Magnetic domains orientation in (Fe$_3$O$_4$/γ-Fe$_2$O$_3$) nanoparticles coated by Gadolinium-diethylenetriaminepentaacetic acid (Gd$^{3+}$-DTPA)

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Abstract

In this work, the magnetic domains (MDs) orientation was evaluated from magnetite/maghemite nanoparticles (Fe$_3$O$_4$/γ-Fe$_2$O$_3$) NPs coated with Gadolinium (Gd$^{3+}$) chelated with diethylenetriaminepentaacetic acid (Gd–DTPA). The (Fe$_3$O$_4$/γ-Fe$_2$O$_3$) superparamagnetic cores were configured by adding a DTPA organic layer and paramagnetic Gd as (Fe$_3$O$_4$/γ-Fe$_2$O$_3$)@Gd–DTPA NPs. The cores were obtained by coprecipitation and coated with additional modifications to the synthesis with Gd–DTPA. Analysis of properties showed that particles 9–12 nm, with Gd–DTPA layer thickness ∼10 nm increased their magnetisation from 62.72 to 75.82 emu/g. The result showed that the structure, particle size, composition, thickness and interface defects, as well as the anisotropy, play an important role in MDs orientation of (Fe$_3$O$_4$/γ-Fe$_2$O$_3$)@Gd–DTPA NPs. Magnetic force microscopy (MFM) analysis showed an MDs uniaxial orientation of 90° at magnetisation and disorder at zero conditions and demagnetisation. The MDs interactions showed uniaxial anisotropy defined in the direction of the magnetic field. These addressable and rotational features could be considered for potential applications to induce hydrogen proton alignment in water by longitudinal spin-lattice relaxation $T_1$ and transversal spin-spin relaxation $T_2$ as a dual contrast agent and as a theranostic trigger.

1. Introduction

The configuration of nanostructures for dual contrast agents ($T_1$–$T_2$) is still a challenge controlling the MDs rotation and promoting the hydrogen proton magnetic moment alignment [1]. Magnetic resonance imaging (MRI) scanning depends on the contrast agent anisotropy, as addressable MDs with respect to a strong static external magnetic field. Typically, this is achieved from 1.5 to 7 T, and pulsed radio frequency (RF) in the order of MHz [2]. The hydrogen protons of physiological media undergo a relaxation process by orientation and return to the original equilibrium. Their orthogonal components are: spin-lattice relaxation $T_1$ produced from magnetisation parallel to the static external magnetic field, and spin-spin relaxation $T_2$ generated from magnetisation decaying on the plane perpendicular to the external field [3]. MRI agents have been based on magnetic moment interactions from paramagnetic ion complexes as gadolinium (Gd$^{3+}$) for $T_1$, or...
superparamagnetic iron oxide nanoparticles (SPIONs), mainly magnetite (Fe₃O₄) and maghemite (γ-Fe₂O₃) for T₂ [4,5].

Since 1988, gadolinium-based contrast media (GBCM) or gadolinium-based contrast agents (GBCAs) have been administered at more than 500 million doses worldwide [6]. Gd³⁺ is a stable lanthanide ion with a high magnetic moment. This is paramagnetic because of its ionised state (3+) from its seven unpaired electrons in the 4f orbital shell, which is the maximum number allowed. Hence seven unpaired electrons promote spin relaxation due to flipping spins and rotational motion with the magnetic field, thereby altering the relaxation of water in physiological media for diagnosis. However, free Gd³⁺ is insoluble and toxic. The Gd³⁺ ions must be linked to organic ligands, conferring more favourable pharmacological and toxicological properties in processing calling chelation. The chelate is derived from the Greek word for ‘claw’ (the gadolinium ion is held by ligands as if in the claw of a lobster) bound by a ringlike molecular cage. Gd³⁺ chelate is a GBCM that is thermodynamically stable and kinetically inert [7–9]. This increases the relaxation rate related to the solvent (water) because of the dipole–dipole interactions between the nuclear spin of the proton and the local magnetic field fluctuation resulting from the unpaired electron spins [10].

