MAGNETIC NANOPARTICLES: BASIC RESEARCH AND BIOMEDICAL APPLICATIONS

Xavier Batlle, Amílcar Labarta, Nicolás Pérez and Pablo Guardia
Departament de Física Fonamental and Institut de Nanociencia i Nanotecnologia, Universitat de Barcelona, 08028- Barcelona, Catalonia, Spain
A.G. Roca, M. P. Morales, C.J. Serna
Instituto de Ciencia de Materiales de Madrid, CSIC, Cantoblanco 28049, Madrid, Spain
F. Bartolomé, L.M. García, J. Bartolomé
Instituto de Ciencia de Materiales de Aragón, Departamento de Física de la Materia Condensada, CSIC-Universidad de Zaragoza, E-50009 Zaragoza, Spain

Introduction

Magnetic nanoparticles (NP) are an ideal system to study finite-size and surface effects, all these yielding new interesting phenomena and enhanced properties with respect to their bulk counterpart [1].

Magnetic NP are an excellent example of nanostructured materials, as they provide the critical building blocks for the booming of nanoscience and nanotechnology. Research on both magnetic nanostructures and nanoparticles has driven the sample physical size towards even-smaller dimensions. Fundamentally, novel properties emerge as the feature size becomes comparable to or smaller than certain characteristic length scales, such as the spin diffusion length or carrier mean free path in electrical transport, leading for example to giant magnetoresistance (The Nobel Prize in Physics 2007), or the magnetic domain wall width in the case of magnetism, leading to single domain NP.

Magnetic (NP) have attracted much research over the recent years due to their potential interests in a variety of biomedical applications [2]. They posses an increasing relevance as diagnostic and therapeutic tools, such as, for example, contrast agents in magnetic resonance imaging, drug delivery to tumour cells and cancer treatment by hyperthermia, and cell separation and purification, among others.

Magnetic nanoparticles for biomedical applications should comply with a variety of requirements, including:

(i) superparamagnetic behaviour at room temperature, in order to avoid particle aggregation;

(ii) large saturation magnetisation, so as to show a largest possible response under the application of a magnetic field;

(iii) a limiting size in the order of 20 nm for *in vivo* applications; and

(iv) bio-compatibility, such that nanoparticles are usually coated with either biological or bio-compatible molecules.

All in all, the potential application of magnetic NP for biomedical purposes relies on the synthesis of high quality materials, from both the crystalline and magnetic points of view [3-6].

Experimental

In this work, we report on the influence of a variety of parameters on the synthesis of iron oxide nanoparticles (magnetite/maghemite Fe_3O_4/Fe_2O_3) by both thermal decomposition of an organic iron precursor in an organic media [3] and co-precipitation methods. It is well known that the former allows the preparation of highly crystalline NP with excellent magnetic parameters [4-6].

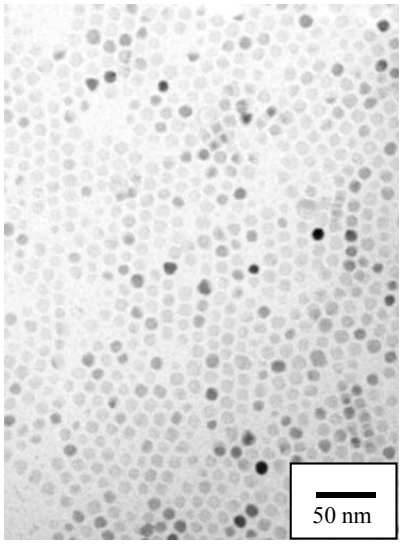

Fig. 1. TEM micrograph of $Fe_{3-x}O_4$ nanoparticles covalently coated with oleic acid with an average diameter of 10.4 ± 1.0 nm

We have studied the role of the reductor and surfactant on the shape, size distribution and the magnetic and electronic properties.

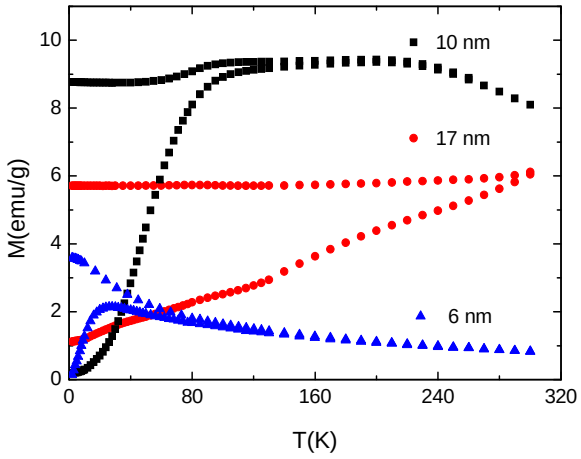

Fig. 2. Inset: Low magnetic field magnetization. Zero-field-cooling and field-cooling curves for $Fe_{3-x}O_4$ nanoparticles covalently coated with oleic acid, as a function of particle size. The cooling field was 50 Oe. The 6 nm particles are superparamagnetic at room temperature.

