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Influence of cobalt doping on the hyperthermic efficiency of magnetite nanoparticles

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ABSTRACT

Magnetite nanoparticles (NPs) are extensively investigated for biomedical applications, particularly as contrast agents for Magnetic Resonance Imaging and as heat mediators in Magnetic Fluid Hyperthermia. For the latter, one of the goal of the research is to obtain materials with improved hyperthermic properties. A valuable strategy is the increase of the magnetic anisotropy of commonly employed magnetite through the total or partial substitution of Fe^{2+} ions with Co^{2+} ions. Here we present a study on a family of 8 nm Co-doped magnetite NPs ($\text{Co}_x\text{Fe}_{3-x}\text{O}_4$), with composition ranging from pure magnetite ($x=0$) to stoichiometric cobalt ferrite ($x=1$), aimed to investigate the evolution of the hyperthermic properties with the increase of Co content. We found that the addition of a small amount of Co is enough to sharply increase the Specific Absorption Rate (SAR). The SAR further increases with x but it reaches a maximum for an intermediate value ($x=0.6$). Such anomalous behavior is ascribed to the intrinsic magnetic properties of the material, and, in particular, to the magnetic anisotropy, which displays the same peculiar trend. The Co-doping thus may represent an effective strategy to improve the poor hyperthermic efficiency of very small magnetite NPs (< 10 nm).

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1. Introduction

One of the most intriguing properties of magnetic nanoparticles (NPs) is the capability to generate heat under an alternating magnetic field thanks to the energy losses occurring during the magnetization reversal [1–3]. This property is the base of a promising application in biomedicine, known as Magnetic Fluid Hyperthermia (MFH), which can be employed as anticancer therapy by thermal ablation or, since cancerous cells are more sensitive to heat than healthy ones, by apoptosis or as coadjuvant for chemo- and radio-therapies [4,5]. In comparison with other hyperthermic treatments, MFH offers a better selectivity as the heat is locally generated in the tissue where the NPs accumulate. Moreover, in principle MFH could be conjugated with Magnetic Resonance Imaging (MRI) providing the opportunity to build up a theranostic nanosystem able to diagnose, treat and monitor the cancer evolution during the therapy. The multifold properties of magnetic NPs can be further exploited by the widespread functionalization reactions at the NPs surface which confer tailored

properties depending on the target application of the nanosystem [3,6].

Among the parameters which can be tuned to optimize the hyperthermic efficiency, the mean size of NPs is one of the most effective [7,8]. The optimal size, however, depends on the composition of the selected material. As instance, for iron oxide ferrites, i.e. magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), which have been the first and most investigated materials for biomedical applications because of their biocompatibility, the optimal size is around 12–24 nm, depending on the oxidation degree and on the applied frequency [7–11]. A further reduction of the particle size is one of the challenges in the material research for biomedical applications since smaller systems are expected to better avoid the immunitary system and have a longer circulation time in blood vessels, thus increasing the probability to target the tumor tissue. In addition, for magnetic carriers, small NPs are more stable against aggregation, avoiding precipitation and consequently the risk of blood vessel occlusion. In order to reduce the NP size while increasing or at least keeping constant the hyperthermic efficiency obtained with the traditional iron ferrites, the research has then to focus on alternative materials. A straight strategy to achieve this goal is to increase the magnetic anisotropy of iron oxide-based materials by replacing, for example, the divalent iron with a more anisotropic cation, like cobalt. It has been already demonstrated,

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indeed, that small sized NPs ($d < 12$ nm) of cobalt ferrite (CoFe_2O_4), which bulk anisotropy constant is *ca.* 20–30 times greater than magnetite, have a larger hyperthermic and MRI contrast efficiency than magnetite NPs of the same size [7,12]. Despite the promising properties of this material, its use in bio-medical application is debated due to the presence of cobalt. While for uncoated cobalt ferrite NPs a non-negligible toxicity is reported in the literature [13,14], the coating with silica or polymers strongly improves their biocompatibility [13,15,16]. However, a low residual toxicity is often still present, depending on the cellular line investigated and on the concentration of the NPs used [17,18]. Moreover, it must be noted that almost all cytotoxicity tests reported in the literature are performed at much lower NPs concentrations than that required by hyperthermia assays. The release of free cobalt ions from the NPs (leaching) is reported in several works, the amount of cobalt released depending on the concentration, on the coating and on the experimental conditions of the tests [17,19,20]. Moreover, another possible source of toxicity is the Co release occurring during the biodegradation of those NPs that have not completely excreted from kidneys, liver or other excretion pathways. In this manifold scenario, the presence of cobalt could in some cases represent a potential source of toxicity, in particular if large amounts of NPs or high concentration are used. A controlled reduction of cobalt content can thus represent a suitable compromise between the needs of limiting the potential toxicity and the advantage of the aforementioned properties of a strong anisotropic material. Indeed, in a recent study of Co-doped NPs grown in the internal cavity of functionalized human ferritin, some of us demonstrated that a small amount of doping (5% w/w) was enough to strongly enhance the hyperthermic efficacy on melanoma cells with respect to the undoped samples, without compromising the cytotoxicity of the material [21]. Moreover, some of us reported that the magnetic anisotropy of 5 nm $\text{Co}_x\text{Fe}_{(8/3-2/3x)}\text{O}_4$ NPs does not increase monotonously with Co reaching a maximum for intermediate composition ($x=0.6$) [22]. These results suggest the possibility to reduce significantly the Co content while achieving performances that match and even out-class those of stoichiometric cobalt ferrite. Although nanocrystalline cobalt ferrite has already been investigated for application in MHF [7,12,23,24], to our knowledge no attention has been paid to the dependence of the hyperthermic efficiency on the cobalt content.