Typically, Gd³⁺ is chelated by diethylenetriamine pentaacetate acid (Gd–DTPA, also known as gadopentate dimeglumine), which is an ionic and hydrophilic complex. The Gd–DTPA (Magnevist®; Berlex Laboratories) has been successfully approved by the Food and Drug Administration (FDA) for clinical imaging in humans because of its intravascular and extracellular administration, and fast urine excretion [11]. GBCAs produce bright signals from the longitudinal interactions of spin–lattice T₁. The fast parallel MDs orientations to the static magnetic field recover after a radio frequency perturbation. The short T₁ produces high signal intensities due to protons that are rapidly relaxed [12]. However, Gd–chelates suffer from low relaxation and contrast efficiency, which hampers their application in clinical diagnosis [13].

To overcome these limitations, it is necessary to enhance the properties of current contrast agents to combine multimodal functions, T₁ and T₂. Unlike gadolinium–based ions, which only act as T₁ contrasting agents, they can be linked over SPIONs. surface for a dual signal. The SPIONs@Gd–DTPA can be tuned like addressable MDs as functions of either T₁ or T₂ according to the control of size, shape, anisotropy and magnetisation [14]. Superparamagnetism is the result of the exchange interaction of iron ions (Fe³⁺/Fe²⁺) in the octahedral sites of the magnetite (Fe₂O₃) structure. The magnetic moments are aligned with the applied magnetic field in Fe₂O₃ NPs below 25 nm for T₂ [15]. Gd–DTPA can be linked on the surface of several nanomaterials by both covalent and non-covalent bonding as (Fe₂O₃@Gd–DTPA) NPs for dual MRI (T₁–T₂) [16]. In addition, SPIONs can be formulated with other organic chains for theranostics from external stimuli such as pH, magnetic fields or photothermal therapy including drug release, diagnosis, or therapy combination. Coated SPIONs improve their biocompatibility, solubility, stability, and bioavailability under physiological conditions [17].

Dual MRI contrast agents would have potential applications in the liver, blood-pool contrast agents (BPCA), lymph node imaging, atherosclerotic plaques, tumour targeting, and imaging of tumour vasculature angiogenesis, including promising theranostic [18]. The multifunctional ferrites have also been developed as theranostic agents in the integration for ultrasound (US) assisted oncotherapy and multimodal imaging [19]. Promising theranostic nanomedicine has added different multifunctional configurations to modulated bioimaging and chemodynamic/photodynamic therapy [20]. Ferrite NPs functionalization has opened novel alternatives in nanomedicine as simultaneous magnetic hyperthermia, photothermal therapy (PTT), photodynamic therapy (PDT), chemodynamic therapy (CDT) and/or multimodal imaging [21].

In this work, (Fe₂O₃/γ–Fe₂O₃) SPIONs were synthesized by the co-precipitation and coated by Gd–DTPA; (1) post-synthesis and (2) in-situ synthesis, processed as (Fe₂O₃/γ–Fe₂O₃)@Gd–DTPA NPs. The structure, composition, bonding, particle size, and coating were analysed by using X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), energy-dispersive X-ray spectroscopy (EDS), transmission electron microscopy (TEM), and X-ray photoelectron spectroscopy (XPS). Superparamagnetic properties and MD orientation were analysed by superconducting quantum interference device (SQUID) magnetometer and MFM, respectively, under an applied magnetic field (H).

2. Methodology

2.1. Materials

Iron (III) chloride hexahydrate (FeCl₃·6H₂O, ACS reagent, 97%), iron (II) chloride tetrahydrate (FeCl₂·4H₂O, reagent plus, 98%), hydrochloric acid (HCl, 36.5%–38.0%, BioReagent), tetraethylammonium hydroxide solution ([(C₂H₅)₂N][OH], 20 wt. % in H₂O), gadolinium (III) chloride hexahydrate (GdCl₃·6H₂O, 99% titration), diethylenetriaminepentaacetic acid ([HOOCCH₂]₂NCH₂CH₂[NCH₂]₂NCH₂COOH, ≥ 99% titration),
sodium hydroxide (NaOH, pellets, 97%) were purchased from Sigma-Aldrich. Distilled water was used for all experiments. All chemical reagents were of analytical grade and used without further purification.

