Journal of Alloys and Compounds 770 (2019) 58–66

Contents lists available at ScienceDirect

Journal of Alloys and Compounds

journal homepage: http://www.elsevier.com/locate/jalcom

Review

Tailoring the magnetic core of organic-coated iron oxides nanoparticles to influence their contrast efficiency for Magnetic Resonance Imaging

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ARTICLE INFO

Article history:
Received 8 May 2018
Received in revised form
31 July 2018
Accepted 14 August 2018
Available online 16 August 2018

Keywords:
Magnetic nanoparticles
Nanomagnetism
Nuclear magnetic resonance
Magnetic resonance imaging

ABSTRACT

An experimental ^{1}H NMR relaxometry investigation on iron oxide nanoparticles with different magnetic core size and coated with PolyAcrylic Acid (PAA), is presented. A full structural, morphodimensional and magnetic characterization of the nanoparticles has been performed by means of X-ray diffraction, Dynamic Light Scattering, Transmission Electron Microscopy, Atomic Force Microscopy and SQUID DC magnetometry. The application of a heuristic model for the field dependence of the NMR relaxivity curves allowed us to evaluate the distance of minimum approach of the solvent molecules from the magnetic centers, and to conclude that the local correlation times, namely the Neél time τ_N and the diffusion time τ_D related to the magnetization reversal and to the diffusion process respectively, depend strongly on the core size. A preliminary evaluation of their r_2 efficiency as Magnetic Resonance Imaging (MRI) contrast agents is also performed by means of a universal scaling law model. The results of our experimental investigation should allow to tailor the physical properties of the nanoparticles for obtaining systems with a resultant contrast efficiency optimized for the in-vivo application of MRI at pre-clinical and clinical level.

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https://doi.org/10.1016/j.jallcom.2018.08.120
0925-8388/

1. Introduction

Magnetic nanoparticles (MNPs) are promising candidates for several magnetic based biomedical applications going from imaging up to cancer therapy [1,2], such as e.g. drug delivery and hyperthermia treatments [3–8]. The most common MNPs have a magnetic core composed by iron, cobalt or nickel oxides and a coating shell constituted of organic moieties like e.g. polymers, sugars, acids, that guarantees their stability and biocompatibility [3–5]. Remarkably, the colloidal stability of coated MNPs greatly depends on their surface properties and influences their distribution and biocompatibility in living tissues [9,10]. Due to their "natural" biocompatibility, the magnetic core of the most widely investigated MNPs for biomedical application is constituted of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), i.e. ferrimagnetic materials in bulk form, assuming a single domain spin structure when their size is below a critical value (*c.a.* 150 nm). Single domain MNPs are generally schematized by assuming the electronic spins substantially aligned by a dominant exchange interaction and moving coherently under the effect of an external field [11–13]. Thus, a so-called "giant" magnetic moment, corresponding to the sum of the aligned atomic spins inside the particle, can be associated to any single particle and it is often oriented along an easy-axis direction (uniaxial anisotropy approximation). As a consequence, the effective magnetic anisotropy energy is characterized by two minima [9] and the energy needed to flip the magnetization from one minimum to the other (i.e the energy to reverse the magnetization along the easy axis) is called anisotropy barrier. When the anisotropy barrier becomes comparable with the thermal energy, as occurs in the superparamagnetic regime, the magnetic moments associated to single particles are free to move with a typical correlation time associated to the magnetization reversal, named Néel time τ_N [14,15]. Due to the reduced size of the magnetite MNPs, the Néel time (τ_N ~10^{-7}÷10^{-10} s at room temperature) is generally the fastest one among the characteristic times of the MNP motion, that include also the rotational or Brownian time (τ_R~10^{-4} s) and the diffusion time ($\tau_{D=}10^{-4}$-10^{-6}s). The spin dynamics emerging from the described picture is crucial in determining the magnetic properties of the MNPs as a function of field and temperature and, consequently, their efficiencies in application like magnetic storage, magnetic transport, MRI and magnetic fluid hyperthermia. For studying this spin dynamics, a technique able to grasp its features in the time window 10^{-3}-10^{-8}s is needed. To this aim Nuclear Magnetic Resonance (NMR), together with Mössbauer Spectroscopy and Neutron Scattering in a more limited range, is an ideal technique, taking into account that it is also easily accessible in standard laboratories and can give a direct measurement of the Magnetic Resonance Imaging (MRI) contrast ability of the investigated compounds.

