyperthermia experiments (20 and 25 kA/m) after the full demagnetization of samples. Hysteresis losses were, then, estimated and may serve as a conservative estimation of the heating efficiency lower bound (as described in Supplementary Data section).

2.3.5. Hyperthermia measurements

For hyperthermia measurements, solutions were prepared in varying concentrations (1–4 mg_{Fe}/mL) of all samples, using deionized water as solvent. The colloidal solutions were exposed first to an applied magnetic field of 20 and 25 kA/m at 765 kHz for 900 s, and subsequently were cooled down with the AC field turned off again for 900 s. The solution temperature was recorded with an optic fiber at steps of 0.4 s. It should be mentioned here that despite the use of a relatively high frequency (765 kHz), analogous frequencies have been utilized in-vitro studies to overcome the limited heating efficiency [3,13]. Specifically, in applications where nanoparticles are involved, nanoscale tissue regions may tolerate larger field-frequency products if we account additional parameters that affect nanoscale tissue heating [28].

To quantify and compare the heating response, the SLP values were calculated from hyperthermia data based on the adiabatic correction, as described in detail in previous works, [29,30] in order to provide reliable SLP values, by avoiding overestimations due to non-magnetic origins. The goal of such procedure is to evaluate the actual temperature rise provoked solely by the magnetic field effect on the magnetic primary iron oxide nanocrystals or colloidal nanocrystal clusters overriding additional non-magnetic heating contributions such as heat-exchange with the surroundings and eddy-current heat losses. A schematic representation of magnetic particle hyperthermia experiment together with its principle of operation is depicted in Supplementary Data section (Fig. S3).

3. Results and discussion

3.1. Magneto-structural characteristics

Colloidal nanocrystal clusters are practically agglomerates of single-core particles assembled in a controllable way that prevents further changes to the number of cores per cluster with time. These complex