2.2. (Fe₃O₄/γ–Fe₂O₃) NPs synthesis
The (Fe₃O₄/γ–Fe₂O₃) NPs were processed by co-precipitation according to the Massart method [22]. Starting from an aqueous solution of HCl, 2 M. From this solution, 25 ml was added to 6.965 g of FeCl₃·6H₂O, 1 M (Fe³⁺ solution), and 6.25 ml were aggregated to 2.51 g of FeCl₂·4H₂O, 2M (Fe²⁺ solution), and each solution was stirred for 30 min. The iron solutions were mixed, from 5 ml of the Fe³⁺ solution and 1.25 ml of the Fe²⁺ solution. The reaction was heated at 80 °C and deoxygenated by argon gas during entire process. (Fe₃O₄/γ–Fe₂O₃) NPs were precipitated by dropwise addition of 30 ml of tetraethylammonium (TEA) hydroxide solution [23]. The solution turned to black. Finally, the NPs were washed several times with distilled water and ethanol, until a pH = 7 was reached.

2.3. Gd–DTPA chelation
The Gd–DTPA was synthesized from GdCl₃·6H₂O (4.49 g, 0.0121 mol) in H₂O (10 ml) was added dropwise to a solution of DTPA (5.0 g, 0.0127 mol) in H₂O (30 ml) containing 2 N NaOH (5.0 ml) solution according Santra et al [24]. A solution of Gd–DTA (200 mg) in distilled water (10 ml) was added for each (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA experiment, post-synthesis and in-situ.

2.4. (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA NPs post-synthesis
The Gd–DTPA solution was added dropwise after (Fe₃O₄/γ–Fe₂O₃) precipitation in experimental conditions of inert atmosphere, at 80 °C under mechanical stirring for 1 h. The suspension was then cooled to room temperature. The final product was precipitated, and the Gd–DTPA and TEA excess were removed by washing several times with ethanol and water (1:1) until the pH was 7. Finally, the sample was freeze-dried. This sample was denoted as MG–1.

2.5. (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA NPs synthesis in-situ
The Gd–DTPA solution was mixed directly with iron solutions (Fe²⁺ and Fe³⁺). Subsequently, 30 ml of TEA hydroxide solution was added dropwise. After 1 h, the solution was cooled to room temperature and precipitated. The nanoparticules were washed several times to remove the unabsorbed Gd–DTPA and TEA, until a neutral pH was reached. The final product was lyophilized. This sample was denoted as MG–2.

2.6. Physical characterisation
The XRD was performed using a Rigaku SmartLab diffractometer with Cu Kα (λ = 1.5406 Å) radiation and a nickel filter. The measurements were carried out at 9 kW (200 mA, 45 kV) at a scanning rate of 0.02°/s, 25–70° range at 2θ. The mean crystallite size was estimated with Scherrer equation: D = 0.9 λ / β cos θ, for (311) reflections. The lattice parameters were calculated from the experimental XRD patterns using PowderCell for Windows, Version 2.4. The FWHM values and sizes were estimated through a modified Scherrer analysis using a pseudo-Voigt function [25]. TEM analysis was performed using a JEOLEMM–2010 microscope at 200 kV. Each sample was dispersed in isopropanol and held in formvar carbon copper grids, 400 mesh. Histograms were obtained from 130 particles for each sample. FTIR analysis was performed in the range of 4000 to 400 cm⁻¹ using a Nicolet 6700 spectrometer. The chemical compositions of the surfaces were analysed by XPS using a Thermo Scientific K–Alpha system equipped with a monochromatic Kα X-ray source. All the signals were calibrated using the adventitious hydrocarbon peak, C 1s, located at 284.6 eV. Furthermore, the powder compositions were recorded by EDS coupled with scanning electron microscopy (SEM) Auriga Zeiss FEG 25 kv. Magnetisation curves were measured using a magnetic property measurement system (MPMS³), Quantum Design, at room temperature under a maximum applied field of 3 T. The topography and MDs analyses were performed by using a scanning probe microscope (SPM) JEOL–JSPM–5200 in the mode atomic force microscope-magnetic force microscopy (AFM–MFM) or Lift Mode. Each powder sample was confined to a carbon adhesive tape and flattened with the pressure of a flat glass. A magnetic tip NSC18, Co–Cr/Al Micromash with an uncoated radius of 8 nm, coated radius < 60 nm and full tip cone angle of 40° was used for MFM characterisation. The magnetisation of the tip was performed using a neodymium magnet. Topography and MFM images were obtained at 180 kHz with a lift height interaction of 5–86 nm, output of 0.011–0.025 Amp/V and H = 12 kOe under saturation conditions. The MFM resolution is not high enough to see features of the nanoparticle dimensions, and single–particle measurement can be performed in principle if the magnetic stray field generated by the particle is sufficiently strong. [26]. The images were processed using the Gwyddion modular program for SPM.[27].
2.7. Magnetic force microscopy (MFM)

The MFM provides the response of the magnetic stray field above the sample. This is detected by a magnetic tip which is oriented perpendicular or normal with respect to the analysis surface. The MFM is a dynamic mode, which traces the topography and phase detection line by line and known as Lift Mode [28].

