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Scaling Laws at the Nano Size: The Effect of Particle Size and Shape on the Magnetism and Relaxivity of Iron Oxide Nanoparticle Contrast Agents

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Abstract

The magnetic properties of iron oxide nanoparticles govern their relaxivities and efficacy as contrast agents for MRI. These properties are in turn determined by their composition, size and morphology. Herein we present a systematic study of the effect of particle size and shape of magnetite nanocrystals synthesized by thermal decompositions of iron salts on both their magnetism and their longitudinal and transverse relaxivities, r_1 and r_2 , respectively. Faceted nanoparticles demonstrate superior magnetism and relaxivities than spherical nanoparticles of similar size. For faceted nanoparticles, but not for spherical ones, r_1 and r_2 further increase with increasing particle size up to a size of 18 nm. This observation is in accordance with increasing saturation magnetization for nanoparticles increasing in size up to 12 nm, above which a plateau is observed. The NMRD (Nuclear Magnetic Resonance Dispersion) profiles of MIONs (Magnetic Iron Oxide Nanoparticles) display an increase in longitudinal relaxivity with decreasing magnetic field strength with a plateau below 1 MHz. The transverse relaxivity shows no dependence on the magnetic field strength between 20 MHz and 500 MHz. These observations translate to phantom MR images: in T_1 -weighted SWIFT (SWEEP imaging with Fourier Transform) images MIONs have a positive contrast with little dependence on particle size, whereas in T_2 -weighted gradient-echo images MIONs create a negative contrast which increases in magnitude with increasing particle size. Altogether, these results will enable the development of particulate MRI contrast agents with enhanced efficacy for biomedical and clinical applications.

Introduction

Due to their high saturation magnetization (M_S), superparamagnetic nanoparticles of magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) are increasingly prominent in biomedical and engineering applications; chief among them are magnetic nanodevices,^{1,2} hyperthermia therapy^{3–7} and contrast agents for Magnetic Resonance Imaging (MRI).¹ In terms of MRI and therapeutics, the growing interest in using Magnetic Iron Oxide Nanoparticles (MIONs) stems from three of their properties: (1) their optimum magnetic behavior renders them potent transverse relaxation agents for medium and high-field MRI. Whereas the

longitudinal relaxivity of macromolecular gadolinium systems typically peaks at 20 MHz and decreases sharply at the higher magnetic fields of now-current clinical scanners, the transverse relaxivity of particulate contrast agents remains constant at high magnetic field. (2) Rapidly alternating magnetic fields cause MIONs to significantly increase the temperature of their immediate surroundings which enables the nanoparticles to readily induce localized cell death.¹ This property, known as hyperthermia, is especially sought after in cancer therapy.⁶ Although it is difficult to tune MIONs so as to optimize both their relaxivities and hyperthermic capability simultaneously, in principle all MIONs are inherently both diagnostic (MRI contrast agents) and therapeutic (hyperthermia agents) in nature rendering them all, in essence, theranostic drugs. (3) In view of the recent toxicity concerns observed with gadolinium-based MRI contrast agents which are likely due to leaching of the gadolinium ion from the complex,^{8, 9} the lower toxicity of iron oxide nanoparticles renders them a particularly attractive clinical alternative, especially for patients suffering from kidney damage.⁸

Iron oxide nanoparticles are undeniably finding increasing applications in diagnostics and biomedical research. A requirement for their successful translation, however, remains a deeper understanding as to how every structural parameter of these materials affects not only their magnetic behaviour but also their longitudinal (r_1) and transverse (r_2) relaxivities. Only then will researchers reliably synthesize nanoparticles of optimized physicochemical properties as required for their MRI applications. Of these parameters, composition, aggregation^{1, 10-12} and surface coatings¹³ have already received attention. Herein we are focusing on the shape and size of the nanoparticles, two parameters that substantially affect the efficacy of this class of contrast agents.

The increase in relaxation rate of water protons induced by superparamagnetic iron oxide nanoparticles originates from dipolar coupling between the magnetic moment of water protons and the electron magnetic moment of the particles. Extensive theoretical modelling, especially by Gillis, Roch and Gossuin,^{10, 11, 14-18} have highlighted the relationship between the structural parameters of MIONs and the magnetic field dependencies of the longitudinal and transverse relaxivities. In term of transverse relaxivity, this relationship is simple: r_2 increases linearly with increasing magnetic field until a plateau is reached around 0.5 T due to an increase in the magnetization of the particles from zero to their saturation value following the Langevin function. This trend was confirmed by Bulte for the USPIO (Ultra Small Particles of Iron Oxide) MION-46L,¹⁹ although a complete, systematic study relating the size of maghemite/magnetite nanocrystals in non-aggregated MIONs to their transverse relaxivity has yet to be reported.²⁰