In fact, in general terms, the magnetic properties of superparamagnetic MNPs can be used in biomedical MR diagnostics [16,17] thanks to their ability to induce inhomogeneities in the local magnetic field felt by the protons of the surrounding water molecules. This effect produces shorter nuclear relaxation times of the water ^{1}H nuclei contained in the tissues where MNPs accumulate, and allows a better contrast in the MR images.

In order to design MNPs with an optimal efficiency in contrasting images, it is important to understand the physical mechanisms beyond the protons nuclear relaxation that, in the presence of a sufficiently strong hyperfine interaction, is sensitive to typical correlation times of the electronic spin dynamics, like τ_D, τ_R, τ_N and, when existing, the chemical exchange time τ_{ex}, which refers to the process in which a water molecule coordinated at the NP surface exchanges with water molecules of the medium. The efficiency is evaluated by means of a parameter called relaxivity, which represents the shortening of the nuclear relaxation rate with respect to the one of the solvent, normalized by the magnetic centers concentration (i.e the quantity of magnetic ions dispersed in fluids, tissues, etc.).

The most important chemico-physical parameters of MNPs that influence the relaxivity are the magnetic core size, the chemical composition and the type of coating used to disperse nanoparticles in the medium. The size of the magnetic core and its composition, normally tuned by partial substitution of iron ions with other transition metal [e.g. Refs. [18–20]] or rare-earth ions [e.g. Refs. [21,22]], are used to modulate the intrinsic magnetic properties of MNPs. On the other hand the type of coating is the principal term for controlling the distance between the dispersant (normally water or saline buffers) and the MNPs core, governing the capability of solvent molecules to pass near (hydrophilic coating) or far away (hydrophobic coating) the magnetic core itself.

In the present work, we studied the effects of the magnetic core size on the nuclear relaxation (longitudinal and transversal) times, by preparing three samples of MNPs constituted of a maghemite core coated by PolyAcrylic Acid (PAA), with different core diameter, d = 10, 14 and 19 nm, synthesized by thermal decomposition [23,24]. PAA was chosen as coating ligand since it is a biocompatible anionic polymer, which grants for the formation of long-term, highly stable water suspension of iron oxide MNPs, also in physiological conditions [25–27].

The local spin dynamics has been probed by proton nuclear magnetic relaxation (^{1}H NMR) measurements performed in a wide frequency range ($10^4 \div 6 \cdot 10^7$ Hz). The fit of the longitudinal NMR dispersion curves (so-called NMR-D relaxivity curves) by means of the Roch model [28] allowed us to evaluate important parameters, such as the magnetization reversal correlation time τ_N and the distance of minimum approach r_d, and to establish a correlation among τ_D, r_d and the main magnetic basic parameters, already partially reported in Ref. [29], as the saturation magnetization M_S, the coercive field H_C and the anisotropy energy barrier Δ, in turn related to the core size.

2. Experimental section

2.1. Sample preparation

All chemicals were of analytical grade and were used as received. Benzyl ether, 108014 Aldrich; Oleic acid, O1008 Sigma-Aldrich; Oleylamine HT-OA100 Aldrich; Iron(III) acetylacetonate, F300 Aldrich; Tetrahydrofuran, 401757 Sigma-Aldrich; Poly(acrylic acid), (M.W. 1800 g/mol), 323667 Aldrich, were purchased from Sigma-Aldrich Co. Water was deionized and filtered with a Milli-Q System (Merck Millipore Co., Germany). Three samples of oleic acid coated γ-Fe_2O_3 MNPs were synthesized by thermal decomposition of metal-organic precursors in high boiling solvents and in the presence of surfactants. Iron(III) acetylacetonate (2 mmol), Oleylamine (2,5 mmol) and Oleic Acid (2 mmol) were dissolved in Benzylether (40 mL) and stirred under nitrogen flow for 15 min at room temperature; the mixture was heated at 200 °C for 30 min and then maintained at 300 °C for a variable duration time to obtain MNPs of different size. Then, the mixture was cooled down to room temperature and the black MNPs precipitate was magnetically separated, cleaned three times with ethanol and re-suspended in toluene. The obtained MNPs were then transformed