The force gradient exerted between the magnetic tip and a magnetic sample allows the deflection of the cantilever and magnetic domain mapping. Because the magnetic forces are in longer range than the atomic forces in AFM, the lift mode decreases the lateral resolution by a factor comparable to the average tip separation (lift distance, $\Delta z$). The spatial resolution resolved at $z$ is less than 30 nm by MFM, whereas AFM technically has atomic resolution. In addition, the spatial resolution dependent on the tip diameter [29].

The fact that in MFM, the tip is placed several nanometers above $\Delta z$ implies that the polarised superparamagnetic nanoparticles in powder below 10–12 nm would be difficult to analyse because of the topological differences. The agglomerates produce elongated aggregates, and the magnetic signals depend on the exchange, magnetostatic and anisotropy energies with respect to $\Delta z$ [30, 31], figure 1.

In practice, working MFM distances between a few nanometers and a few tens of nanometers are used. Because of strength force gradient rapidly decays with distance from the surface. Fast scans with tip surface distances as small as 10–20 nm can be achieved using this method. The magnetisation within the sample reaches its equilibrium configuration as a result of exchange interactions, anisotropy and demagnetizing field.

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**Figure 1.** Single magnetic domains detected by MFM from Fe$_3$O$_4$/\(\gamma\)-Fe$_2$O$_3$ NPs. The parallel lines of magnetic field define the uniaxial orientation observed over the surface. The tip diameter is longer that SPIONs and acts as attractive magnet.

**Figure 2.** (a) The (Fe$_3$O$_4$/\(\gamma\)-Fe$_2$O$_3$)@Gd–DTPA NPs configuration (b) XRD: MG-1 and MG-2 with cubic spinel structure plus Gd–DTPA amorphous contribution.
3. Results and discussion

3.1. (Fe₃O₄/γ-Fe₂O₃)@Gd–DTPA NPs: structure, size and coating.

The (Fe₃O₄/γ-Fe₂O₃)@Gd–DTPA NPs configuration was defined as superparamagnetic cores plus Gd³⁺ magnetic moments spread in the DTPA amorphous layer over the NPs, figure 2(a). The powder diffraction peaks were matched at 2θ = 30.1°, 35.4°, 43.0°, as shown in 53.39°, 56.9° and 62.6°, corresponding to the

| Sample       | a₀ (Å) | d(311) (Å) | FWHM | XRD     | TEM     | AFM-MFM  |
|--------------|--------|------------|------|---------|---------|----------|
| (Fe₃O₄/γ-Fe₂O₃) | 8.378  | 2.525      | 0.876| 10.96 ± 1.42 | 11.58 ± 1.69 | 14.4 ± 1.1 |
| MG-1         | 8.358  | 2.520      | 1.194| 9.72 ± 1.15  | 9.88 ± 1.89  | 11.8 ± 2.1 | 2.5      |
| MG-2         | 8.366  | 2.522      | 1.058| 9.45 ± 1.42  | 9.07 ± 1.53  | 16.1 ± 4.2 | 10.5     |

Table 1. (Fe₃O₄/γ-Fe₂O₃)@Gd–DTPA NPs: lattice parameters, size and Gd–DTPA thickness.