For longitudinal relaxivity, the relationship is more complex as it incorporates two different origins: the Néel relaxation which is based on flipping of the magnetic moments of the crystal from one anisotropy direction to another and the Curie relaxation that involves the diffusion of water protons near the magnetic crystals. The contribution of each mechanism to the longitudinal relaxivity varies with both the strength of the applied magnetic field and the anisotropy of the maghemite or magnetite crystals, the latter being in turn a function of the size of the crystals⁵ with larger iron oxide crystals being characterized by high crystal anisotropy.¹² For large nanoparticles, at low applied magnetic field, the magnetic moment is free to flip from one anisotropy direction to another and both the Néel relaxation and the Curie relaxation contribute to the longitudinal relaxivity which follows the Freed spectral density.²¹ At high magnetic field, however, the magnetic moment is locked with the magnetic field direction and Néel relaxation is no longer possible. The relaxivity is now governed by the Ayant spectral density.²² Very small iron oxide crystals, on the other hand, are characterized by smaller anisotropy energy so that the locking of the particle magnetization onto the anisotropy direction is attenuated but, importantly, not completely

removed. This distinction is particularly important at the lower frequency of the NMR dispersion profiles.¹⁶

The relaxivities and the magnetic field dependencies of the relaxivities, given by the Nuclear Magnetic Relaxation Dispersion (NMRD) profiles, of iron oxide nanoparticles are a function of the anisotropy energy of the crystals, which in turn determines their Néel relaxation time. The anisotropy energy is a function of four parameters:¹⁰

1. The bulk magnetocrystalline anisotropy field, which depends on the chemical composition and the crystallographic structure of the material. Both maghemite (γ - Fe_2O_3) and magnetite (Fe_3O_4) have inverse spinel structures, although the bulk saturation magnetization of the former (73.5 emu/g) is lower than that of the latter (92 emu/g).²³
2. The demagnetizing field, which is determined by the shape of the crystal. This component is equal to zero for perfectly spherical crystals and increases with the elongation of the crystals.
3. The surface anisotropy field. Surface spin canting have a net impact on the magnetism of small iron oxide nanoparticles.^{24, 25} In terms of relaxivity, we have previously demonstrated that this translates, among other effects, to a greater influence of the nature of the polymer coating on the smaller nanoparticles, and of the chemical functionalities anchoring the polymer coating on the surface of the iron oxide crystals.¹³
4. The mutual anisotropy induced by the dipolar coupling between nearby crystals in agglomerated structures, such as in SPIOs (Small Particles of Iron Oxide). This component increases in significance as the intercrystal distance decreases. It is thus a key component to the change in relaxivity for particulate responsive contrast agents which are based on biomarker-induced controlled aggregation of MIONs.

The size of the iron oxide core affects the anisotropy energy, and consequently the relaxivity of the contrast agents, in multiple ways. The surface spin canting induced by the organic coating has a greater impact for smaller nanocrystals and the anisotropy energy increases with increasing particle size. This, in turn, increases the Néel relaxation time and decreases the Néel component of water relaxation, particularly at high magnetic field.

With the exception of the study by Lin,²⁶ previous reports relating the influence of nanoparticle size on the transverse relaxivity of non-agglomerated MIONs,^{27, 28} have been limited to no more than two or three different sizes and to measurements at a single applied magnetic field. The effect of crystal size on longitudinal and transverse NMRD profile has yet to be reported. Moreover, to the best of our knowledge, the effect of the shape of the nanocrystals, a component of their anisotropy energy, on the relaxivity of the nanoparticles has not been studied. The effect of particle size and shape on relaxivity should reflect, at least in part, the relationship between particle size and magnetic property, specifically saturation magnetization (M_S), remanence (M_R), and coercivity (H_C). Systematic studies on this relationship, however, remain sparse. As such, it remains difficult to clearly establish the scaling law between nanoparticle size and magnetic property. The report herein aims to validate the current theoretical model on longitudinal and transverse relaxivity described above with a systematic study relating the effect of the size and shape of iron oxide nanocrystals on their magnetic properties and on the magnetic field and temperature dependence of both r_1 and r_2 . Oleic acid-coated iron oxide nanoparticles were synthesized by.

Results and discussion

Synthesis

high temperature thermal decomposition of either $\text{Fe}(\text{acac})_3$ or $\text{Fe}(\text{oleate})_3$ according to the procedures developed by Sun et al.²⁹ and Jana et al.,³⁰ respectively. The procedure of Sun resulted in irregularly faceted nanoparticles that were grown in size in a stepwise fashion: larger nanoparticles were produced by adding a layer of iron oxide to nanoparticles one size smaller. This, unfortunately, results in increasingly greater polydispersity as the nanoparticles become larger. Spherical nanoparticles, on the other hand, were synthesized in one-pot method from $\text{Fe}(\text{oleate})_3$ precursors. Each of these two techniques resulted in MIONs with lower degrees of polydispersity and enhanced magnetic properties than those produced by coprecipitation of $\text{Fe}(\text{II})$ and $\text{Fe}(\text{III})$ salts in basic aqueous solutions.³¹ Irregularly faceted nanoparticles of diameter 4.9 ± 1.1 nm, 7.1 ± 1.4 nm, 9.4 ± 1.9 nm, 10 ± 2 nm, 15 ± 3 nm and 18.3 ± 2.8 nm, and spherical nanoparticles of size 8.7 ± 1.3 nm, 13 ± 1 nm, and 16 ± 2 nm were synthesized (Figure 1). Each of these procedures was reported to produce MIONs composed of magnetite and not maghemite. This feature would be beneficial given the higher bulk saturation magnetization of magnetite over maghemite. It should be noted, however, that since both formulations have the same inverse spinel structure, it is not possible, especially at the nanosize, to distinguish with certainty between the two compositions. Therefore, without further experimental proof as to the composition of our nanocrystals, they are referred to as MIONs or iron oxide nanoparticles throughout the text. Importantly, XRD characterization indicates good agreement between crystallite sizes determined from the XRD patterns and sizes measured by TEM (Figure 2). For faceted nanoparticles 4.9 and 15 nm in diameter (as measured by TEM), an XRD crystallite size of 4.8 and 12.1 nm were calculated. Similarly, for spherical nanoparticles 8.7 nm in diameter, an XRD crystallite size of 6.0 nm was determined.

