Relaxivity of manganese ferrite nanoparticles

Peters, Joop A.

DOI
10.1016/j.pnmrs.2020.07.002

Publication date
2020

Document Version
Final published version

Published in
Progress in Nuclear Magnetic Resonance Spectroscopy

Citation (APA)
Peters, J. A. (2020). Relaxivity of manganese ferrite nanoparticles. Progress in Nuclear Magnetic Resonance Spectroscopy, 120-121, 72-94. https://doi.org/10.1016/j.pnmrs.2020.07.002

Important note
To cite this publication, please use the final published version (if applicable).
Please check the document version above.

Copyright
Other than for strictly personal use, it is not permitted to download, forward or distribute the text or part of it, without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license such as Creative Commons.

Takedown policy
Please contact us and provide details if you believe this document breaches copyrights.
We will remove access to the work immediately and investigate your claim.
Manganese ferrite nanoparticles are superparamagnetic and have very high saturation magnetization, which makes them candidates for application as MRI contrast agents. Because these nanoparticles are very effective enhancers of transverse relaxation, they are particularly suitable as negative ($T_2$-weighted) contrast agents. The magnitude of the relaxivity of nanoparticulate Mn ferrites seems to be determined mainly by the method of preparation, their dimensions, and their saturation magnetization.
1. Introduction

Magnetic resonance imaging (MRI) is a powerful tool in medical diagnostics, producing images that reflect differences in intensities of $^1$H NMR resonances, usually of water protons. These intensities are proportional to local $^1$H concentrations and can be modulated by longitudinal ($R_1 = 1/T_1$) and transverse ($R_2 = 1/T_2$) relaxation rates, and by a number of other factors, including diffusion. In the initial paper reporting the invention of MRI, Lauterbur demonstrated that the contrast in images of phantoms can be altered by enhancement of the water $^1$H relaxation rates by the addition of the paramagnetic MnSO$_4$ [1]. Later, paramagnetic contrast agents (CAs) based on other paramagnetic ions such as Gd$^{3+}$, Dy$^{3+}$, Ho$^{3+}$, and Fe$^{3+}$ were introduced [2].

The efficacy of a relaxation rate enhancing CA is usually expressed by its relaxivity, the longitudinal or transverse relaxation rate enhancement normalized for a solution with a concentration of 1 mM of paramagnetic metal ions ($r_1$ and $r_2$, respectively). MRI CAs can be distinguished according to the ratio $r_2/r_1$, CAs that increase $R_1$ significantly more than $R_2$ give rise to bright areas in $T_1$-weighted images and are called positive or $T_1$ CAs. $T_2$ or negative CAs increase $R_2$ of water protons significantly more than $R_1$ and produce dark areas in $T_2$- or $T_2^*$-weighted images.

The CAs that are most frequently applied in clinical practice are positive Gd$^{3+}$-based agents. Free Gd$^{3+}$ ions are toxic, and therefore their presence in vivo must be avoided. For the current clinical Gd$^{3+}$-based CAs, this is achieved by sequestering the metal ion using a strong chelating ligand, usually a DTPA- or DOTA-derivative [3–6].

Features of MRI include high spatial and temporal resolution, deep tissue penetration, and lack of ionizing radiation. However, the low sensitivity of the presently applied clinical MRI CAs is a serious shortcoming, particularly because most of these CAs distribute rather unselectively over the body. Nanoparticles (NPs) may be employed to overcome this by delivering a high payload of CA and thus creating high local concentrations in regions of interest such as tumors and arterial plaques. The local accumulation may be further enhanced by attachment of targeting vectors to the NPs and/or by exploiting the enhanced permeability and retention effect, the propensity of NPs to accumulate in tumors through the leaky neovascularature.

Gd$^{3+}$-based CAs have been in use for more than three decades and have proven to be generally extremely safe. Only 0.03% of all administrations (about 100 million worldwide) gave rise to serious adverse effects [7,8]. The high thermodynamic and kinetic stability of the Gd$^{3+}$-chelates are important safety factors; the half-life of the undissociated complex is large relative to the residence time in the body. However, reports of nephrogenic systemic fibrosis associated with linear Gd$^{3+}$-based MRI contrast agents (Gd$^{3+}$-complexes of DTPA derivates) in people with late-stage renal failure [8–10] and observations of long-term Gd$^{3+}$ retention and accumulation in the brains of patients with normal renal function [11–15], have given rise to concerns regarding this class of compounds. Although macrocyclic CAs (DOTA derivates) show higher kinetic stability than linear agents by multiple orders of magnitude, low levels of deposition of Gd$^{3+}$ have been reported for these agents as well.

The concerns about Gd$^{3+}$-based CAs have sparked renewed interest in the use of Gd$^{3+}$-free CAs, such as Mn-based CAs, for example [6,16]. Both high spin $d^4$ Mn$^{2+}$ and $d^6$ Mn$^{3+}$ complexes are paramagnetic and have potential as MRI CAs. Due to the higher electronic symmetry of Mn$^{2+}$, the electronic relaxation rates of Mn$^{2+}$ are usually considerably slower than those of Mn$^{3+}$, making the latter more favorable for optimal longitudinal relaxivities. Free Mn$^{2+}$ is less toxic than Gd$^{3+}$ and it plays an important role as a cofactor in many enzymatic reactions, including the antioxidant enzyme superoxide dismutase, as well as enzymes involved in neurotransmitter synthesis and metabolism in the brain. Therefore, there is almost no risk associated with long-term accumulation. However, its normal concentration in organisms is very low, for instance, 0.3–1 μg L$^{-1}$ in human blood [17]. Despite its important biological role, high concentrations of free Mn$^{2+}$ are neurotoxic, and therefore Mn$^{2+}$ needs to be sequestered for safe application as an intravenous CA in humans. Largely due to its lower charge, complexes are usually less stable than corresponding ones of Gd$^{3+}$. It is important to ensure that the dissociation of Mn-based CAs is minimized in order to avoid any adverse side effects such as neurotoxicity. On the other hand, given the inherently low sensitivity of MRI CAs, the increase in relaxation rate should be as high as possible. Finding a balance between kinetic stability and optimal sensitivity is an important challenge in the design of Mn-based CAs for human applications.

Superparamagnetic iron oxide nanoparticles (USPIOs) have found application in MRI as negative or $T_2$ CAs and ultrasmall iron particles (USIPs) are used as positive or $T_1$ CAs [18]. During the last decade, manganese ferrites have attracted much attention, mainly because of their applications as $T_2$ CAs in highly sensitive MRI probes. NPs based on mixed Mn-Fe oxides are interesting in this respect because they can be tuned to optimize the $R_1$ to values that are higher than for iron oxides, whereas ultrasmall NPs usually have higher $R_2$ values thanks to the slower electronic relaxation rate of Mn as compared to that of Fe. Here, Mn-ferrite NPs with potential as MRI CA are reviewed with a focus on the relaxivity aspects at magnetic field strengths between 0.5 and 1.5 T, at which most clinical MRI scanners operate currently [19,20]. Mixed Mn-Zn ferrites are included in this review but other mixed ferrites such as those with Co and Ni are not because these materials may be cytotoxic [21–24] and thus not very attractive for application as MRI CA.

2. Relaxivity of superparamagnetic nanoparticles

Superparamagnetic NPs with sizes less than about 20 nm usually contain a single Weiss domain, which means that the electron spins in an NP are aligned to produce a large overall magnetic moment that is the sum of the magnetic moments of the magnetic atoms that compose that NP. A single molecule of MnFe$_2$O$_4$ has a magnetic moment of a few μB (μB = Bohr magneton). But a spherical NP of MnFe$_2$O$_4$ with a diameter of 10 nm contains 6840 molecules and therefore has an overall magnetic moment that is a factor 6840 higher than that of a single molecule. The overall magnetization vector usually has two stable antiparallel orientations with respect to the crystallographic axes, which are denoted as the easy directions. Superparamagnetism is a regime where the correlation time of flipping of the overall magnetic moment is shorter than the experimental measuring time or in other words, the thermal energy of the system (kBT) is greater than the energy barrier between easy directions of the overall magnetic moment. Consequently, the magnetization in the absence of a magnetic field is zero. The state at lower temperatures is called the blocked (ferromagnetic) state and the transition temperature between the two regimes is the blocking temperature ($T_B$). At high temperatures, the superparamagnetic regime is limited by the Curie temperature ($T_C$), where the thermal energy exceeds the energies of the antiferromagnetic coupling between two adjacent nearest metal cations (the superexchange). Above $T_C$, the system becomes paramagnetic.