Figure 3. TEM images: (a), (b) (Fe₃O₄/γ-Fe₂O₃) NPs showed a semi-spherical morphology, (c) (Fe₃O₄/γ-Fe₂O₃) structure, SAED versus XRD; (d), (e) MG-1: (Fe₃O₄/γ-Fe₂O₃)@Gd–DTPA NPs, (g), (h) MG-2: (Fe₃O₄/γ-Fe₂O₃)@Gd–DTPA NPs and (f), (i) SAED displayed an amorphous contribution, by Gd–DTPA. Gd–DTPA thickness was measured in figures (e), (h). Inset figures (a), (d), (g) size distribution of the nanostructures.

distribution [32]. The MFM images show MDs defined by the local magnetic structure of superparamagnetic nanoparticles.
inverse cubic spinel structure with crystallographic planes (220), (311), (400), (422), (511) and (440), respectively, figure 2(b). The lattice parameters (a₀), FWHM values and sizes were obtained through a modified Scherrer analysis using a pseudo-Voigt function [25]. The (Fe₃O₄/γ–Fe₂O₃) NPs had a₀ = 8.3743 Å. The Fe₃O₄ lattice distortion from a₀ = 8.396 Å was associated to surface oxidation, due to Fe²⁺ cation vacancies led to surface oxidation as maghemite (γ–Fe₂O₃, a₀ = 8.346 Å, JCPDS file 39–1346) [33]. Therefore, the (Fe₃O₄/γ–Fe₂O₃) NPs showed small shift peak positions, which were attributed to the oxidation from the surface as γ–Fe₂O₃ to the Fe₃O₄ core. In addition, MG–1 and MG–2 showed lattice distortion due to interphase defects (table 1). (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA NPs showed scattering effects, intensity reduction and amorphous contribution in both cases. These signals are mainly associated with the amorphous Gd–DTPA coating over (Fe₃O₄/γ–Fe₂O₃) NPs. No additional contribution from the gadolinium phase was observed in the XRD patterns. Normally, free Gd³⁺ ions can be randomly incorporated into the (Fe₃O₄/γ–Fe₂O₃) lattice by cation vacancy occupation at octahedral sites (0.7357–0.8285 Å) and replacing the Fe ions [34]. This has been avoided by the Gd–DTPA chelation, and the Gd³⁺ magnetic moments could be confined only over the (Fe₃O₄/γ–Fe₂O₃) surface by DTPA covalent bonding [35]. DTPA is derived from the linear amine, diethylenediamine, by the addition of five acetate groups. The resulting ligand was octadentate with three nitrogen donor atoms and five carboxylate oxygen donor atoms [36], as shown in figure 2(a). The coating mechanism of (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA NPs is related to the chelating agent DTPA, which can be stable in a solid or liquid state by two valences, auxiliary and principal. Its functional group contains donor atoms such as O and N, which can be coordinated to Gd³⁺, Fe²⁺ and Fe³⁺. DTPA has affinity for the metal cations to form stable complexes and reverse the metal binding after chemical treatment for encapsulation of Gd³⁺ and ferrites. The order of affinity of the contrast agent chelator endogenous ions is Gd³⁺ > Fe⁵⁺ > Fe³⁺ [37]. The (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA structures did not change after weeks of storage in the powder. Gd–DTPA protected the (Fe₃O₄/γ–Fe₂O₃) surface of the environment. Naked (Fe₃O₄/γ–Fe₂O₃) NPs were unstable in water after washing. However, the coated NPs increased their stability in water from 3 to 4 h.

Figure 4. Topography and profiles from AFM-MFM for (Fe₃O₄/γ–Fe₂O₃)@Gd–DTPA NPs: (a) (Fe₃O₄/γ–Fe₂O₃) NPs, (b) MG–1, and (c) MG–2. The tip coated radius and magnetic forces decreased the spatial resolution.

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The (Fe$_{3}$O$_{4}$/γ–Fe$_{2}$O$_{3}$) NPs had a mean diameter of 11.58 ± 1.69 nm, as shown in figure 3(a), (b). The SAED exhibited the diffracted rings corresponding to the planes: (220), (311), (400), (422), (511) and (440); of the inverse cubic spinel as XRD, figure 3(c). The MG–1 had average particle size of 9.88 ± 1.89 nm coated by amorphous Gd–DTPA with thickness of 2.5 nm figures 3(d), (e). The MG–2 NPs had particle size of 9.07 ± 1.53 nm, and Gd–DTPA coating of 10.5 nm figures 3(g), (h). The characteristic SAED rings from (Fe$_{3}$O$_{4}$/γ–Fe$_{2}$O$_{3}$)@Gd–DTPA showed the amorphous coating contribution in figures 3(f), (i). The Fe$_{3}$O$_{4}$ nanoparticles prepared by coprecipitation of ferrous and ferric ions in aqueous solution produced NPs agglomeration effect. This method allows the elimination of the organic bases by washing. The Fe ions at the NPs surface can be linked to –OH, –COOH, or –NH$_{2}$ to increase their stability. The coprecipitation route allowed to define the contrast of the Gd–DTPA coating by TEM. It is possible to use other synthesis methods as colloidal or solvothermal. However, the oleic acid, n-octylamine, or oleylamine used in these routes are not eliminated from the NPs. A better option to reduce the agglomeration is the dispersion in citrate acid. However, the application of organic dispersants reduces the contrast of amorphous Gd–DTPA layer using TEM [38, 39].