While the high temperature decomposition syntheses result in particles of high magnetization and low polydispersity, the resulting nanoparticles are stabilized by hydrophobic surfactants. Consequently, the particles can only be dispersed in organic solvents such as hexanes or chloroform. Since relaxivity is a measure of water proton relaxation rate, the particles must undergo a phase transfer to an aqueous suspension in order to measure the effect of their size on r_1 and r_2 . The primary concern is that the MIONs must be rendered hydrophilic while preserving both their composition and their surface anisotropy. Indeed, we have previously reported that replacement of the oleic acid coating with a hydrophilic polyethylene glycol (PEG) polymer can adversely affect $M_S r_1$, and r_2 , particularly if the anchoring group (the terminal portion of the PEG that holds the macromolecule to the surface of the nanoparticle) is a weak iron chelator.¹³ For our intended study, the effect of the solubilizing polymer on anisotropy energy must thus be minimized as much as possible. Achieving water dispersibility therefore required the use of a non-invasive phase transfer agent such as hexadecyltetramethylammonium bromide (CTAB), which does not interrupt the binding environment of the surface iron cations with oleic acid and oleylamine. The hydrophobic tail of CTAB intercalates in between those of the oleylamine and oleic acid surfactants bound to the crystal, leaving the positively charged ammonium exposed to the solvent (Figure 3), thereby rendering the nanoparticles readily dispersible in water. Notably, the initial ligand coverage is not altered by the CTAB coating. This was established by three complementary measurements: FT-IR of the oleic acid-coated and oleic acid/CTAB-coated nanoparticles demonstrated that CTAB does not replace oleic acid, nor does it disturb substantially its packing. ZFC/FC and magnetic hysteresis measurements further indicated that neither the blocking temperature, T_B , nor the saturation magnetization, M_S were affected by the supplementary CTAB layer. These data were identical to those published in our earlier studies.¹³

CTAB-coated MIONs are stable in water over extended periods of time and the coating process has been shown to be effective in both the phase transfer of nanoparticles as well as attenuating particle aggregation in water.^{32, 33} This last point is of particular importance as particle aggregation strongly affects their mutual anisotropy, which in turn substantially affects both r_1 and r_2 . The lack of particle aggregation in aqueous suspensions of the CTAB-coated MIONs studied herein was established by Dynamic Light Scattering (DLS). In each case, the hydrodynamic diameter was ca. 6–10 nm larger than that of the metallic core determined by TEM. It should be kept in mind though, that the level of aggregation observed with CTAB coating is highly dependent on the nature and concentrations of salts present in the solution. All studies described therein were performed in pure water so as to further minimize aggregation.

Magnetism

The magnetic hysteresis of the irregularly faceted nanoparticles measured at 300 K are shown in Figure 4. As expected, since the measurements were performed above the blocking temperature, no hysteresis, that is zero magnetic remanence and coercivity are observed. Additionally, the particles reach their saturation magnetization at 0.5 T as expected for superparamagnetic nanoparticles.³⁴ At room temperature, the saturation magnetization increases with increasing crystal size until a size of 12 nm, above which M_S becomes independent of crystal size and a plateau at ca. 43 emu/g is reached.

The relationship between particle size and saturation magnetization is currently not well understood. For most measurements performed at 5 K, which is well below the blocking temperature, Roca,^{27, 35} Goya³⁶ and Guardia³⁷ observed that the size of the magnetite or maghemite crystal has negligible effect on M_S , with the exception of very small nanoparticles (4 nm) for which slightly smaller saturation magnetization is observed. However, as the temperature at which the hysteresis is measured increases so does the effect of crystal size on saturation magnetization. At 77 K, which is still below the blocking temperature, Lin observed a distinct dependency of crystal size on M_S which ranges between 57 emu/g and 85 emu/g for particles ranging between 8 and 18 nm in size.²⁶ At 300 K, this trend is further accentuated. Goya previously observed that not only does the saturation magnetization decrease as the measurement temperature increases, but that this decrease is more pronounced for very small crystals (4 nm).³⁶ Decreasing M_S with decreasing particle size is generally attributed to increasing surface spin canting due to increasing disorder of the oleic acid and oleylamine surface binding ligands as the particles decrease in size.^{24–26} In this respect, our measurements are in agreement with previous observations with the added benefit that since we have evaluated more than three particle sizes, the trend and the size required to reach a plateau in M_S is now clearly established.

Measurements performed below the blocking temperature are characterized with a hysteresis which, in accordance with published literature, is also a function of particle size (Figure 5). The magnetic coercivity, H_C , increases as the particles become larger with $H_C = 0.013$ T and 0.032 T for nanoparticles 7.1 nm and 18 nm in size, respectively.