Several theoretical models have been developed for the understanding of the proton relaxivities of aqueous suspensions of superparamagnetic iron oxide NPs [25], and they can also be applied for Mn-ferrites. These models generally provide a good qualitative description of structure-relaxivity relationships.
The proton relaxivity of superparamagnetic NPs in aqueous media has inner- and outer-sphere contributions. The inner-sphere contributions arise from water protons that exchange between metal atoms at the surface and the bulk and generally can be modeled by the Solomon-Bloembergen-Morgan equations in a way similar to Gd$^{3+}$ and Mn$^{2+}$ chelates [16,18,26]. Often the inner-sphere relaxivity is neglected because it is assumed to be small compared to the outer-sphere relaxivity. The latter is due to water protons diffusing along the particles, without being bound. The outer sphere contribution to the relaxivity is determined by various mechanisms: (1) The Brownian rotation of the NP and (2) the flip of the crystal magnetization vector from one easy direction of anisotropy to another (the Néel relaxation). The correlation times associated with these mechanisms are $\tau_B$ and $\tau_N$, respectively. For a spherical particle, these correlation times are given by Eqs. (1) and (2), where $\eta$ is the dynamic viscosity, $K$ the anisotropy constant of the material, $k_B$ the Boltzmann constant, $T$ the absolute temperature, $V$ the volume of the NP, and $d$ its diameter.

$$\tau_B = \frac{\pi \eta d^3}{2k_B T}$$

$$\tau_N = \tau_0 e^{\eta V / k_B T}$$

Mn-ferrite NPs are predominantly used as $T_2$ CAs. Only the ultrasmall NPs have sufficiently large $r_1/r_2$ ratios at 0.5–1.5 T to be suitable for application as $T_1$ or dual $T_1$-$T_2$ CAs. An important parameter governing both $r_1$ and $r_2$ of NPs is the magnetization, expressed as magnetic moment of the nanoparticle (m$_{NP}$) per unit volume (M) or per unit of mass (m), respectively (see Eq. (3)). Here, $\rho$ is the density. Since saturation of the magnetization of Mn-ferrites generally occurs below 0.5 T (see below), the magnetization considered here usually is the value at saturation ($M_s$ or $m$). It would be convenient to express the magnetization in an analogous manner to relaxivities, i.e. per mole magnetic metal. In the literature, however, $\sigma$-values are usually expressed per kg bare NPs, but a few authors express them per kg metal, per kg Fe, or per kg coated NPs. Unless stated otherwise, the $\sigma$-values in the present review are expressed in $A m^2$ kg$^{-1}$ bare NP.

$$M = \frac{m_{NP}}{V} (A m^{-1}) \quad \text{or} \quad \sigma = \frac{m_{NP}}{V \rho} (A m^2 kg^{-1})$$

$M$ is proportional to the Larmor frequency shift associated with the NP ($\Delta \omega$), which at the equator (defined relative to the B$_0$-axis) on the surface of a spherical particle is given by Eq. (4), where $\gamma_M$ is the gyromagnetic ratio of the $^1$H nucleus and $\mu_0$ the permeability of a vacuum.

$$\Delta \omega = \frac{\gamma_M M}{3} = \frac{\gamma_M \rho \sigma}{3}$$

Recently, Vuong et al. have reviewed studies on the modeling of outer-sphere relaxation rates induced by superparamagnetic NPs [25]. Relaxation rates as a function of the $^1$H Larmor frequency ($\omega$) have been described with models for the motional averaging regime (MAR), which is defined by the condition $\Delta \omega \tau_D < 1$ ($\tau_D = d^2/4D$), where $\tau_D$ is the diffusion correlation time and $D$ the water diffusion coefficient. The longitudinal relaxation can then be described by Eq. (5) [27], where $C_{NP}$ is the number of particles per m$^3$, $L(x)$ is the Langevin function ($L(x) = \coth x - x^{-1}$) with $x = m_{NP} H / k_B T$.

$$R_1 = \frac{8\pi}{135} \frac{(H^2)}{4\pi} \frac{m_{NP}}{N} C_{NP} \frac{\mu_0 M}{D} \Delta \omega$$

For low anisotropy energy, the Néel relaxation dominates ($\tau_N \ll \tau_B$). Eq. (4) is given by Eqs. (6)–(8), $P$ is an empirical function depending on the anisotropy energy, and $J_f$ and $J_a$ are the Freed and Ayant spectral densities, respectively [27].

$$R = 14P \frac{L(x)}{x} f_a(\omega_H, \tau_D, \tau_N) + 14(1-P) \frac{L(x)}{x} + 6 \left[ 1 - 2 \frac{L(x)}{x} - L^2(x) \right] f_a(\omega_H, \tau_D, \tau_N) + 6L^2(x) f_a(\omega_H, \tau_D)$$

$$J_f(\omega, \tau_D, \tau_N) = Re \left( \frac{1 + (1/4)z^4}{1 + z^2 + (4/9)z^4 + (1/9)z^8} \right)$$

$$J_a(\omega, \tau_D) = \frac{1 + (5/8)z^2 + (1/8)z^4}{1 + z^2 + (1/2)z^4 + (1/6)z^6 + (1/64)z^8} \left[ \frac{z}{2 \omega \tau_D} \right]^{1/2}$$

When the anisotropy energy is so high that the magnetic moment of the particle is fixed on its anisotropy axis, the Brownian relaxation dominates the Néel relaxation and then, according to the rigid dipole model, $R$ is given by Eqs. (7)–(10) [28].

$$R = \left[ 14 \frac{L(x)}{x} f_a(\omega_H, \tau_D, \tau_N) + 6L^2(x) f_a(\omega_H, \tau_D) + 6 \left[ 1 - 2 \frac{L(x)}{x} - L^2(x) f_a(\omega_H, \tau_D, \tau_N) \right] \right]$$

$$\tau_D = \frac{2L(x)}{x - L(x)} \tau_B$$

$$\tau_N = \frac{x}{L(x)} \left( \frac{1}{\sinh x} \right) \tau_B$$

Simulations with the above models typically give $^1$H NMRD profiles as shown in Fig. 1. These profiles show that the highest $r_1$ values in the range of the currently most used clinical MRI scanners (0.5–1.5 T or LF = 20–64 MHz) can be reached with small NPs ($d \leq 10$ nm) that have high magnetization. The transverse relaxation is ascribed to the magnetic field inhomogeneities created by the superparamagnetic NPs, which leads to loss of phase coherence of the precessing nuclear spins. Various models have been developed to describe the resulting enhancement of transverse relaxation rates of spherical superparamagnetic NPs [18,25,29–32]. Three regimes can be distinguished with limits defined by the diffusion correlation time ($\tau_D$), the static correlation time ($\Delta \omega^{-1}$), and the correlation time $\tau_C$ (half the time interval between successive 180° pulses in a Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence).

### 2.1. The motional averaging regime (MAR)

This regime is also called the outer-sphere regime and can be applied for small particles if $\tau_D \Delta \omega < 1$. Under this condition, protons experience a large range of magnetic fields during their diffusion along the NPs. This results in a motional averaging effect of these NPs. For high magnetic field strengths ($> 1$ T), the transverse relaxation rate can then be described by Eq. (12) [32,33].

$$R_2 = R^*_2 = 16 \frac{16}{45} f_a(\Delta \omega)^2$$

Here $R_2$ and $R^*_2$ are the transverse relaxation rates measured in the presence and absence of refocusing pulses, respectively, and $f_a$ is the volume fraction of the NPs. Since the relaxation rate is proportional to $(\Delta \omega)^2$, it is also proportional to $M^2$ (or $\sigma^2$, see Eq. (4)), which is for Mn-ferrites at magnetic field strengths larger than 1 T, usually at the saturation value ($M^2$ or $\sigma^2$) or somewhat higher due to a paramagnetic contribution to the magnetization (see Section 3.2).
2.2. The static dephasing regime (SDR).

For relatively large NPs, when $D_D x > 2.72$, the diffusion can be practically neglected and $R_2^*$ is solely dependent on $D x$. Its magnitude can then be approximated by \[ R_2^* = \frac{2\pi}{3\sqrt{3}} \Delta \omega \] (13)

Eq. (13) is also a good approximation for $R_2$ as long as $D_D < D_L$ \[ D_L = \frac{1}{1.49} \left( \frac{1.52 + f x}{5/3} \right) \] (14)

with $x = \Delta \omega \tau_{CP}$. In the SDR regime, $r_2$ is linearly proportional to $M$.

2.3. The partial refocusing regime (PRR).

When $D_D > D_L$, the refocusing of the transverse magnetization during the CPMG pulse sequence becomes inefficient, which results in a decrease in $R_2$ compared to $R_2^*$ to an extent that depends on the magnitude of $\tau_{CP}$ according to Eq. (15) \[ R_2 = \frac{1.8f x^{1/3}(1.52 + f x)^{5/3}}{\tau_D} \] (15)

It can be concluded that upon an increase of the size of NPs, $R_2^*$ increases linearly with $D_D$ until the SDR is reached, where after $R_2^*$ as a function of $\tau_D$ is constant. In the MAR, $R_2$ and $R_2^*$ are equal, whereas, in the PRR, $R_2$ becomes smaller than $R_2^*$ if $\tau_D > \tau_L$ (see Fig. 2). Therefore, maximum relaxivities will occur for NPs with diameters that correspond to the transition between MAR and SDR. The region with maximum $R_2$ moves to smaller diameters upon an increase of $\tau_{CP}$. A gap between $R_2$ and $R_2^*$ and dependence of $R_2$ on $\tau_{CP}$ are indications that the sample is in the PRR.
Although sharp transitions between the regimes shown in Fig. 2 are not realistic, this model reasonably describes the relaxation behavior of Mn-ferrite NPs, at least qualitatively. A more elaborate model has been described, that predicts a smooth cross-over between the MAR and the SDR regimes [25,38].