Here we report the synthesis and characterization of a family of 8 nm non-stoichiometric cobalt ferrite, $\text{Co}_x\text{Fe}_{3-x}\text{O}_4$ with $0 \leq x \leq 1.0$ and the investigation of their ability to generate heat under an alternating magnetic field. Samples were synthesized by thermal decomposition of metal acetylacetonates in high-boiling solvents in the presence of surfactants. This method allows for obtaining high crystalline, size-controlled MNPs with tuned composition from magnetite to stoichiometric cobalt ferrite. The hyperthermic efficiency of the obtained samples was found to have a non-monotonous trend with Co-content, reaching maximum values for the intermediate composition $x=0.6$. A complete structural and magnetic characterization was performed in order to correlate this peculiar behavior with the properties of the material.

2. Materials and methods

2.1. Synthesis

All the samples were prepared under inert atmosphere using commercially available reagents. Hexane (99%), phenyl ether (Ph_2O , 99%), benzyl ether (Bn_2O , 99%), 1,2-hexadecanediol (HDD) (97%), oleic acid (OA) (90%), oleylamine (OAM) (70%), lauric acid

(LA) and cobalt(II) acetylacetonate (97%) were purchased from Aldrich Chemical Co. and Iron(III) acetylacetonate (99%) from Strem Chemicals, Inc. Absolute ethanol was from Fluka. All chemicals were used as received.

In a typical synthesis, $\text{Fe}(\text{acac})_3$ and $\text{Co}(\text{acac})_2$ (in various proportions, 1 mmol total), OA (0.64 ml, 2 mmol), OAM (0.64 ml, 2 mmol) and HDD (0.67 g, 2.3 mmol) were mixed and magnetically stirred under a flow of nitrogen in Ph_2O (30 ml). The mixture was kept at 200 °C for 2 h under a blanket of nitrogen and vigorously stirred, then heated to reflux for 1 h. The black-brown mixture was cooled down to room temperature and EtOH was added to the mixture, under ambient conditions, causing the precipitation of a black powder which was separated *via* centrifugation (5000 rpm, 10 min). The black product was dispersed by sonication in EtOH several times, then centrifuged (5000 rpm, 10 min) and dried. The product could be readily dispersed into hexane.

Samples with different metal compositions were obtained by modifying the initial metal ratio in the reaction synthesis. However, since the effective metal Co:Fe ratio was found systematically lower than the nominal one (see discussion below, Section 3.1), the reaction conditions were modified to increase the incorporation of Co in the final products by changing the kind and amount of surfactants and/or the solvent used (benzyl ether or phenyl ether). The experimental conditions used for the synthesis of the different samples are reported in Table 1.

In the following, the synthesized $\text{Co}_x\text{Fe}_{3-x}\text{O}_4$ samples will be labeled as CoFe $_{zz}$, where z is the cobalt content (i.e. $zz=06$ for $x=0.6$).

2.2. Structural characterization

Size and morphology of the NPs were determined by Transmission Electron Microscopy (TEM), using a CM12 PHILIPS microscope operating at 100 kV. Samples were prepared by drop drying a diluted suspension of NPs in hexane onto 200 mesh carbon-coated copper grids. The recorded images were analyzed with the Image Pro-Plus[®] software. The mean diameter and the size distribution of each sample were obtained from a statistical analysis over 500–900 particles.

Powder X-Ray Diffraction (XRD) measurements were carried out using a Bruker D8 Advance diffractometer equipped with a $\text{CuK}\alpha$ radiation and operating in θ - 2θ Bragg Brentano geometry at 40 kV and 40 mA. Lattice parameters, a , and mean crystallite diameters, d_{XRD} , were evaluated using the TOPAS[®] software (Bruker) by the method of Fundamental Parameter Approach considering a cubic spatial group $Fd3m$.

ICP-AES measurements were performed in triplicate by a Varian 720-ES Inductively Coupled Plasma Atomic Emission Spectrometer (ICP-AES). For the analysis, about 1 mg of sample was digested by concentrated aqua regia (HCl suprapure and HNO_3 sub-boiled in 3:1 ratio) in the presence of H_2O_2 , diluted with ultrapure water ($\geq 18 \Omega$) and then analyzed using Ge as internal

Table 1
Experimental conditions used for the synthesis of $\text{Co}_x\text{Fe}_{3-x}\text{O}_4$ samples.

Sample	x nominal ^a	x effective ^b	Surfactant	Solvent
Fe	0	0	AO, OAM	Bn_2O
CoFe02	0.3	0.2	AO, OAM, HDD	Ph_2O
CoFe04	0.5	0.4	AO, OAM, HDD	Ph_2O
CoFe06	0.9	0.6	AO, OAM	Bn_2O
CoFe09	1	0.9	LA	Bn_2O
CoFe10	1	1	OAM	Bn_2O

^a x calculated from the Fe and Co precursors ratio.

^b x calculated from the Co:Fe ratio obtained from elemental analysis (ICP-AES).

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