An interesting observation is made when comparing the experimental hysteresis measured at room temperature for the irregularly faceted crystals synthesized from thermal decomposition of $\text{Fe}(\text{acac})_3$ to the spherical ones produced from $\text{Fe}(\text{oleate})_3$ precursor (Figure 6). Whereas the faceted crystals present a pure superparamagnetic behavior with a clear saturation magnetization reached at 1.0 T, the spherical nanoparticles do not. The failure of the spherical crystals to reach a saturation value clearly indicates the presence of a paramagnetic contribution to the magnetism of spherical nanoparticles. This observation would suggest that the synthetic procedure followed to obtain the spherical nanoparticles does not yield crystals that are purely magnetite and/or maghemite in composition.

However, since Dunlop and coworkers observed similar changes in the hysteresis of arrays of oriented iron particles of different shape,³⁸ another interpretation could be that the lack of a clear saturation magnetization could be due to the shape of the nanocrystals which is a primary component of their configurational anisotropy. Muxworthy and Paterson have previously determined that for equidimensional particles of magnetite, the interaction of the domain structure and grain geometry has a significant influence on the coercivities; the configurational anisotropy that depends on the magnetization direction within the grain is independent but of similar magnitude to the magnetocrystalline anisotropy.³⁹ Regardless of the interpretation, the consequences of this small change in the shape of the magnetic hysteresis curve on the longitudinal and transverse relaxivities of the MIONs is severe (*vide infra*).

Size dependence of longitudinal and transverse relaxivities

The longitudinal and transverse relaxivities of hydrophilic CTAB-coated MIONs as a function of their size and shape is shown in Figure 7. The transverse relaxivity, r_2 , of the irregularly faceted nanoparticles somewhat, but not entirely, mirror the magnetic data previously discussed. Note that the magnetic (SQUID) data and the relaxivity measurements were performed on the same batch of nanoparticles. For irregularly faceted nanoparticles, transverse relaxivity measured at 1.4 T (60 MHz) and 37°C increases linearly with increasing particle size from $53 \text{ mM}^{-1} \text{FeS}^{-1}$ for 4.9 nm nanoparticles to $156 \text{ mM}^{-1} \text{FeS}^{-1}$ for 18 nm nanoparticles. Unlike hysteresis measurements, for which the saturation magnetization measured at 1.4 T plateaus for particle greater than 12 nm in size – no such plateau is observed in the transverse relaxivity of these nanoparticles measured at the same magnetic field.

The longitudinal relaxivity of the irregularly faceted nanoparticles is also dependent on the size of the crystal. This relationship is more complex in nature and is more pronounced at lower applied magnetic field (*vide infra*) where the same trend for longitudinal relaxivity is observed as for transverse relaxivity: the relaxivity increases with increasing crystal size. At 60 MHz, however, where the Curie relaxation mechanism is predominant, a more complex trend is observed where r_1 is relatively invariant of size between 8 nm and 18 nm (Figure 8a).

In contrast, the spherical nanoparticles synthesized by thermal decomposition of Fe(oleate)_3 do not show any size dependency of their transverse, nor longitudinal relaxivities (Figure 7). Moreover, in each case, the spherical nanoparticles have significantly worse r_2 than the faceted analogs of similar size. For 16 nm nanoparticles for instance, the spherical MIONs have half the transverse relaxivity as the faceted ones. A similar trend is observed for longitudinal relaxivity. In each case, for a same particle size, the r_1 of the spherical MION is less than a third that of the faceted MIONs. The shape of the crystal does influence its demagnetizing field, which in turn influences its anisotropy energy and thus also the relaxivities.

These results show the limits of the simpler relationship recently reported by Gossuin and Sandre who proposed that the transverse relaxivities of MIONs could be predicted solely from the size of the particles impermeable to water proton and their saturation magnetization.⁴⁰ Indeed, our observations highlights a crucial dependence on the shape of the crystal cores. This dependence could be the result of either varying configurational anisotropy between faceted and spherical grains or to a slight difference in the composition of the core. Neither of these parameters was taken in consideration by Gossuin and Sandre. Indeed, it appears that magnetite and maghemite cannot be considered equivalent with regards to relaxivity, and that the synthetic procedure followed to synthesize the iron oxide core has a substantial effect on the efficacy of the MIONs.

Field dependence of longitudinal and transverse relaxivities: NMRD profiles

The NMRD profiles, which highlight the dependence of the longitudinal and transverse relaxivities on the applied magnetic field are shown in Figure 8. Regardless of crystal size, the USPIOs do not demonstrate any field dependence of their transverse relaxivities between 20 MHz (0.5 T) and 500 MHz (11.7 T). This observation is in agreement with previous calculations by Gillis among others¹⁸ that demonstrated that r_2 increases linearly with increasing magnetic field following a Langevin function only until saturation magnetization is reached, beyond which r_2 plateaus. The magnetic hysteresis of the USPIOs indicates that in each case, saturation magnetization is reached by 0.5 T (Figure 4). It thus follows that r_2 should be constant for any magnetic field beyond this value.

The dependence of the longitudinal relaxivity on the applied magnetic field is more complex and highlights the dependence of r_1 on the two different mechanisms: the Néel relaxation and the Curie relaxation, the proportion of each contribution being further dependent on the size of the crystal. Strictly speaking, the Curie relaxation arises from diffusion of the proton into the inhomogeneous nonfluctuating magnetic field created by the mean crystal moment aligned onto B_0 . The Néel relaxation, on the other hand, is due to the fluctuations of the electronic magnetic moments of the superparamagnetic crystals. Iron oxide nanoparticles can only induce proton relaxation when the condition $\omega_I \tau_C < 1$ is reached, where ω_I is the angular frequency of the proton precession and τ_C is the global correlation time. τ_C is a function of the translational diffusion correlation time, τ_D , a parameter of the Curie relaxation, and the Néel relaxation time, τ_R . τ_R is in turn a function of the crystal anisotropy: the larger the crystal, the greater its anisotropy constant, the longer the Néel relaxation time, and the smaller the contribution of the Néel relaxation mechanism to the overall proton relaxation.