Coating a bare superparamagnetic NP with a diamagnetic substance naturally has consequences for its relaxivity. Taking into account the distance dependence of $\Delta \tau$, $f$, and $\tau_{g}$, the following scaling may be applied for spherical NPs coated with a water-impermeable layer:

$$
\Delta \tau_{imp} = \Delta \tau_{core} \left( \frac{d_{core}}{d_{imp}} \right)^{3} \quad (16)
$$

$$
f_{imp} = f_{core} \left( \frac{d_{imp}}{d_{core}} \right)^{3} \quad (17)
$$

$$
\tau_{D,imp} = \tau_{D,core} \left( \frac{d_{imp}}{d_{core}} \right)^{2} \quad (18)
$$

Here, the subscripts imp and core denote the parameters for the coated and the bare NP, respectively. Substituting Eqs (16)-(18) into Eqs. (12), (13), and (15) gives the effect on $R_{2}$ and $R_{2}^*$ of coating with an impermeable layer [39].

For water-permeable coatings, the situation is more complicated; the value of $f$ cannot be calculated directly from the diameters before and after coating and the self-diffusion into the pores may be slower than in the bulk water; which may increase the local $\tau_{g}$ [40]. The latter effect will, by contrast, lead to an increase in $r_{2}$ in the MAR, no $r_{2}$-effect in the SDR, and a decrease in $r_{2}$ in the PRR on such coating. Monte Carlo simulations have shown that, also in the region of transition between MAR and SDR, decreased $R_{2}^*$ values are obtained [41]. Furthermore, protons exchanging between locations close to the paramagnetic centers and the bulk might contribute to the relaxivity of these systems. It should be noted that coating, particularly when it involves coordination of paramagnetic metal ions on the surface of the core, may influence the value of $\sigma_{s}$ as well (see Section 3.5).

3. Reliability of manganese ferrite nanoparticles

3.1. Magnetization of manganese ferrite nanoparticles

Nanoparticulate assemblies of single domain manganese ferrites exhibit superparamagnetic behavior. A typical curve of the magnetization $\sigma$ against the magnetic field strength $H$ at room temperature is fully reversible without magnetic coercivity and remanence (see for example Fig. 3) [42]. The latter is essential for biomedical applications because coagulation due to residual magnetization outside of a magnetic field is undesirable. Saturation of the magnetization for NPs with diameters larger than 5 nm generally occurs below 0.5 T at values that are higher than for Fe$_{3}$O$_{4}$ nano-assemblies. The curve of the magnetization as a function of the magnetic field strength $H$ can be described by a Langevin function (22), where $m_{np}$ is the magnetic moment of a single particle. Fitting of the experimental $\sigma-H$ curve with this equation affords the saturation magnetization $\sigma_{s}$ (in A m$^{2}$ kg$^{-1}$), often expressed as emu g$^{-1}$) and $m_{np}$. The ratio $\sigma_{s}/m_{np}$ is equal to the number of particles per kg (N) and $m_{np} = n\mu_{mol}$, where $n$ is the number of molecules (formula units) per NP and $\mu_{mol}$ is the magnetic moment per molecule ferrite [43].

$$
\sigma = \sigma_{s} \left[ \coth x - \frac{1}{x} \right] = N m_{np} \left[ \coth x - \frac{1}{x} \right] \quad \text{with} \quad x = \frac{m_{np}H}{k_{B}T} \quad (22)
$$

NPs with high $\sigma_{s}$ values are favorable for application as T$_{2}$ CAs as well as for efficient heat generation in AC magnetic field hyperthermia therapy of cancer and other diseases [44]. The generation of heat has also been exploited to induce drug release from capsules with a thermolabile shell loaded with MnFe$_{2}$O$_{4}$ NPs and the anti-cancer medicine doxorubicin [45]. Therefore, it is important to design nanoparticles with high and tunable $\sigma_{s}$ values. The main parameters that can be tuned to optimize the relaxivity are the composition of the ferrite, the size of the NPs, their shape, and their coating.

Spinel ferrites are ceramic ferrimagnetic iron oxide compounds with a complex crystal structure in which oxygen anions are in a face-centered cubic arrangement (space group Fd3m), while the much smaller intervening 2- and 3-valent metal cations occupy two different sublattices, denoted by A (or $T_{d}$) and B (or $O_{h}$). In the unit cell, the metal ions are coordinated by oxygen atoms, 8 of the 64 A-sites tetrahedrally and 16 of the 32 B-sites octahedrally whereas the remaining sites are not occupied (see Fig. 4) [46,47]. The general formula of these spinels can be represented as $[\text{M}^{2+}];\text{Fe}^{3+}];[\text{M}^{2+}\text{Fe}^{3+}];\text{M}^{2+}\text{Fe}^{3+}];\text{O}_{4}$, where M is a metal, usually a transition metal or Mg. The superscripts A and B indicate the location of the metal ions and square and round brackets are used for the A-and B-sites, respectively. Two limiting arrangements can be discriminated: (1) structures with 8 M$^{2+}$ ions at A-sites and 16 Fe$^{3+}$ ions at B-sites (i = 0) are called normal spinels and (2) structures having 8 Fe$^{3+}$ ions at the A-sites and B-sites occupied with both 8 Fe$^{3+}$- and 8 M$^{2+}$-ions (i = 1) are denoted as inverse spinels. In the above molecular formula, i is the fraction of M$^{2+}$ ions at B-sites and is called the degree of inversion [48]. The thermodynamically most stable distribution of
metal ions over the A- and B-sites depends on many factors including (1) the ion size: the smaller cations generally have a preference for tetrahedral A-sites, (2) the electronic configuration of the metal ions involved and their crystal field stabilization, (3) the Coulomb energy of the charged ions in the spinel lattice [47,49,50]. The normal spinel is the thermodynamically most stable Mn-ferrite, whereas most other ferrites of divalent ions show a preference for inverse spinel structures [47,51]. The net magnetic moment of these metal ferrites (M = Mn2+, Fe2+, Co2+, Ni2+, Cu2+, Zn2+), \( \mu_{\text{mol}} \) at 0 K decreases with the number of unpaired d-electrons from 5 to 0 \( \mu_B \) [53]. Moreover, the net magnetic moment of these metal ferrites (M = Mn2+), is dependent on the degree of inversion.

It should be noted that the values of \( \sigma_s \) are maximal at 0 K and decrease to 0 at the Curie temperature \( (T_C) \), where the materials become paramagnetic (see for example Fig. 5). The shape of a curve of \( \sigma_s \) as a function of the temperature is the resultant of the curves for the sublattices A and B, which sometimes may lead to a non-continuous shape [46]. Furthermore, the values of many magnetic properties of NPs are not the same as those of bulk materials. For example, the Curie temperature of MnFe2O4 tends to increase whereas \( \sigma_s \) generally decreases with decreasing particle size (see Section 3.2) [46,47,54,55]. The value of \( T_C \) is dependent on the strength of the superexchange interaction between the A and the B sublattices and therefore on the cation distribution over these sites. An increase in \( i \) corresponds with the replacement of the Mn2+-Fe3+ AB-superexchange interaction by the stronger Fe3+-Fe3+ interaction leading to a rise of \( T_C \).

For the MAR (see Section 2.1), \( r_2 \) is proportional to \( \sigma_s^2 \) and if it is assumed that the members of the MFe2O4 series (M is a transition metal ion) have about the same density, it follows that \( r_2 \) is approximately proportional to the square of the number of unpaired electrons of the metal ion M. Fig. 6 shows that this is in reasonable agreement with the experimental \( r_2 \) data. The high relaxivity of MnFe2O4 NPs has been exploited in tests of targeted probes based on these NPs demonstrating the potential in the detection of various types of diseases and in cell tracking [53,56–58].

3.2. Influence of the size of the nanoparticles

The size of NPs may influence the magnitudes of \( \sigma_s \) and \( \tau_D \), which are both parameters governing the transverse relaxivity (see Section 2). Often, the \( \sigma_s \) values of NPs are lower than predicted by estimation from the magnetic moments of the metal ions inside each particle. Moreover, an inspection of published \( \sigma_s \)-H curves shows that these curves sometimes continue to increase linearly with the magnetic field strength after “saturation”, particularly for the smallest NPs. This suggests that there is a paramagnetic contribution to the magnetization in addition to the superparamagnetic one. Therefore, a better fit can be obtained by including a term in Eq. (22) to account for this paramagnetic contribution.

![Fig 4. Structure of the unit cell of a cubic spinel. The four shaded octants are mutually identical, as are the unshaded octants. Reproduced from Ref. [46] with permission. Copyright 2008, John Wiley & Sons, Inc.](image)

![Fig 5. The temperature dependence of \( \sigma_s \) of some bulk ferrites. Data from ref. [47].](image)
It should be noted that in Ref. [53] \( \sigma_s \) is expressed per mass of magnetic atoms, whereas other data in the present paper are expressed per mass of ferrite (formula weight) unless stated otherwise. The lines are intended only as guides to the eye.