The AFM–MFM topography analysis was performed by Lift mode in a scanned area of 300 × 300 nm. The (Fe$_{3}$O$_{4}$/γ–Fe$_{2}$O$_{3}$) NPs, MG–1 and MG–2 nanostructures exhibited a roughness of 23. 49, 45.15 and 62.00 nm, respectively, figures 4(a)–(c). This difference was associated with the thickness of the Gd–DTPA layer. The particle sizes in average were measured by profiles of figure 3(a) 14.4 ± 1.1 nm, 3(b) 11.8 ± 2.1 nm and 3(c) 16.1 ± 4.2 nm for (Fe$_{3}$O$_{4}$/γ–Fe$_{2}$O$_{3}$) NPs, MG–1 and MG–2, respectively. In the case of MG–2, this formed agglomerations of 44.2 ± 4.5 nm on average due to Gd–DTPA.

3.2. (Fe$_{3}$O$_{4}$/γ–Fe$_{2}$O$_{3}$)@Gd–DTPA NPs bonding and composition

The FTIR spectra of GdCl$_{3}$·6H$_{2}$O, DTPA and synthesised Gd–DTPA are shown in the figure 5(a). In the GdCl$_{3}$·6H$_{2}$O spectrum, the bands at 3372, 1160 and 640 cm$^{-1}$ are assigned to asymmetric and symmetric stretching and bending vibrations of H–O–H [40]. The Gd–Cl interaction was observed in a broad transmittance band at 1402 cm$^{-1}$. The band at 1628 cm$^{-1}$ is a consequence of the chemical interaction between Gd$^{3+}$ and H$_{2}$O [41]. In the case of DTPA, the bands at 1736, 1696 and 1633 cm$^{-1}$ correspond to C=O bending in –COOH [42]. Comparing the FTIR spectra of GdCl$_{3}$·6H$_{2}$O and DTPA with Gd–DTPA synthesised, the broad band that contains the two wavenumbers, 1626 and 1595 cm$^{-1}$, belonging to asymmetric and symmetric stretching vibrations of –COO$^{-}$ of DTPA, respectively, in Gd$^{3+}$ coordination [43]. The peak at 1736 cm$^{-1}$ disappeared in the Gd–DTPA spectrum, indicating that the carboxyl proton dissociates, and the oxygen atom was coordinated to the metal, indicating the successful attachment of Gd$^{3+}$ and DTPA [44].

![Figure 5](image-url)

**Figure 5.** (Fe$_{3}$O$_{4}$/γ–Fe$_{2}$O$_{3}$)@Gd–DTPA NPs bonding: (a) FTIR spectra of GdCl$_{3}$·6H$_{2}$O, DTPA and synthesized Gd–DTPA (b) FTIR from MG–1 and MG–2, the band at 1626 cm$^{-1}$ was associated to Gd–DTPA bonding; (c) wide-scan XPS spectra exhibited the bonding energies of Fe 3p, C 1s, O 1s and Fe 2p, and mainly Gd photoelectron lines at 1219, 1186 and 143 eV.
The Gd–DTPA thin coating and (Fe₃O₄/γ-Fe₂O₃) NPs produced the FTIR spectra shown in figure 5(b). The (Fe₃O₄/γ-Fe₂O₃) NPs had a characteristic band of Fe–O at 570 cm⁻¹. The structural defects showed a wide broadening in the MG–1 and MG–2 spectra. The deflection band at 630 cm⁻¹ was defined by Fe₃O₄ surface oxidation as (Fe₃O₄/γ-Fe₂O₃) NPs, which matched well with the XRD data. The broad band centred at 3354 cm⁻¹ was related to the stretching vibrations of –OH adsorbed on (Fe₃O₄/γ-Fe₂O₃) [45]. This band was shifted to 3408 cm⁻¹ in the nanostructure spectra of MG–1 and MG–2. This shift was attributed to the N–H stretching vibration, due to DTPA contribution [46]. In addition, DTPA has a characteristic peak at 1682 cm⁻¹ from the C=O stretching vibration. The band at 1626 cm⁻¹, confirmed the (Fe₃O₄/γ-Fe₂O₃)@Gd–DTPA NPs as a result of carboxyl bonds in the MG–1 and MG–2 spectra, figure 5(b).