Large superparamagnetic crystals are characterized by higher anisotropy constants such that the anisotropy energy is larger than the thermal energy which maintains the direction of the crystal magnetic moment close to that of the anisotropy axis. The magnetic vector is locked along the B_0 direction, the Néel relaxation becomes negligible and the Curie relaxation dominates. As a result, for the larger crystals of size 15 nm and 18 nm, the longitudinal relaxivity follows Ayant's model. The relaxivity plateaus at very high value – 150 $\text{mM}^{-1}\text{Fe}^{-1}\text{s}^{-1}$ for 18 nm crystals and 125 $\text{mM}^{-1}\text{Fe}^{-1}\text{s}^{-1}$ for 15 nm crystals – up to ca. 1 MHz beyond which r_1 decreases sharply with increasing magnetic field and becomes nearly negligible above 100 MHz.

For superparamagnetic iron oxide crystals of medium size – 9.4 nm and 10 nm – the anisotropy energy is smaller than for the large crystals, but it is still large enough to prevent any precession of the magnetic moment. The magnetic fluctuations then arise from jumps in the moment between different easy axis. This does not affect the high field component of the relaxivity where the Curie relaxation still dominates. Beyond 10 MHz, r_1 still decreases sharply with increasing magnetic field. At low magnetic field, however, the relaxivity now follows Freed's model where the electron Larmor precession frequency is set to zero. As a result, at low magnetic field, the relaxivity continues to decrease with decreasing crystal size as the anisotropy energy also decreases. Importantly, however, a peak in proton longitudinal relaxation rate now appears at intermediary fields between 2 MHz and 10 MHz. This peak in the profile shifts to higher magnetic field strength as the crystal decreases in size. The presence of a maximum value in r_1 arises from the combination of the high-field (Ayant) and low-field (Freed) contribution to relaxivity weighed according to the Langevin function.

Very small iron oxide crystals – 4.9 nm and 7.1 nm – on the other hand, are characterized by smaller anisotropy energy such that locking of the particle magnetization onto the anisotropy direction is attenuated but, importantly, not completely removed.¹⁶ The longitudinal

relaxivity profile can then be calculated by a linear combination of two extreme models: one where the anisotropy energy is assumed to be infinite,¹⁰ and the other, the classical outer-sphere theory of high susceptibility paramagnetic material, where the anisotropy energy is assumed to be zero.^{41, 42} As a result, as the crystal becomes smaller, the longitudinal relaxivity decreases, and the peak of the profile shifts to higher magnetic field.

Temperature dependence of r_1 and r_2

The temperature dependence of both the longitudinal and transverse relaxivities for small (4.9 nm), medium (10 nm) and large (15 nm) nanoparticles is shown in Figure 9. Longitudinal relaxivity displays relatively little dependence on temperature with a trend that depends on the size of the nanoparticles. For both small (4.9 nm) and, to a greater extent, large (15 nm) MIONs, r_1 increases with increasing temperature. For medium sized crystal (10 nm), on the other hand, r_1 decreases with increasing temperature. In each case, the data becomes significantly noisier above 45°C, which may reflect a lack of stability of the CTAB coating and increased spin canting at higher temperature.

Transverse relaxivity displays a consistent and steep dependency on temperature, with r_2 increasing exponentially as temperature decreases. This trend is further accentuated the larger the nanoparticles. Although it is questionable as to why the longitudinal relaxivity does not follow the same temperature dependence as the transverse relaxivity, the observation for the latter are in agreement with the Ayant spectral density. At 60 MHz, the magnetic moments of the nanoparticles are locked on to the magnetic field direction, such that Néel relaxation is negligible and the primary component to relaxivity is the Curie relaxation. In this case, the transverse relaxation rate is inversely proportional to the diffusion coefficient, which decreases as the temperature decreases.

MRI phantoms

SWIFT (SWEEP Imaging with Fourier Transform) and T_2^* -weighted gradient echo MR images of equimolar iron concentrations of colloidal suspensions (phantoms) of CTAB-coated USPIOs of size varying from 5 nm to 18 nm measured at 9.4 T are shown in Figure 10. These images confirm the trends in longitudinal and transverse relaxivities reported above. The MIONs function as effective T_1 contrast agents which results in a positive contrast in SWIFT images. The contrast observed in the SWIFT images mirror the longitudinal relaxivities discussed above. Particles > 5nm in size have similar r_1 and give similar contrast, little dependency on the particle size is observed. Similarly, the USPIOs are remarkable T_2 contrast agents, which severely decrease the signal intensity of gradient-echo images. In this case the larger the nanoparticles, the higher their transverse relaxivity, and the darker the gradient-echo images. Since the transverse relaxivity increases with crystal size at a much steeper rate than longitudinal relaxivity, the effect of crystal size on gradient-echo images is more pronounced than on SWIFT images. Importantly, these images highlight the effectiveness of the SWIFT pulse sequence in obtaining purely T_1 -weighted images with a positive contrast for MION contrast agents which have very short T_2 's.⁴³ Unlike for gradient-echo images, in the case of SWIFT the very short T_2 's of the suspensions do not influence the contrast. T_1 -weighted gradient echo images are significantly affected by the very short T_2 's of colloidal suspensions of iron oxide nanoparticles. As a result, MIONs actually show negative contrast in T_1 -weighted gradient-echo images, such that it is difficult to correlate directly signal intensity to crystal size or aggregation.⁴⁴