A similar approach has been followed by Bulte et al. to fit the magnetization curves of iron oxide NPs [59]. Fitting of \( \sigma-H \) curves with Eq. (23) provides \( m_{np}, \sigma_s, \) and \( C_{para} \). If the paramagnetic contribution is negligible, division of \( \sigma_s \) by \( m_{np} \) gives the number of superparamagnetic molecules (\( N \)) and thus also the weight or the volume of one NP can be calculated if the molecular weight and the density of the ferrite, \( n \) and \( \mu_{mol} \) are known.

\[
\sigma = \sigma_s \left( \coth \frac{x}{x} + C_{para} \right) \quad \text{with} \quad x = \frac{m_{np}H}{kT} = \frac{n\mu_{mol}H}{kT}
\]  

(23)

The paramagnetic contribution may be due to surface anisotropy effects due to atomic disorder and symmetry breaking. These effects result in orientations of surface spins that are not parallel with those of the core (this effect is also known as spin-canting). Canting of the surface spins in random directions results in a surface layer with net zero magnetization: a magnetically dead layer. The reduction in \( \sigma_s \) due to a dead layer can be related to its thickness (\( D_L \)) by Eq. (24), where \( d \) is the diameter of the NP. Simulations of \( \sigma_s \) as a function of \( d \) show that even a thin dead layer results in a large decrease in the value of \( \sigma_s \) of NPs with small diameters because the volume of the magnetically dead layer increases relative to that of the total volume of the NP (see Fig. 7).

\[
\sigma_s = \sigma_{s, bulk} \left( \frac{d - 2D_L}{d} \right)^3
\]

(24)

Alternative Eq. (25) has been used in various publications to estimate the effect of a dead layer on the magnitude of \( \sigma_s \) [61,63–66].

\[
\sigma_s = \sigma_{s, bulk} \left( 1 - \frac{6D_L}{d} \right)
\]

(25)

Since the magnetic moments of Mn\(^{2+}\) and Fe\(^{3+}\) are both 5 \( \mu_B \), the net magnetic moments of the normal and the inverse structures are identical (5 \( \mu_B \) at 0 K). Therefore, it may be expected that at a given temperature, MnFe\(_2\)O\(_4\) NPs always have the same \( \sigma_s \). However, the experimental \( \sigma_s \) values are found to be in the range of 2–90 A\(^2\) m\(^{-2}\) kg\(^{-1}\). In Fig. 8, values of \( \sigma_s \) obtained by fitting of 41 different published \( \sigma-H \) curves on spherical MnFe\(_2\)O\(_4\) NPs [64,67–86] with Eq. (23) are displayed as a function of the reported diameters.

(d) determined by transmission electron microscopy (TEM). Although the data points are rather scattered, they show a clear increasing trend in \( \sigma_s \) with \( d \). Fitting of these data with Eq. (24) gives as best-fit parameters \( \sigma^0_{s, bulk} = 74 \) A\(^2\) m\(^{-2}\) kg\(^{-1}\) and \( D_L = 0.4 \) nm. Considering the large extent of scattering in Fig. 8, the value for \( \sigma^0_{s, bulk} \) is in reasonable agreement with that measured in bulk material (80 A\(^2\) m\(^{-2}\) kg\(^{-1}\)) [47]. A comparison of the best-fit value for \( D_L \) with the cell dimensions of the unit cell of MnFe\(_2\)O\(_4\) (0.85 nm) suggests that the dead layer is formed mainly by the outer surface layer. This layer probably contains metal ions that are not fully coordinated, which may give rise to spin disorder. If in Fig. 8 only the data of NPs prepared using one particular procedure are considered, a better fit is obtained. For example, the red squares in Fig. 8, represent data for a series of MnFe\(_2\)O\(_4\) NPs that were prepared by thermolysis of metal salts in the presence of oleyamine (OA). The latter had a threefold role: it served as a solvent, as a reducing agent and as a capping agent. The resulting NPs showed \( \sigma_s \) values (at 300 K) increasing with the particle size.
from about 33 to 80 A² kg⁻¹ (after correction for the weight of the oleylamine at the surface).

The application of the fitting procedure described above gives \( D_{\text{bulk}} = 81 \text{ A}^2 \text{ kg}^{-1} \) and \( D_t = 0.3-\text{nm as best-fit parameters.} \)

The influence of the NP diameter on the transverse relaxivity through \( \tau_d \) is dependent on the operative regime. From Fig. 2, it may be concluded that for a particular \( \sigma_t \) value, maximum transverse relaxivities may be expected in the SDR between \( \tau_d \) and \( \tau_t \). Fig. 9 displays a plot of \( \sigma_t \) versus \( d \) in which the borders between the SDR and the MAR and PPR are represented by lines simulated with \( \tau_d = 2.72/\Delta \omega \) and \( \tau_0 = \tau_{\text{L}} \), respectively. Since under the SDR regime, \( \tau_d \) is linearly proportional to \( \Delta \omega \) and thus also to \( \sigma_t \) (see Eqs. \( 3 \) and \( 4 \)), the highest transverse relaxivities will be found for the highest \( \sigma_t \) values in the SDR in Figs. 2 and 9.

Almost all single-crystalline Mn-ferrite superparamagnetic NPs have core diameters below 20 nm and the maximum \( \sigma_t \) reported is for \( \text{Zn}_{0.4}\text{Mn}_{0.6}\text{Fe}_2\text{O}_4 \) (175 A² m⁻² kg⁻¹ magnetic atom ≈ 107 A² m⁻² kg⁻¹ material). Accordingly, very high \( \tau_2 \) values (860 s⁻¹ mM⁻¹, see Section 3.3.3) have been reported for this system [87]. As can be seen in Fig. 9, the relaxivity is near the boundary of the MAR and the SDR and thus is approximately the highest possible \( \tau_2 \) within this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since this class of CAs. Increasing the diameter by coating with a water-impermeable diamagnetic layer is counter-effective since...
870 K where it freezes [97]. At lower temperatures, the equilibration of the cation distribution becomes extremely slow.

A complicating factor in studies of Mn-ferrites may be the occurrence of the redox equilibrium between Mn$^{2+}$ and Fe$^{3+}$ (Mn$^{2+}$ + Fe$^{3+}$ ↔ Mn$^{3+}$ + Fe$^{2+}$) and (partial) oxidation of Mn$^{2+}$ to Mn$^{3+}$ by air. The latter may already occur during the synthesis, for example by co-precipitation, particularly under highly basic conditions [99]. Oxidation can be prevented by working in a strictly inert atmosphere, particularly during hydrolytic procedures at high pH. An elegant way to remove traces of Mn$^{3+}$ in ferrites is by reduction into Mn$^{2+}$ with hydrogen peroxide in an acidic medium (2Mn$^{3+}$ + H$_2$O$_2$ → 2Mn$^{2+}$ + O$_2$ + 2H$^+$) [100,101]. A hydrothermal synthesis of Mn$_{0.85}$Zn$_{0.15}$Fe$_{1.85}$O$_4$ carried out under less strictly inert conditions has been reported to result in contamination with 1% α-Fe$_2$O$_3$ and 2% Mn$_3$Zn$_2$O$_4$ [102].

Because Mn$^{3+}$-ions prefer a location in the B-site thanks to a relatively high crystal-field stabilization, oxidation also affects Mn$^{2+}$. Since, after oxidation, the magnetic moment of Mn is no longer the same as that of Fe$^{3+}$ but decreases from 5 to 4 $\mu_B$, the $\sigma_S$-value is influenced by changes in both the degree of oxidation and the degree of inversion.

For a full understanding of the magnetic properties of spinel Mn-ferrites knowledge of the stoichiometry, the valence of the metal ions, and their distribution over the A- and B-sites is indispensable, requiring measurements that are challenging [103]. Unfortunately, many publications lack complete information in this respect. The molar ratio Mn:Fe can be determined by inductively coupled plasma optical emission spectroscopy (ICP-OES) or by X-ray powder diffraction (XRD), and NPD can afford cation distribution data. The latter technique may also provide the magnetic moments of the A- and B-sites. $^{57}$Fe Mössbauer spectra have been used to obtain information on valences of the Fe-cations and their distribution, but it cannot always be used to determine the location of Fe$^{3+}$-ions [98], X-ray absorption fine structure (XAFS), X-ray absorption near edge structure (XANES), electron energy loss spectroscopy (EELS), X-ray photoelectron spectroscopy (XPS), and low-temperature spin-echo $^{55}$Mn- and $^{57}$Fe-NMR studies have been applied to determine the valences of metal ions in Mn-ferrites [52,67,104,105].

The thickness of a dead layer on the NP is also dependent on the preparation procedure. For example, the preparation of MnFe$_2$O$_4$ NPs by co-precipitation of MnCl$_2$ and FeCl$_3$ in aqueous NaOH has been reported to produce NPs with a thicker dead layer than by precipitation with aqueous solutions of alkanolamines. A similar phenomenon was observed with MnFe$_2$O$_4$ NPs prepared by solvothermal procedures using oleylamine as both the solvent and the capping agent [78]. These effects were attributed to the coordination of metal ions by the amines, which provides a higher surface spin order [60,78].