The XPS spectra showed photoelectron lines at bonding energies of 55, 285, 530 and 710 eV, corresponding to Fe 3p, C 1s, O 1s and Fe 2p, respectively [47]. The elemental surface compositions are shown in table 2. The carbon are shown increased from 37.98 at % in MG–1 and MG–2, and small amounts of nitrogen were
associated with the DTPA coating. Therefore, the Gd$^{3+}$ ion was located by energy photoelectron lines at 1186 and 1219 eV for Gd$3d_{3/2}$ and Gd$3d_{5/2}$, respectively and a small peak in 143 eV for Gd$4d$ [16, 48], figure 5(c).

A quantitative composition analysis was performed using EDS–SEM. The EDS spectra showed the atomic compositions of Fe, C, O and Gd. Gd$^{3+}$ atoms were not detected in MG–1, because of their low concentration over the (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$ NPs surface below the detection limit (<1% minimum detectable mass fraction), figure 6. The results matched well with the atomic percentages observed in the XPS analysis.

### 3.3. Magnetic analysis

The characteristic closed hysteresis loops were obtained from (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$ NPs, MG–1 and MG–2 at 300 K and applied field $H = \pm 30$ kOe as SPIONs, figure 7. The MG–1 and MG–2 exhibited low remanence ($H_R$) and coercivity ($H_C$) values. The MG–1 magnetisation ($M_2$) (62.72 emu g$^{-1}$) and $H_C$ (27.82 Oe) were different comparing with (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$ NPs, $M_5$ (70.58 emu g$^{-1}$), and $H_C$ (22.44 Oe). These differences were associated with (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$ lattice distortion, as a consequence of interphase defects in (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$@Gd–DTPA NPs thin coating (2.5 nm), and small disruption that could be caused by Gd–DTPA in the long-range order of magnetic spins from (0.06 at % Gd$^{3+}$) [49]. The (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$@Gd–DTPA NPs in-situ changed $M_{2\theta}$ to 75.82 emu/g and $H_C$ to 18.94 Oe. A major Gd$^{3+}$ quantity of local magnetic moments were dispersed over (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$ surface by chelation Gd–DTPA and their organic interactions. The layer thickness (10.5 nm and 0.72 at % Gd$^{3+}$) increased the local alignment of Gd$^{3+}$ magnetic moments by applied magnetic field [33, 50].

MFM measurements of SPIONs in powder are a real challenging. These NPs can be attracted to the magnetic tip. In these cases, the tips can be cleaned by argon or nitrogen flow at a low pressure and recovered. The main requirement for AFM-MFM is that this sample must be flat. The powders show differences between topological features owing to pronounced hills and valleys. In addition, the orientation of MDs implies the assembly and agglomeration of nanoparticles due to the exchange between neighbouring MDs, and magnetostatic interactions. The scanning of areas below 500 × 500 nm define the topography and the MDs mapping in SPIONs. Therefore, the MDs local magnetic structure is defined by their alignment in the direction of applied magnetic field and collinear magnetic field lines in the lift mode. The MDs were evaluated by scanning areas of 300 × 300 nm as attractive and repulsive shifting interactions by the magnetic tip over the NPs surface [51]. MFM lift mode images showed magnetisation ($H^\uparrow$) and demagnetisation ($H = 0$) sequences in figure 8 for 8(a) (Fe$_3$O$_4$)/γ–Fe$_2$O$_3$ NPs, 8(b) MG–1 and 8(c) MG–2. The arrows in the profiles indicated the orientation of the
The response of the magnetic stray field above sample showed a random distribution of MDs at initial conditions ($H = 0$) in the three cases. The MDs were aligned at ($-12 \text{kOe} < H < 12 \text{kOe}$) in the direction of magnetic field lines. These results showed uniaxial anisotropy. The MDs returned to the initial conditions (disorder), under demagnetisation conditions in all cases [52]. The MDs reorientation showed faster relaxation of MG-1 and MG-2 by Gd–DTPA coating than naked ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$) NPs (see the sequence in the supplementary information, S1 (available online at stacks.iop.org/NANOX/2/020019/mmedia)). The naked ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$) NPs require more relaxation time to recover the initial conditions. The saturation conditions indicated that ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$)@Gd–DTPA NPs were oriented owing to their superparamagnetic behaviour, because of their low coercivity and remanence. The MFM showed that the local magnetic structure is defined by particle size, shape, and composition in coherence with the magnetisation. The agglomeration showed the same MDs orientation at magnetization conditions [53].