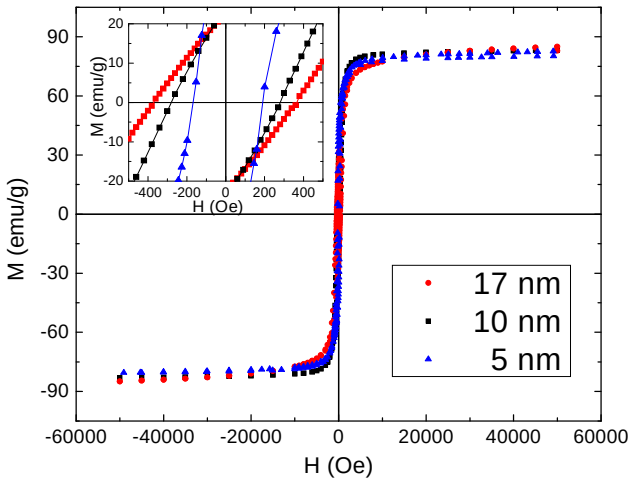

Fig. 3. Magnetization curves at T = 5 K for $Fe_{3-x}O_4$ nanoparticles surfacted with oleic acid, as a function of the particle size (5-17 nm). Inset: Low magnetic field region of the hysteresis loop.

Iron oxide NPs in the 5-50 nm range were synthesized in the presence of a variety of coatings (oleic and decanoic acids, PVA, TMAOH, dextrane…), with controlled shape from pseudo-spherical to cubic and cube-octahedral (Figure 1), thus opening a new range of sizes not reachable before.

Results and discussion

All the materials show a narrow size distribution with high crystal quality, as revealed by transmission electron microscopy (TEM). Besides, the smallest particles show superparamagnetic behaviour at room temperature (Figure 2).

Surprisingly enough, saturation magnetization M_s is size independent in the 5-20 nm range and almost reaches the expected value for bulk magnetite at low temperatures, being higher in those NP for which the surfactant is covalently bonded to the surface (Figures 3 and 4).

A variety of colloidal suspensions of quasi non-interacting NP and mean diameter of about 5 nm were studied in further detail. We have developed a new analytical model to account for the surface contribution to the effective energy barrier distribution of anisotropy, which is still under hot debate in literature [6].

This model enables us to transform the volume anisotropy distribution into the effective energy barrier distribution obtained with the $T\ln(t/t_0)$ scaling method [7], and demonstrates that surface anisotropy causes the broadening of the energy barrier distribution in magnetic nanoparticles (not shown).

X-ray absorption spectra (XAS) in the $L_{2,3}$ edges suggest charge transfer from the NP to the surfactant due to covalent bond. X-ray magnetic circular dichroism (XMCD) confirms the dependence of the magnetic moment on the surface bond and suggests that the orbital momentum is more effectively quenched in covalently bonded NPs. Besides, a low-temperature value $\langle S_z \rangle$ = 3.63 μ_B/f.u. is obtained in the latter, which is very close to those reported for bulk samples (3.90-3.95 μ_B/f.u.) (not shown) [8].

High resolution TEM suggests that all the foregoing is related to the crystal quality of the NP associated with the temperature of the synthesis procedure.

All in all, covalently bonded NPs show bulk-like magnetic and electronic properties, while NPs with just protective coatings show particle-like properties [8] (Figure 5).

The potential application of magnetic NP for biomedical purposes relies on the synthesis of high quality materials, mainly regarding crystallinity and magnetic response.

Synthesis based on the high temperature decomposition of Fe organometallic precursors in an organic medium in the presence of a surfactant have proven successful for the preparation of monodisperse NP (see for example Figure 1). This method is currently of common use to prepare iron oxide NP because of its simplicity and reproducibility.

However, while these methods are limited to a maximum particle size of about 20 nm, the NP obtained are typically hydrophobic due to the non-polar organic acids used as surfactants (e.g. oleic acid) to promote

steric hindering and avoid agglomeration.

On the contrary, the synthesis of iron oxide NP by co-precipitation allows reaching a very wide range of sizes, but, although the NP are hydrophilic, they show a much lower magnetic response and a marked tendency to agglomerate (Figures 3 and 4).

Therefore, it is essential to develop new synthetic routes, based on the decomposition of organometallic precursors, in order to extent the range of achievable particle sizes above 20 nm without significant deterioration of their magnetic properties, and to ligand-exchange the NP to a hydrophilic coating.