3.3.1. Stoichiometric manganese ferrites (MnFe$_2$O$_4$)

Bulk material and ceramically prepared NPs usually have about 20% of the Fe$^{3+}$ cations located in the tetrahedral A-sites ($i = 0.2$). Since the magnetic moments of Mn$^{2+}$ and Fe$^{3+}$ are both 5 $\mu_B$, the net magnetic moments of the normal and the inverse structures are expected to be identical (5 $\mu_B$ at 0 K). However, in practice, the net magnetic moment is always about 4.6 $\mu_B$ near 0 K [51]. Single crystals of MnFe$_2$O$_4$ generally appear to obey the relation (26) [106].

\[
m = 5 - 2i
\]  

Several explanations have been put forward to explain this. Šimša and Brabers suggested, based on high field susceptibility measurements, that the spin moments A and B sublattices of the inverse structure of a molecule MnFe$_2$O$_4$ are not co-linear, but that the Mn$^{3+}$-spins in the B sublattice are canted to the direction of the total magnetization by about 53°. DFT calculations have suggested that the most stable MnFe$_2$O$_4$ structures have Mn$^{3+}$-ions at the A site in the high spin state ($\mu = 5$ $\mu_B$), whereas those at the B sublattice are in an intermediate spin state ($\mu = 3$ $\mu_B$) [107]. A more likely explanation is that oxidation of Mn$^{2+}$ to Mn$^{3+}$ is involved, leading to a structure that can be represented as [Mn$^3_2$Fe$^{3+}_2$]($\mu$-Fe$^{2+}_2$-$\mu$-Fe$^{3+}$)$^4$O$_4$. This structure was supported by low-temperature spin-echo $^{55}$Mn- and $^{57}$Fe-NMR studies [52,104,105,108].

Similarly, it was demonstrated that the initial cation distributions of NPs prepared by wet co-precipitation of Fe$^{2+}$ and Mn$^{2+}$ and subsequent air oxidation at 343 K appeared to be different: [Mn$_{0.48}$Fe$_{0.52}$]$^4$O$_4$ [109]. Upon heating at 573 K, the cation distribution of this material changed irreversibly to become identical to that of ceramically prepared material. Chen et al. and Zhang et al. prepared similar systems by wet co-precipitation at 298 K followed by digestion at about 370 K for 2 h. The resulting compounds have been shown to have a metastable random cation distribution corresponding with the ratio of the Fe and Mn cations in the synthesis mixture [63,98]. Usually, the as-synthesized materials of aqueous co-precipitations have higher inversion degrees than ceramically prepared manganese ferrites. A 1/2 ratio Mn:Fe afforded systems with an initial high value of 0.61–0.67 because the thermal energy at 298 K is insufficient for redistribution of the cations. This as-synthesized mixture appeared to contain both divalent and trivalent Mn. Upon heating of this mixture up to 873 K in a vacuum, the Mn$^{3+}$ was reduced completely and irreversibly to Mn$^{2+}$ whereas no change of the oxidation state of Fe$^{3+}$ was observed by EELS spectroscopy. In this way, equilibrium states at lower $i$-values were reached ($i = 0.29–0.40$ at 298 K) [63,98].

Heat treatment of the same as-synthesized Mn-ferrite in air can result in partial oxidation of Mn$^{2+}$ to Mn$^{3+}$[63,109], which as shown by EXAFS studies, is accompanied by a relatively small change in the degree of inversion [42,110]. Since the Mn$^{3+}$ shows a preference for the octahedral sites, Mn$^{3+}$-ions in the A-sites exchange with Fe$^{3+}$-cations in the B-sites upon oxidation to Mn$^{3+}$. This may result in the formation of non-stoichiometric ferrites, in which the positive charge of these structures is probably counterbalanced by some cation vacancies in the crystals [42,63,106,111]. From the magnetic moments of Fe$^{3+}$, Mn$^{3+}$, and Mn$^{3+}$ (5, 5, and 4 $\mu_B$, respectively), it follows that the net magnetic moment per molecule decreases, which agrees well with the experimentally determined decrease in $\sigma_S$ with the oxidation, which for particles of the same size is also reflected in a decrease in $r_2$ [42,63,112].

A polycrystalline microparticulate sample of Mn-ferrite that was obtained by a heat treatment at 1400 °C for 24 h followed by quenching in water adopted a normal spinnel structure ($i = 0.2$) and can be described as [Mn$_{0.8}$Fe$_{0.2}$]($\mu$-Fe$_{1.8}$)$^4$O$_4$. Non-hydrolytic thermal decomposition of metal-complexes typically resulted in high purity magnetic cores with controllable particle sizes and higher magnetization than for hydrolytically prepared ferrites [53]. In this way, a series of NPs of high quality single crystalline metal spinel ferrites MnFe$_2$O$_4$ (M = Mn$^{2+}$, Fe$^{3+}$, Cu$^{2+}$, Ni$^{2+}$) was prepared [53]. The MnFe$_2$O$_4$ NPs with a size of 12 nm had an $\sigma_S$ value of 79 A m$^2$ kg$^{-1}$, which is higher than the $\sigma_S$ for Fe$_3$O$_4$ NPs of the same size (73 A m$^2$ kg$^{-1}$) and about the same as bulk MnFe$_2$O$_4$ (80 A m$^2$ kg$^{-1}$) [47].

In Table 1, relaxivities reported for single domain MnFe$_2$O$_4$ NPs are compiled together with the parameters that govern their magnitude. These NPs all have $d < 21$ nm. From Fig. 9, it can be concluded that the transverse relaxivity is in the MAR. With these NPs, $r_2$ values up to 450 s$^{-1}$ mM can be reached. The trends in $r_2$ are roughly in agreement with those calculated using Eq. (12) (see Fig. 11). In these calculations, the effects of the coating, which
are difficult to predict, were not taken into account. It is noticeable that all but one experimental values are higher than the calculated ones. Possibly, this may be attributed to the effect of the coatings. If the coatings were impermeable to water, the opposite effect would be expected according to Eq. (19). Probably almost all applied coatings were at least partly permeable. Possibly, the coatings increased the ordering at the core surface, which would lead to a rise in $r_S$ and thus also in $r_2$. Other possible $r_2$ increasing effects may be due to significant inner-sphere contributions by water or proton exchange between the coating and the bulk and to a local decrease of $r_0$ in the coating.

3.3.2. Non-stoichiometric manganese ferrites (Mn$_x$Fe$_{3-x}$O$_4$)

Relaxivities of non-stoichiometric manganese ferrites and parameters on which they depend are summarized in Table 2. Several groups have reported that the $r_S$ of Mn$_x$Fe$_{3-x}$O$_4$ NPs as a function of $x$ has a maximum at $x \approx 0.4–0.6$ (see Fig. 12) [119,121–124]. For example, spherical Mn$_x$Fe$_{3-x}$O$_4$ NPs with a diameter of about 18.5 nm, prepared by a thermal decomposition method of metal oleates, exhibited an almost linear increase in $r_S$ from 50.8 to 89.5 Am$^2$kg$^{-1}$ (mass of Fe + O) at 300 K between $x = 0$ and $x = 0.43$ (see Fig. 12) [122]. The $r_S$ values for systems with $x$ between 0 and 0.43 varied almost linearly (see Fig. 12) [122].