The temperature influences the MDs orientation of ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$)@Gd–DTPA NPs because of the thermal barrier is reduced as the particle size becomes in the superparamagnetic diameter. MDs can randomly change their direction with respect to temperature. The diffusion in the magnetisation magnitude increases rapidly with temperature when $T < T_c$ and saturates at $T_c$. Beyond $T_c$, SPIONs diffusion becomes isotropic and independent of temperature [54, 55].

The MFM-zoom shows the MDs alignment ($H^\uparrow$) in the 3D images, figure 9. The profiles indicated the deflection by attractive and repulsive interactions magnetic lines in the range of $-20$ to $20$ deg. The parallel lines indicate the uniaxial anisotropy defined by the MDs orientation at $90^\circ$ for the ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$)@Gd–DTPA NPs, figure 9. The parallel magnetic lines had sizes of 2.01 nm for ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$) NPs, 1.36 nm for MG-1 and 1.22 nm for MG-2. The noise was resolved to 0.02 deg in the MFM.

Local Gd$^{3+}$ dispersion over ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$) NPs surface introduced small differences; however, the MDs alignment and coherence were achieved owing to the shape, size, defects and amorphous Gd–DTPA layer. The main control parameter for SPIONs as carriers and diagnosis is the MDs orientation. Anisotropy plays an important role in magnetic stimulation. The shape related to the semispherical shapes of NPs introduces strong magnetic field over a larger magnetic volume [56]. This anisotropy is a key parameter for the RF tuning and can be modified from the NPs shape. The ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$)@Gd–DTPA NPs can be considered to induce proton interactions along the z-axis for spin-lattice relaxation time, $T_1$ at $90^\circ$ flipping and the alignment in the xy-plane.

Figure 9. MFM-Zoom measurements of ($\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$)@Gd–DTPA NPs in saturated magnetisation ($H^\uparrow$) and profiles; (a) $\text{Fe}_3\text{O}_4/\gamma\text{Fe}_2\text{O}_3$ (b) MG-1, and (c) MG-2.
in a magnetic moment net of zero for spin-spin relaxation time $T_2$ as dual ($T_1-T_2$) by pulsed RF. As a reference, the spin-echo scans employ two RF pulses with flip angles of 90° and 180° that produce a spin echo. The 180° pulse serves to refocus the transverse magnetisation, cancelling the dephasing effects caused by inhomogeneities in the local magnetic field $[57]$, as shown in figure 10.

4. Conclusions

The $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)@\text{Gd-DTPA}$ NPs were synthesised by coprecipitation. The Gd–DTPA Gd–DTPA chelation allowed the addition of Gd$^{3+}$ magnetic moments over $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)$ surface. The $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)$ NPs with sizes of 9–12 nm were coated with Gd–DTPA, 10.5 nm of thick, and atomic Gd concentration 0.72%. The addition of Gd$^{3+}$ ions with large magnetic moment (7.9 $\mu_B$) to this surface increased the magnetisation from 70.58 emu/g for $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)$ NPs to 75.82 emu/g for $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)@\text{Gd-DTPA}$ NPs. The sum of superparamagnetic cores and paramagnetic local domains dispersed by Gd–DTPA coating allowed the MDs alignment 90° owing to the uniaxial anisotropy. These returned to random distribution by demagnetisation. The $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)@\text{Gd-DTPA}$ could induce dual relaxation ($T_1-T_2$) in water proton by MRI. Future analysis of the $(\text{Fe}_3\text{O}_4/\gamma-\text{Fe}_2\text{O}_3)@\text{Gd-DTPA}$ NPs toxicity and additional experiments must be performed before any application.

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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).
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