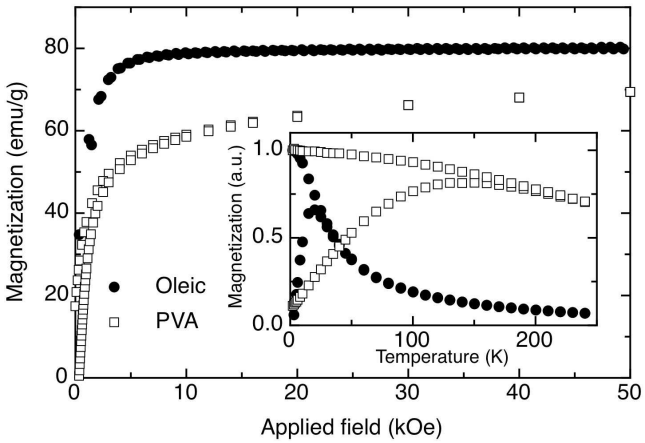

Fig. 4. First magnetization curves at T = 5 K for 5 nm $Fe_{3-x}O_4$ nanoparticles: covalently coated with oleic acid (solid circles) and surface-protected (no surface chemical bond) with polyvinyl alcohol (PVA) (empty squares) Inset: Low magnetic field magnetization. Zero-field-cooling and field-cooling curves measured at 50 Oe for the same samples.

Taking all the foregoing into account, we have ligand-exchanged the oleic-acid coated $Fe_{3-x}O_4$ nanoparticles in this work, to make them water-dispersable, either with a polar organic acid (for example, dimercaptosucinic acid, DMSA) or by silanization.

In the case of the organic coating, DMSA is used since one of its two carboxyl groups also forms a chemical bond to the NP surface, while other funcional groups in the carbon chain (the second carboxyl and two thiol groups) make the coating hydrophilic. Particles are transferred to water and stabilized at pH ≈7 with DMSA by mild stirring in an aqueous solution at room temperature.

In the case of the silane surface ligand exchange, the shell consists of silica with amine functional groups decorating the outermost surface, by using amino-silanes, such as aminopropyl silane (APS). Mixing a certain, small, quantity of APS in a diluted suspension of hydrophobic oleic-acid coated nanoparticles in a nonpolar solvent (e.g., hexane, acetone…), ligand exchange is promoted after mild stirring during a period of time. A certain amount of acid or base (acetic acid or ammonium hydroxide solution, respectively) may be optionally added to the mixture to promote silane hydrolysis, either in acid or alkaline medium.

Depending on proportion of reagents, time and amount of acid or alkali added, the thickness of the silica coating may be varied. The silica-coated particles may be extracted by precipitation from the nonpolar solvent and redispersed in water. Extra growth of the silica may be performed via variants of the Stöber method using either aminated or non-aminated silanes, for example adding some amount Tetraethyl Orthosilicate (TEOS) to an aqueous ethanol solution.

DMSA-coated $Fe_{3-x}O_4$ NPs have been used successfully as contrast agents in magnetic resonance imaging (not shown) and are internalized by HeLa cells after incubation (not shown).

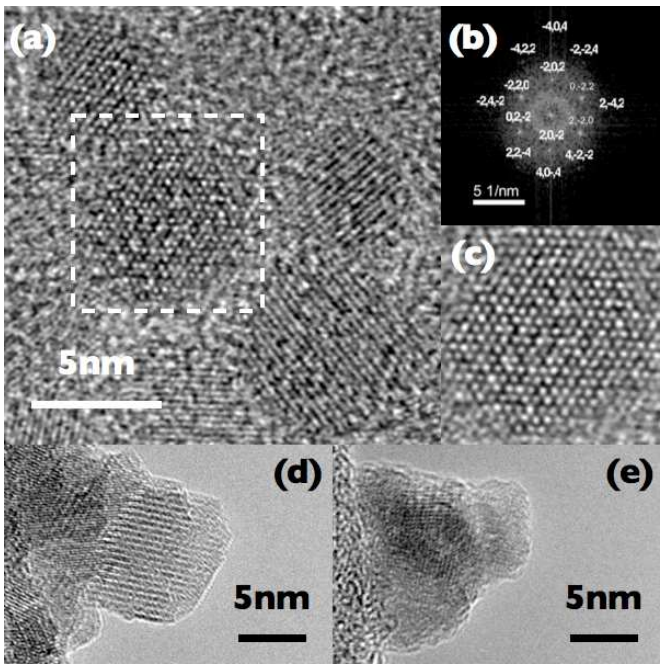

Fig. 5. (a) High resolution TEM images for oleic acid-coated $Fe_{3-x}O_4$ nanoparticles; (b) Fourier transform of the selected area framed in (a) along the <111> zone axis; (c) reconstruction of the lattice by inverse Fourier transform using only indexed diffraction spots in the latter; (d, e) High resolution TEM images for PVA-protected $Fe_{3-x}O_4$ nanoparticles.