### Table 1

| Coating | $d_{TEM}$ (nm) | $d_{DLS}$ (nm) | $\sigma_s$ (Am$^2$kg$^{-1}$) | $T$ (K) | $B_0$ (T) | $r_1$ (s$^{-1}$ mM$^{-1}$) | $r_2$ (s$^{-1}$ mM$^{-1}$) | Ref. |
|---------|----------------|----------------|-----------------------------|---------|----------|--------------------------|--------------------------|-----|
| PEG-PEI | 3              | 1             | RT                          | 3       | 43       | 57                       | 107                      | [113] |
| PEG-PEI | 9              | 1             | RT                          | 3       | 57       | 107                      | 107                      | [113] |
| PEG-PEI | 18             | 1             | RT                          | 3       | 107      | 107                      | 107                      | [113] |
| DMSA    | 6              | 49            | 1.5                         | 208     | [53]     |                           |                          |     |
| DMSA    | 9              | 71            | 1.5                         | 265     | [53]     |                           |                          |     |
| DMSA    | 12             | 79            | 1.5                         | 358     | [53]     |                           |                          |     |
| PEG-PPG-PEG-di-succ | 10 | 29 | 1.6 | 300 | 1.5 | 236 | 228 | [114] |
| DMSA    | 7.6            | 215           | 53                          | 9.4     | 18.6     | 228                      | [115]                     |     |
| TP80    | 12             | 41            | 40                          | 298     | 1.5      | 384                      | [74]                      |     |
| DMSA    | 15             | 90            | RT                          | 4.5     | 422      | [87]                      |                          |     |
| TEG     | 7              | 39            | 0.5                         | 126     | 85       |                          |                          |     |
| Au@CTAB | 12             |               |                             | 1.5     | 4.0      | 56                       | [116]                     |     |
| CTAB    | 8.6            | 55            | 293                         | 9.4     | 197      | [42]                      |                          |     |
| CTAB    | 8.2            | 66            | 293                         | 9.4     | 346      | [42]                      |                          |     |
| Citric acid | 18 | 95 | 76 | 310 | 1.5 | 19.0 | 394 | [76] |
| DA-PEG$_{10000}$ | 6 | 48 | RT | 1.5 | 249 | [80] |
| DA-PEG$_{20000}$ | 6 | 13 | 48 | RT | 1.5 | 249 | [80] |
| DA-PEG$_{30000}$ | 6 | 19 | 48 | RT | 1.5 | 199 | [80] |
| DA-PEG$_{40000}$ | 6 | 23 | 48 | RT | 1.5 | 189 | [80] |
| DA-PEG$_{50000}$ | 6 | 27 | 48 | RT | 1.5 | 189 | [80] |
| DA-PEG$_{60000}$ | 12 | 22 | 88 | RT | 1.5 | 448 | [80] |
| DA-PEG$_{70000}$ | 12 | 24 | 88 | RT | 1.5 | 449 | [80] |
| DA-PEG$_{80000}$ | 12 | 29 | 88 | RT | 1.5 | 400 | [80] |
| DA-PEG$_{90000}$ | 12 | 35 | 88 | RT | 1.5 | 298 | [80] |
| DA-PEG$_{100000}$ | 12 | 42 | 88 | RT | 1.5 | 288 | [80] |
| Gal-PEG$_{10000}$ | 6 | 20 | 36 | 298 | 1.5 | 13.3 | 65 | [81] |
| Gal-PEG$_{20000}$ | 7.5 | 23 | 43 | 298 | 1.5 | 18.6 | 88 | [81] |
| Gal-PEG$_{30000}$ | 9 | 25 | 52 | 298 | 1.5 | 12.3 | 104 | [81] |
| Gal-PEG$_{40000}$ | 12 | 31 | 66 | 298 | 1.5 | 7.4 | 174 | [81] |
| Gal-PEG$_{50000}$ | 14 | 32 | 77 | 298 | 1.5 | 14.4 | 301 | [81] |
| Gal-PEG$_{60000}$ | 6 | 20 | 36 | 298 | 0.8 | 63 | [81] |
| Gal-PEG$_{70000}$ | 7.5 | 23 | 43 | 298 | 0.4 | 1.3 | 102 | [81] |
| Gal-PEG$_{80000}$ | 9 | 25 | 52 | 298 | 0.9 | 0.3 | 137 | [81] |
| Gal-PEG$_{90000}$ | 12 | 31 | 66 | 298 | 2.3 | 2.3 | 262 | [81] |
| Gal-PEG$_{100000}$ | 14 | 32 | 77 | 298 | 1.3 | 3.36 | [81] |
| CTAB | 21 | 63 | 308 | 0.5 | [117] |
| NDOPA-PEG$_{500}$ | 7.8 | 61 | RT | 3 | 448 | [79] |
| Phosphorylated mPEG$_{20000}$ | 2 | 8 | 19 | 300 | 3 | 8.4 | 21 | [86] |
| Phosphorylated mPEG$_{30000}$ | 3 | 9 | 25 | 300 | 3 | 8.2 | 22 | [86] |
| Phosphorylated mPEG$_{40000}$ | 3.9 | 13 | 29 | 300 | 3 | 7.0 | 27 | [86] |
| PEG$_{500}$ | 6.4 | 34 | 310 | 9.4 | 0.7 | 118 | [66] |
| DHCA | 14 | 43 | 300 | 7 | 125 | [69] |
| DHCA | 8 | 32 | 75 | 300 | 7 | 241 | [69] |
| DHCA | 3.9 | 21 | RT | 7 | 6.7 | 27 | [118] |
| CREKA | 4.1 | 19 | RT | 7 | 6.8 | 25 | [118] |
| mPEG$_{1000}$ | 3.1 | 26 | 300 | 3 | 9.9 | 23 | [119] |
| PEG6000 | 47.8 | 78 | RT | 1.5 | 1.24 | 61 | [120] |
| CTAB | 19.5 | 306 | 1.5 | 296 | [82] |

---

$^{a}$ CREKA = Cys-Arg-Glu-Lys-Ala; CTAB = cetyltrimethylammonium bromide; DA = dodecanoic acid; DHCA = 3,4-dihydroxyhydrocinnamic acid; DMSA = 2,3-dimercaptopropanoic acid; mPEG = methoxy polyethylene glycol; NDOPA-PEG = nitrodopamine-polyethylene glycol-carboxylate; PEG = polyethylene glycol; gal = gallol; PEI = poly(ethylene imine); PEG-PPG-PEG-di-succ = disuccinate of poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol); TEG = tetraethylene glycol; TP80 = tri-aminated polysorbate 80.

$^{b}$ Diameter of core as determined by TEM.

$^{c}$ Hydrodynamic diameter as determined by DLS.

$^{d}$ Expressed per mass bare MnFe$_2$O$_4$. Values reported as expressed per mass Mn(+Fe) atoms were corrected.

$^{e}$ Magnetic field strength or temperature at which the relaxivities were measured

$^{f}$ Expressed per mM of Mn + Fe
NPs with an increase of the ratio Fe $^{3+}$/Mn$^{2+}$ in the A-site [119,121], (2) random exchange coupling [121,123]. Citrate coated particles with a lower $r_2$ value exhibited a record high $r_2$ of 904 s $^{-1}$ at 7 T and 300 K, which is 4 times higher than $r_2$ of 216 s $^{-1}$ of the corresponding citrate coated magnetite, which was considered as an Fe$^{2+}$-deficient magnetite with 1/3 vacancy. The $\sigma$-$H$ curves showed a clear saturation and no paramagnetic contribution. Mn$^{2+}$ appeared to be located mainly in the A-sites. A maximum magnetization at $\sigma_2 = 80.3$ A m $^{-2}$ kg $^{-1}$ (at 300 K) was observed for NPs with $x = 0.35$. However, the highest $r_2$ value was observed for NPs with $x = 0.77$. This has been explained by the formation of aggregates in this sample as witnessed by dynamic light scattering (DLS) [110]. In a recent study on 8.5 nm NPs of metal-doped ferrites prepared by solvothermal decomposition of metal acetylacetonates, the variations of $\sigma_2$-values of Mn$_{0.3}$Fe$_{1.7}$O$_4$ NPs with $x = 0.35$ were relatively small; a vague maximum was observed for $x = 0.7$ ($\sigma_2 = 78$ A m $^{-2}$ kg $^{-1}$ at 300 K) [115]. Co-doping with Zn$^{2+}$ resulted in an increase of $\sigma_2$ up to 125 A m $^{-2}$ kg $^{-1}$ for Zn$_{0.2}$Mn$_{0.8}$Fe$_{2.0}$O$_4$ (see also section 3.3.3). These NPs were coated with a dodecylamine modified (isobutylene-alt-maleic anhydride) polymer. The $r_2$ values were only modest (21–72 s $^{-1}$-mM$^{-1}$ at 3 T and 300 K) and they did not reflect the trends observed in $\sigma_2$-values. Possibly, the relatively low $r_2$ can be ascribed to impermeability of the applied polymeric coating layer to water.

Preparation by co-precipitation afforded Mn$_{0.3}$Fe$_{1.7}$O$_4$ NPs with a diameter of about 20 nm that showed a linear decrease in $\sigma_2$ from 86.0 to 4.6 A m $^{-2}$ kg $^{-1}$ between $x = 0$ and 0.75 [130]. At the same time, the Curie temperature decreased from 610 to 510 K, suggesting that the AB-supercarzione is increasing upon replacement of Fe$^{2+}$ by Mn$^{2+}$.

Other preparation procedures generally result in materials with lower $\sigma_2$ values and thus lower $r_2$ values. Contamination with other metal ions and partial oxidation may influence $\sigma_2$ as well.

3.3.3. Manganese ferrites doped with zinc (Zn$_{x}$Mn$_{1-x}$Fe$_{2}$O$_4$

Doping of Mn$^{2+}$ with another metal ion that has a lower magnetic moment including Mn$^{2+}$ [42] Fe$^{2+}$, and Zn$^{2+}$ has substantial effects on the magnitude of $\sigma_2$ because these cations change the antiferromagnetic superexchange interaction between the A-sites and the B-sites [87]. EXAFS spectra indicated that the divalent metal ions prefer the tetrahedral A sites and the substitution of Mn$^{3+}$ and Fe$^{3+}$ [112]. In the long term, these NPs appeared to aggregate, which may explain these high $r_2$ values. The aggregation could be avoided by surface coating with sodium tricitrate [127]. Oxidation of Mn$^{2+}$ to Mn$^{3+}$ may disturb the trend described above, because of the lower magnetic moment of the latter (4 $\mu_B$ as compared to 5 $\mu_B$ for Mn$^{2+}$). The positions of the Fe- and Mn-edge peaks in the XANES spectra of Mn$_{0.3}$Fe$_{1.7}$O$_4$ NPs prepared by hydrothermal decomposition of Fe(acac)$_3$ and Mn(acac)$_2$ under an inert gas (Ar) have indicated the presence of considerable amounts of Mn$^{3+}$ and Fe$^{3+}$ [112].