Conclusions

The longitudinal and transverse relaxivities of USPIOs, and consequently the brightness of SWIFT (T_1 -weighted) and gradient echo (T_2^* -weighted) MR images of their colloidal

suspensions, are highly dependent on both the size of the iron oxide crystal and on the procedure followed to synthesize them. Irregularly faceted nanoparticles synthesized by thermal decomposition of $\text{Fe}(\text{acac})_3$ present substantially higher longitudinal and transverse relaxivities than those of similar size synthesized from $\text{Fe}(\text{oleate})_3$ precursors. This observation holds true for several particle sizes even though all nanoparticles are characterized by a superparamagnetic behavior (magnetic hysteresis) and inverse spinel structure (XRD) indicative of either a magnetite or maghemite composition. The transverse relaxivity of the irregularly faceted USPIO increases linearly with crystal size and is independent of the applied magnetic field between 20 MHz and 500 MHz. Both observations are in agreement with our current understanding of transverse relaxivity. R_2 increases linearly with increasing crystal size according to the Langevin function and increases linearly with applied magnetic field until the saturation magnetization is reached, beyond which a plateau is observed. Moreover, transverse relaxation rates of aqueous colloidal suspensions are highly dependent on temperature: r_2 decreases noticeably as the temperature increases from room temperature (20°C) to body temperature (37°C). This parameter should be taken into consideration when evaluating MIONs intended for clinical applications at room temperature. Their efficacy as T_2 -weighted contrast agents in spin echo images will invariably be worse *in vivo* than *in vitro* measurements performed at room temperature.

The longitudinal relaxivity is also dependent on both the size of the nanoparticles and on the procedure followed to synthesize them. As the particles increase in size, an increase in r_2 is followed, albeit to a lower extent, by an increase in r_1 . The NMRD profile presents a size-dependency which corresponds to a change in anisotropy constants and thus a change in the mechanism of proton relaxation, with the Néel relaxation preferred for smaller nanoparticles at weaker magnetic fields while the Curie relaxation predominates for larger crystals and at higher magnetic fields. Importantly, the longitudinal relaxivity always decreases significantly above 10 MHz, a factor that limits the efficacy of MIONs as positive T_1 contrast agents for high field MRI.

Experimental section

General considerations

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Water was distilled and further purified by a Millipore cartridge system (resistivity $18 \times 10^6 \Omega$). TEM images were collected on a JOEL JEM1210 and an FEI Tecnai T12. Relaxivities were measured at 37 °C and 1.4 T (60 MHz) on a Bruker Minispec mq60. Magnetic resonance images were acquired on a 9.4-T, 31-cm horizontal bore magnet (Magnex Scientific, Oxford, UK) interfaced with a Varian INOVA console (Varian, Palo Alto, CA, USA). The magnet was equipped with a gradient insert capable of reaching 450 mT/m in 200 s (Resonance Research, Inc., Billerica, MA). The radiofrequency (r.f.) coil assembly consisted of a linear surface coil (12 mm diameter). Magnetic data (hysteresis plots) were recorded on a commercial SQUID magnetometer (MPMS-XL - Quantum Design) and obtained at 10 K by using maximum applied fields up to 1 T in field cooling treatment. Powder X-ray diffraction (XRD) was performed using a PANalytical X-Pert PRO MPD X-ray diffractometer equipped with a cobalt source and an X-Celerator detector. Data was collected over the range of 10–90° 2θ at a scan rate of 0.68° per minute. The diffraction patterns were compared with the reference powder diffraction files (PDF) for magnetite (no. 19–629). $1/T_1$ ^1H NMRD profiles were measured on a fast field-cycling Stelar SmartTracer relaxometer (Mede, Pv, Italy) over a continuum of magnetic field strengths from 0.00024 to 0.25 T (corresponding to 0.01–10 MHz proton Larmor frequencies). The relaxometer operates under computer control with an absolute uncertainty in $1/T_1$ of $\pm 1\%$. Additional $1/T_1$ and $1/T_2$ data points in the range 20–60 MHz

were obtained on a Bruker WP80 NMR electromagnet adapted to variable-field measurements (20–60 MHz proton Larmor frequency) Stellar Relaxometer. $1/T_2$ relaxation rates at $B = 11.74$ T were acquired on a Bruker Avance III spectrometer operating at 500 MHz.