Besides, we have extended above 20 nm the particle size range by using decanoic acid as capping ligand (Figure 6) [9]. The nanoparticles also show high saturation magnetization of about 80-83 emu/g at low temperature, almost size-independent and close to the

value for the bulk counterpart.

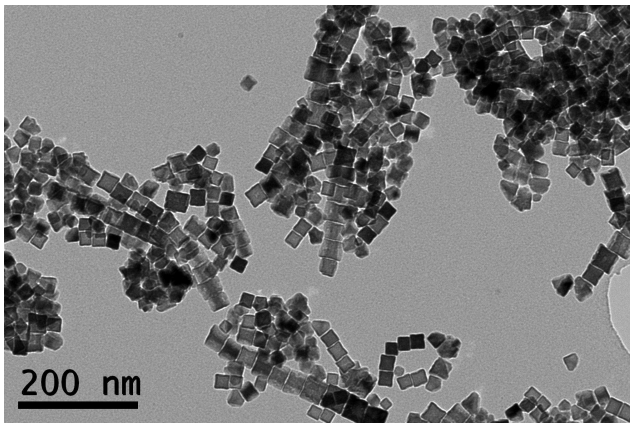

Fig. 6. TEM micrograph of 26(5) nm iron oxide nanoparticles coated with decanoic acid.

Decanoic acid-coated nanoparticles may be transferred to water by using tetramethyl ammonium hydroxide, which allows further individual coating with silica in a tetraethyl orthosilicate solution. Consequently, these iron oxide nanoparticles are tunable in size and highly magnetic.

Conclusions

Iron oxide nanoparticles (magnetite/maghemite Fe_3O_4/Fe_2O_3) prepared by thermal decomposition of an organic iron precursor in an organic media are excellent systems to study both,

(i) basic properties of magnetic nanoparticles (superparamagnetism, surface contribution to the magnetic properties, static and dynamic properties…), and

(ii) potential biomedical applications (magnetic resonance imaging, drug delivery and selective magnetophoresis), after making the particles water-dispersable by ligand exchange and surface chemical functionalization.

Acknowledgments

The funding from the Spanish MEC (NAN2004-08805-CO4-02, NAN2004-08805-CO4-01, CONSOLIDER CSD2006-12, MAT2005–02454 and MAT2006-03999), and from the Catalan DURSI (2005SGR00969) are acknowledged.

References

[1] For example, see the review paper, X. Batlle and A. Labarta; Finite-size effects in fine particles: magnetic and transport properties; *Journal of Physics D: Applied Physics* **35** (2002) R15.

[2] For example, see the review paper, P. Tartaj, M.P. Morales, S. Veintemillas-Verdaguer, T. González-Carreño and C.J. Serna; The preparation of magnetic nanoparticles for applications in biomedicine**;** *Journal of Physics D: Applied Physics* **36** (2003) R182.

[3] S. Sun and H. Zeng; Size-Controlled Synthesis of Magnetite Nanoparticles; *Journal of the American Chemical Society* **124** (2004) 273.

[4] A.G. Roca, M PMorales, K. O'Grady and C.J. Serna; Structural and magnetic properties of uniform magnetite nanoparticles prepared by high temperature decomposition of organic precursors; *Nanotechnology.* **17** (2006) 2783.

[5] P. Guardia, B. Batlle-Brugal, A.G. Roca, O. Iglesias, M.P. Morales, C.J. Serna, A. Labarta and X. Batlle; Surfactant effects in magnetite nanoparticles of controlled size; *Journal of Magnetism and Magnetic Materials* **316** (2007) e756.

[6] N Pérez, P. Guardia, A. G. Roca, M.P. Morales, C.J. Serna, O Iglesias, F Bartolomé, L.M. García, X Batlle and A Labarta ; Surface anisotropy broadening of the energy barrier distribution in magnetic nanoparticles; *Nanotechnology* 19 (2008) 475704.

[7] X. Batlle M. García del Muro, and A. Labarta; Interaction effects and energy barrier distribution on the magnetic relaxation of nanocrystalline hexagonal ferrites; *Physical Review B* **45** (1997) 6440.

[8] N Pérez, F Bartolomé, L.M. García, J. Bartolomé, M.P. Morales, C.J. Serna, A Labarta, and X Batlle (submitted)

[9] P. Guardia, A. Labarta and X. Batlle (submitted).