Tuning of the ratio Mn/Fe in Mn-ferrites prepared by thermal decomposition of Mn(acac)$_3$ and Fe(acac)$_2$ is difficult because the decomposition temperatures of these complexes differ significantly (522 and 459 K, respectively). Therefore, the simultaneous incorporation of Fe$^{3+}$ and Mn$^{3+}$ is often not possible without the formation of a second phase of, for example, MnO, which is washed out during subsequent washing procedures. Since Mn(acac)$_3$ decomposes at about the same temperature as Fe(acac)$_3$, it might be a more suitable precursor than Mn(acac)$_2$ in the preparation of Mn$_{0.3}$Fe$_{1.7}$O$_4$ NPs. A series of Mn$_{0.3}$Fe$_{1.7}$O$_4$ NPs ($x = 0.29$–0.77, core diameter 5–6.5 nm) has been prepared by decomposition of Mn(acac)$_3$ and Fe(acac)$_2$ in a molar ratio 1:2 using a polyol as the solvent, which served also as a mild reducing agent for the Mn$^{2+}$ as well as for the surface coating of the NPs. The $x$-value of the product was dependent on the choice of the polyol [110,129]. It was assumed that Mn$^{3+}$ is almost completely reduced under the conditions applied whereas Fe$^{3+}$ is not. There will likely be vacancies to ensure that there is no excess positive charge on the spinel framework. A structure with $x = 0$ would resemble maghemite, which can be considered as an Fe$^{2+}$-deficient magnetite with 1/3 vacancy. The $\sigma$-$H$ curves showed a clear saturation and no paramagnetic contribution. Mn$^{3+}$ appeared to be located mainly in the A-sites. A maximum magnetization at $\sigma_2 = 80.3$ A m $^{-2}$ kg $^{-1}$ (at 300 K) was observed for NPs with $x = 0.35$. However, the highest $r_2$ was observed for NPs with $x = 0.77$. This has been explained by the formation of aggregates in this sample as witnessed by dynamic light scattering (DLS) [110]. In a recent study on 8.5 nm NPs of metal-doped ferrites prepared by solvothermal decomposition of metal acetylacetonates, the variations of $\sigma_2$-values of Mn$_{0.3}$Fe$_{1.7}$O$_4$ complexes with $x = 0.35$ were relatively small; a vague maximum was observed for $x = 0.7$ ($\sigma_2 = 78$ A m $^{-2}$ kg $^{-1}$ at 300 K) [115]. Co-doping with Zn$^{2+}$ resulted in an increase of $\sigma_2$ up to 125 A m $^{-2}$ kg $^{-1}$ for Zn$_{0.2}$Mn$_{0.8}$Fe$_{2.0}$O$_4$ (see also section 3.3.3). These NPs were coated with a dodecylamine modified (isobutylene-alt-maleic anhydride) polymer. The $r_2$ values were only modest (21–72 s $^{-1}$-mM$^{-1}$ at 3 T and 300 K) and they did not reflect the trends observed in $\sigma_2$-values. Possibly, the relatively low $r_2$ can be ascribed to impermeability of the applied polymeric coating layer to water.

Preparation by co-precipitation afforded Mn$_{0.3}$Fe$_{1.7}$O$_4$ NPs with a diameter of about 20 nm that showed a linear decrease in $\sigma_2$ from 86.0 to 4.6 A m $^{-2}$ kg $^{-1}$ between $x = 0$ and 0.75 [130]. At the same time, the Curie temperature decreased from 610 to 510 K, suggesting that the AB-supercarzione is increasing upon replacement of Fe$^{2+}$ by Mn$^{2+}$.

Other preparation procedures generally result in materials with lower $\sigma_2$ values and thus lower $r_2$ values. Contamination with other metal ions and partial oxidation may influence $\sigma_2$ as well.
Mn²⁺ in the normal spinel of MnFe₂O₄ with diamagnetic Zn gives a mixed ferrite [ZnₓMn₁₋ₓFe₂]O₄ (x = 0–1). In this case, part of the antiferromagnetic coupling between Mn²⁺ in the A-sites and Fe³⁺-ions in the B-sites is removed. The magnetic moment of the A-site is proportional to x and no net moment at 0 K for x = 0 (110 A m² kg⁻¹) and 3 T) [79]. Mixed Zn-Mn ferrites prepared by a hydrothermal precipitation method (at 453 K) showed, at room temperature, curves with a smooth decrease of r₂ from about 65 to 20 A m² kg⁻¹ over the A- and the B-sub-lattices, at the relatively low preparation temperature. Mössbauer spectroscopy study on 12 nm Mn₀·₆₅Zn₀·₃₅Fe₂O₄ has indicated that an irreversible phase transition to a stable phase occurs by cation rearrangement upon heating above about 500 K [133].

An alternative rationalization might be a preference for the normal spinel structure at x < 0.6, which would be in line with the degree of inversion of MnFe₂O₄, which is 0.2 [46]. Large particles (>100 nm) prepared by co-precipitation followed by calcining at 1373 K showed a similar trend [134]. From the fitting of the depen-

Table 2

| x    | Coating | d_{1nm} (nm) | d_{1LS} (nm) | σ_s (Am² kg⁻¹) | T (K) | B_0 (T) | r_1 (s⁻¹ mM⁻¹) | r_2 (s⁻¹ mM⁻¹) | Ref. |
|------|---------|--------------|--------------|---------------|------|--------|---------------|---------------|------|
| 1.12 | None    | 3            | 44           | 310           | 3    | 1.97   | 15            | 125           |
| 1.13 | None    | 4.6          | 43.2         | 310           | 3    | 1.49   | 18            | 125           |
| 1.09 | None    | 4.8          | 42.0         | 310           | 3    | 0.84   | 50            | 125           |
| 1.12 | None    | 5.9          | 44.8         | 310           | 3    | 0.68   | 98            | 125           |
| 0.6  | DMSA    | 9.3          | 52.8         | 313           | 0.47 | 220    | 220           | [90]          |
| 0.6  | DMSA    | 12.5         | 75.0         | 313           | 0.47 | 379    |               | [90]          |
| 0.6  | DMSA    | 16.3         | 84.7         | 313           | 0.47 | 420    |               | [90]          |

a Dam-PMA = dodecylamine modified poly(isobutylene-alt-maleic anhydride) (6 kDa); DMSA = 2,3-dimercaptosuccinic acid; mPEG = methoxy polyethylene glycol; PEG = polyethylene glycol; PG = propylene glycol; TEG = tetraethylene glycol.

b Diameter of the core as determined by TEM.

c Hydrodynamic diameter as determined by DLS.

d Expressed per mass bare MnFe₂O₄ unless stated otherwise.

e Magnetic field strength or temperature at which the relaxivities were measured.

f Expressed per mM of Mn + Fe.

g At 300 K.
h Expressed per mass Fe + O atoms.
Stable distribution of the metal cations over the A- and B-sites with 
Zn²⁺ also located in the B-sites.

Fairly high σs (98 A m² kg⁻¹ Fe for uncoated material) and r₂ 
(338 s⁻¹ mM⁻¹ Fe) has also been achieved with monodisperse 
lipid-PEGylated Mn-Zn ferrite NPs with a shell-core structure 
[135]. This material has been used as a basis for theranostics.

Generally, the Curie temperature (Tc) of a manganese ferrite 
reduces with Zn-doping. This can be exploited in the design of 
self-regulation agents for hyperthermia, which have a Curie 
temperature slightly above physiological temperature and, therefore, 
lose the magnetization and their heating effect as soon as the tem-
perature rises above Tc [136,137].

Reported transverse relaxivities and saturation magnetization 
of Zn-doped Mn-ferrite NPs of various sizes are compiled in 
Table 3.

3.4. Influence of the shape of the nanoparticles

Vuong et al. have shown by Monte Carlo simulations that the 
shape of NPs also affects their magnetic properties. In the MAR, 
spherical superparamagnetic NPs are more effective F₂ Cs than 
linear ones, whereas, in the SDR, the shape has not much effect 
on the transverse relaxivity [140]. However, an experimental study 
on Mn-ferrites covered with oleic acid suggests that truncated 
octahedral nanostructures possess lower and plates possess higher 
σs values and r₂ values [141]. Replacement of the oleic surface 
layer of these plates by more water-soluble FA-Gd(DTPA)-PEG-
DIB chains resulted in a decrease in σs, most likely due to a 
decrease in Fe content of the particles, but the r₂ value rose signific-
ants [141]. Possibly this can be ascribed to an exchange 
contribution to the relaxivity by the Gd³⁺-chelates. An investigation 
on the doping of SPIO particles by ion exchange with Mn²⁺ and Zn²⁺ 
showed that the σs values of the resulting NPs (covered with 
citrate) were strongly dependent on their shapes. For NPs with 
Mn/Fe = 1/13–15, the order of the magnitudes of both 
σs and the 
corresponding r₂ values was octapods > cubes > spheres (see 
Fig. 14) [142]. Surprisingly, the same authors reported, for similar 
particles with an Mn/Fe molar ratio of 1/5, that the order of σs and 
r₂ was cubes ≈ octapods > plates [143]. It should be noted that it is 
not clear whether in the above studies the NPs have the same vol-
umes and whether canting effects can be excluded. Another study 
on various shapes of MnFe₂O₄ showed the order: needles 
(400 × 8 nm) > rods (800 × 30 nm) > wires (1000 × 35 nm) [144].