MRI

Magnetic resonance images were acquired on a 9.4-T, 31-cm horizontal bore magnet (MagneX Scientific, Oxford, UK) interfaced with a Varian INOVA console (Varian, Palo Alto, CA, USA). The magnet was equipped with a gradient insert capable of reaching 450 mT/m in 200 s (Resonance Research, Inc., Billerica, MA). A linear surface coil (12 mm diameter) was used. Gradient echo images were acquired using following parameters: $T_R = 60$ ms, $T_E = 2.4$ ms, field of view (FOV) = $5\text{ cm} \times 5\text{ cm}$, matrix = 512×256 , slice thickness = 5 mm, flip angle = 30° . In SWIFT sequence, RF excitation was performed with a hyperbolic secant pulse having a time-bandwidth product of 256, an excitation of bandwidth of 125 kHz, and a flip angle of 22° . The pulse was oversampled by a factor of 32. Data were collected in 256 pulse gaps of 6 μ s. The repetition time, including 2 ms pulse length, was 3.04 ms, the diameter of the FOV was 4 cm, and isotropic voxel size = 0.156 mm. Data in k-space consisted of 128,000 spokes. The terminus of the k-space vectors describe the isotropically distributed points on a sphere located in up to 32 interleaved spirals. The total acquisition time was 6 min.

NMRD

The water proton $1/T_1$ longitudinal relaxation rates were measured at 37°C using the standard inversion–recovery method with typical 90° -pulse width of 3.5 μ s, 16 experiments of 4 scans. The reproducibility of the T_1 data was estimated to be $\pm 1\%$. The temperature was controlled with a Stellar VTC-91 airflow heater equipped with a copper–constantan thermocouple (uncertainty $\pm 0.1^\circ\text{C}$). The $1/T_2$ data were measured using the Carr–Purcell–Meiboom–Gill pulse sequence (CPMG) at 37°C . At 11.74 T, 0.3 mL of the solution was inserted into a 5 mm NMR tube and 16 scans were acquired using t_{CP} values between 1 and 120 ms with a 90° -pulse width of 11 μ s. The data at 20, 40 and 60 MHz were measured on 0.2 mL of the solutions using 16 scans, t_{CP} values between 0.5 and 80 ms with a 90° -pulse width of 11 μ s. All experimental $1/T_1$ and $1/T_2$ values of relaxation rates were corrected for diamagnetic contributions using a solution of water at pH = 6.

4.9 nm faceted iron oxide nanoparticle seeds

Oleic-acid functionalized iron oxide nanoparticles were synthesized according to a procedure developed by Sun, et. al.²⁹ Briefly, $\text{Fe}(\text{acac})_3$ (2.2 g, 6.0 mmol), 1,2-hexadecanediol (7.8 g, 30 mmol), oleic acid (5.7 mL, 18 mmol) and oleylamine (5.8 mL, 18 mmol) were dissolved in benzyl ether (60 mL) in a round bottom flask. The mixture was stirred vigorously under nitrogen and heated for 2 h at 200°C followed by 1 h at 300°C . During this time, the mixture became black. The black suspension was then cooled to room temperature, and ethanol (120 mL) was added. The reaction mixture was centrifuged (10 min, 6000 rpm), and the black precipitate was collected. The product was re-suspended in *n*-hexane (90 mL) with oleic acid (0.15 mL) and oleylamine (0.15 mL). The suspension was centrifuged (10 min, 6000 rpm) to remove undispersed residue. Ethanol (120 mL) was then added to precipitate the nanoparticles, which were re-suspended and stored in *n*-hexane.

7.1, 9.4, 10, 15, and 18 nm faceted iron oxide nanoparticles

Oleic acid functionalized iron oxide nanoparticles of sizes larger than 6 nm were synthesized according to the step-wise procedure of Sun et al. using the 6 nm nanoparticles as seeds.²⁹ Briefly, $\text{Fe}(\text{acac})_3$ (0.73 g, 2.0 mmol), 1,2-hexadecanediol (2.6 g, 10 mmol), benzyl ether

(20 mL), oleic acid (2.8 mL, 2.0 mmol), and oleylamine (2.9 mL, 2.0 mmol) were dissolved in a round bottom flask under a flow of nitrogen. A sample of iron oxide nanoparticle seeds (2.0 mmol, dispersed in hexanes, 2 nm smaller than the intended final nanoparticle size) was added and the mixture was heated to 100 °C for 30 min, and then to 200 °C for 1 h. The temperature was increased to 300 °C for 1 h. The mixture was cooled to room temperature and ethanol (120 mL) was added. The reaction mixture was centrifuged (10 min, 6000 rpm), and the black precipitate was collected. The product was re-suspended in *n*-hexane (90 mL) with oleic acid (0.15 mL) and oleylamine (0.15 mL). The suspension was centrifuged (10 min, 6000 rpm) to remove undispersed residue. Ethanol (120 mL) was then added to precipitate the nanoparticles, which were re-suspended and stored in *n*-hexane.

Spherical 8.7, 13, and 16 nm iron oxide nanoparticles

Oleic acid functionalized spherical iron oxide nanoparticles were synthesized according to the procedure of Jana et. al.³⁰ Briefly, Fe(oleate)₃ (0.2 g, 0.2 mmol) and oleic acid (0.1 g, 0.6 mmol) were dissolved in 1-octadecene (4 mL). The solution was refluxed at 320 °C for 30 min under nitrogen after which the mixture was cooled to room temperature and a minimum amount of ethanol was added to precipitate the particles. The mixture was centrifuged (10 min, 6000 rpm), and the black precipitate was collected. The sample was redispersed in hexane, another minimum amount of ethanol was added. The precipitated particles were centrifuged (10 min, 6000 rpm) and redispersed in *n*-hexane. Spherical nanoparticles 13 and 16 nm in diameter were synthesized analogously using five and eight equivalents (0.28 g, 1.0 mmol and 0.45 g, 1.6 mmol; respectively) of oleic acid.

Surfactant functionalization

Functionalization of oleic acid coated nanoparticles with hexadecyltrimethylammonium bromide (CTAB) was performed as previously published.¹³ Briefly, oleic acid coated nanoparticles (10 mg) and CTAB (10 mg) were suspended in chloroform (5 mL) and the black mixture was stirred overnight. The solvent was removed under reduced pressure and the resulting brown solid re-suspended in mQ water. The particles were filtered through a microfilterfuge to remove large particulate cluster and stored in mQ water.

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Fig. 1.

TEM images of faceted oleic-acid functionalized nanoparticles synthesized by high temperature thermal decomposition of Fe(acac)₃ precursors (a – f) according to the procedure of Sun et al.²⁹ Spherical oleic acid functionalized nanoparticles were synthesized from Fe(oleate)₃ precursors (g – i) according to procedure of Jana et. al.³⁰ Nanoparticle size and polydispersities (to one standard deviation) are a) 4.9 ± 1.1 nm, b) 7.1 ± 1.4 nm, c) 9.4 ± 1.9 nm, d) 10 ± 2 nm, e) 15 ± 3 nm, and f) 18 ± 3 nm, g) 8.7 ± 1.3 nm, h) 13 ± 1 nm, and i) 16 ± 2 nm.

Fig. 2.

XRD spectra of a) 8.7 nm spherical MIONs, b) 4.9 nm faceted MIONs, c) 15 nm faceted MIONs, d) the reference pattern for magnetite (JCPDS #19-0629), and e) the reference pattern for maghemite (JCPDS #39-1346). Crystallite sizes, as calculated from the Scherrer equation, were determined to be 6, 5, and 12 nm, respectively, in good agreement with the sizes determined by TEM analysis, indicating the particles are predominantly monocrystalline in nature. The peak at $2\theta = 37^\circ$ in XRD pattern (a) originates from the silicon background.

Fig. 3.
Chemical structure of a) oleic acid coated iron oxide nanoparticles, and b) oleic acid and CTAB coated iron oxide nanoparticles.

Fig. 4.

a) Experimental room temperature magnetic hysteresis for faceted crystals 4.9 nm (a), 7.1 nm (b), 9.4 nm (c), 10 nm (d), 15 nm (e), and 18 nm (f). No magnetic coercivity is observed at temperatures above their blocking temperatures. b) Saturation magnetization increases with particle size until the crystal size reaches 15 nm.

Fig. 5.

Magnetic hysteresis plots collected at 10 K of faceted iron oxide nanoparticles 7.1 nm (dashed) and 18 nm (solid) in diameter. The magnetic coercivity increases from 0.013 T for the 7.1 nm nanoparticles to 0.032 T for the 18 nm nanoparticles (inset).

Fig. 6. Magnetic hysteresis plots of faceted 9.4 nm (solid line) and spherical 8.7 nm (dashed line) nanoparticles at 298 K. No magnetic coercivity is observed at temperatures above the blocking temperature of the nanoparticles. Note that the faceted nanoparticles, synthesized according to the procedure of Sun et. al.²⁹ present a clear saturation magnetization while the spherical nanoparticles synthesized according to the procedure of Jana et al.³⁰ do not.

Fig. 7.

Longitudinal (r_1 , a) and transverse (r_2 , b) relaxivity of Fe₃O₄@CTAB nanoparticles for faceted nanocrystals synthesized according to the procedure of Sun et. al.²⁹ (filled circles) and spherical nanocrystals synthesized according to the procedure of Jana et. al.³⁰ (open circles). For faceted nanocrystals, r_2 increases with particle size whereas r_1 remains invariant for particles ≤ 8 nm in size. Both r_1 and r_2 of spherical nanocrystals do not demonstrate any reliable size dependence. Error bars on the x-axis represent polydispersity of crystal size (one standard deviation), and y-axis error bars represent error in relaxivity (one standard deviation, $n = 3$). Experimental conditions: $B = 1.4$ T, $T = 37$ °C, mQ water, pH = 6.

Fig. 8. Standardized longitudinal (r_1 , a) and transverse (r_2 , b) NMRD profile of MION@CTAB nanoparticles as a function of crystal size for faceted nanoparticles: 4.9 nm (open squares), 7.1 nm (open triangles), 9.4 nm (open circles), 10 nm (x), 15 nm (filled triangles), and 18 nm (filled circles) in diameter. Experimental conditions: mQ water, pH = 6, T = 37°C.

Fig. 9.

The effect of temperature on longitudinal (r_1 , a) and transverse (r_2 , b) relaxivities of faceted nanoparticles, MION@CTAB. The decrease in transverse relaxivity with increasing temperature is more pronounced for nanocrystals composed of larger ferrite crystals. Faceted nanoparticles were 4.9 nm (x), 8.7 nm (open triangles), and 15 nm (filled circles). Experimental conditions: mQ water, pH = 6, 1.4 T.

Fig. 10.

MR images of colloidal suspensions of CTAB-coated MIONs of various crystal size in water. In each case, $[\text{Fe}]_{\text{total}} = 4 \text{ mM}$. Top: average crystal size in nm of MIONs imaged in each tube. a) T₁-weighted SWIFT image, b) T₂*-weighted gradient echo image.