3.5. Effects of coating and attachment of targeting vectors

Coating of NPs is essential for their colloidal stability under 
physiological conditions [67]. NPs prepared by ceramic methods 
or by solvothermal procedures in an organic solvent are hydropho-
bic. Often oleic acid and oleylamine are applied during these 
procedures. Ligand exchange and/or coating with a hydrophilic compound is required to make the NPs dispersible in an aqueous 
medium. Moreover, a surface coating can be used to reduce the 
toxicity by preventing leaching of metal ions, to control biodistri-
bution, to hide NPs from the immune system, and to serve as an 
anchor for targeting vectors. Coating of a bare Mn-ferrite NP gener-
ally will result in a decrease of its σs. As stated above (see Eqs. (19) 
and (20)), a water-impermeable coating decreases the transverse 
relaxivity in the MAR but does not affect it outside this regime, 
obviously provided that after the coating, the system does not 
move from the SDR into the MAR. However, a different situation 
arises when the surface bonding chemistry influences the spin dis-
order at the surface, for example by occupying the missing O-
atoms and thus reducing the disorder. Since then the surface 
surfaces resembles more the core, the thickness of the dead layer decreases, 
and usually also the paramagnetic contribution to the magnetiza-
tion [60,78,145]. In that case $\sigma_s$ and $r_2$ may increase. Moreover, surface coating with ligands having exchangeable protons may give rise to a significant exchange contribution to both the longitudinal and transverse relaxivity. Surface coatings that require basic covering Mn-ferrite NPs with a layer of Fe$_3$O$_4$ have advantages for application in hyperthermia therapy. The core–shell interaction between the two magnetic phases has a beneficial effect on the heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher heating efficiency of this type of NPs [150].

The effect of the coating of MnFe$_2$O$_4$ NPs (6 and 12 nm diameter) with a series of amphiphilic dodecanoic-PEG block polymers of molecular weights between 1 and 20 K has been investigated systematically (see Table 1) [60]. For both particle sizes, $r_2$ as a function of the molecular weight of the coating polymer started to decrease steeply above 2 K. Possibly this is due to a reduction of the permeability of the coating for water at high MWs, due to a changeover of the conformation of the dodecanoic-PEG chains from the mushroom regime with folded chains in a relatively thin water-permeable layer to the brush regime with unfolded chains in a thick and less water-permeable layer. A similar effect has been observed recently with PEGylated zeolite NPs [147]. Likewise, Zn$_{0.15}$Mn$_{0.55}$Fe$_2$O$_4$ NPs having a core diameter of 8 nm and coated with NDOPA-PEG$_{1200}$ of various PEG chain lengths showed a maximum in $r_2$ for $n = 600$ Da ($r_2 = 552$ s$^{-1}$ mM$^{-1}$ at 3 T and room temperature, see Table 3) [79].

Encapsulation of polycrystalline MnFe$_2$O$_4$ NPs (100–150 nm diameter) in a mesoporous silica layer of 20–25 nm thickness followed by attachment of folic acid through an aminopropyl-silica linker afforded a targeting T$_2$ CA [148]. The $\sigma_s$ value decreased with the two consecutive coating steps from 95 to 99 A m$^2$ kg$^{-1}$ to successively 73–75 and 60–63 A m$^2$ kg$^{-1}$ [139]. The mesoporous silica layer can be exploited as a drug carrier, as was demonstrated for the anti-cancer drug doxorubicin. Other theranostic NP-systems were prepared by first coating MnFe$_2$O$_4$ NPs with meso-2,3-dimercaptosuccinic acid (DMSA) [115]. In the next step, chitosan was attached covalently to the DMSA of such NPs. The free ammonium groups of chitosan were then available for transport of negatively charged drugs. In this way, multimodal theranostics (MRI/drug delivery/hyperthermia therapy) were obtained [149]. The $\sigma_s$ value (normalized by the total sample weight) decreased with increasing thickness of the coating, which was ascribed to spin canting effects due to the coating of the surface.

Covering Mn-ferrite NPs with a layer of Fe$_3$O$_4$ has advantages for application in hyperthermia therapy. The core–shell interaction between the two magnetic phases has a beneficial effect on the heating efficiency of this type of NPs [150]. Superparamagnetic core–shell NPs MnFe$_2$O$_4$@Fe$_3$O$_4$ with a diameter of 12.5 nm after coating with chitosan have been reported to display much higher $r_2$ values ($184.1$ s$^{-1}$ mM$^{-1}$ Fe at 9.4 T and 298 K) than monophasic NPs of comparable size ($96.6$ and $83.2$ s$^{-1}$ mM$^{-1}$ Fe for Fe$_3$O$_4$ and MnFe$_2$O$_4$, respectively), although the saturation magnetization of all these NPs was about the same ($62–69$ A m$^2$ kg$^{-1}$ at 298 K) [83].

---

### Table 3

Diameters, saturation magnetization and relaxivities of Zn$_{x}$Mn$_{1-x}$Fe$_2$O$_4$ NPs.

| $X$ | Coating* | $d_{TEM}$ (nm)$^b$ | $d_{LS}$ (nm)$^c$ | $T$ (K)$^d$ | $B_0$ (T)$^e$ | $\sigma_s$ (Am$^2$ kg$^{-1}$)$^g$ | $r_2$ (s$^{-1}$ mM$^{-1}$)$^h$ | Ref. |
|-----|----------|-------------------|-------------------|-------------|-------------|----------------|----------------|-----|
| 0   | DMSA     | 15                |                   | 4.7         | 125         | 422            |                 | [87] |
| 0.1 | DMSA     | 15                |                   | 4.7         | 140         | 516            |                 | [87] |
| 0.2 | DMSA     | 15                |                   | 4.7         | 154         | 637            |                 | [87] |
| 0.3 | DMSA     | 15                |                   | 4.7         | 166         | 754            |                 | [87] |
| 0.4 | DMSA     | 15                | 17                | 4.7         | 175         | 860            |                 | [87] |
| 0.8 | DMSA     | 15                |                   | 4.7         | 137         | 388            |                 | [87] |
| 0.72| DMSA     | 10                | 295               | 1.5         | 30          | 125            |                 | [138]|
| 0.3 | None     | 7.7               |                   | RT          | 3           | 95              |                 | [79] |
| 0.4 | None     | 7.7               |                   | RT          | 3           | 89              |                 | [79] |
| 0.2 | NDOPA-PEG$_{2000}$ | 7.7           | 22                | RT          | 3           | 110             | 250             | [79] |
| 0.2 | NDOPA-PEG$_{600}$    | 7.7             | 25                | RT          | 3           | 110             | 433             | [79] |
| 0.2 | NDOPA-PEG$_{500}$    | 7.7             | 34                | RT          | 3           | 110             | 552             | [79] |
| 0.2 | NDOPA-PEG$_{2000}$   | 7.7             | 47                | RT          | 3           | 110             | 194             | [79] |
| 0.5 | None     | 8.0               | 20.3              | RT          | 1.5         | 42              | 263             | [139]|
| 0.5 | Fe$_3$O$_4$     | 10.0             | 27.0              | RT          | 1.5         | 49              | 323             | [139]|
| 0.5 | Fe$_3$O$_4$     | 12.3             | 28.6              | RT          | 1.5         | 53              | 286             | [139]|
| Zn$_{0.12}$Mn$_{0.26}$Fe$_2$O$_4$ | Dam-PMA      | 8.5               | 21                | RT          | 3           | 93              | 65              | [128]|
| Zn$_{0.2}$Mn$_{0.8}$Fe$_2$O$_4$  | Dam-PMA      | 8.5               | 20                | RT          | 3           | 82              | 51              | [128]|

---

Fig. 14. The effect of the shape on $\sigma_s$ and $r_2$ of Mn-doped USPIO particles. Mn/Fe ratios: spheres 1/12, cubes 1/13, octapods 1/15 with diameters of 17, 23, 32 nm as measured by TEM, respectively. Temperature 310 K. The $r_2$ values were measured at 7 T. Data from ref. [142].
Covering of Zn$_{0.5}$Mn$_{0.5}$Fe$_2$O$_4$ NPs with a shell of Fe$_2$O$_4$ resulted in a decrease of $\sigma_2$ at 10 K but the value of $\sigma_2$ of the core–shell system at 300 K was up to 25% higher than that of the core alone (see Table 2) [139]. This effect was ascribed to exchange coupling between the core and the shell, which was assumed to be ferrimagnetic at 10 K and ferromagnetic at 300 K. As expected, the higher $\sigma_2$ values for the Zn$_{0.5}$Mn$_{0.5}$Fe$_2$O$_4$@Fe$_2$O$_4$ systems at 300 K resulted also in higher $r_2$ values. A significant increase of $\sigma_2$ was also achieved by applying MnFe$_2$O$_4$ as a shell on a core of single-domain ferrimagnetic elemental Fe [151]. The resulting Fe@MnFe$_2$O$_4$ NPs (core diameter 12 nm, total diameter 16 nm) displayed an unusual $\sigma$–$H$ curve with a negligible coercivity while the core alone had a significant coercivity, probably due to the dominance of the superparamagnetic contribution over the slow magnetization of the ferromagnetic core. At higher external magnetic field strengths, the core contribution became dominant resulting in an overall $\sigma_2$ which is the volume average of the contributions of the core and the shell (149 A m$^2$ kg$^{-1}$ at 300 K). This value is higher than those of Fe$_2$O$_4$ and MnFe$_2$O$_4$ NPs with the same particle size, which exhibited $\sigma_2$ values of 95 and 101 A m$^2$ kg$^{-1}$, respectively. Accordingly, these Fe@MnFe$_2$O$_4$ NPs after making them aqueous dispersible by an additional coating with DMSA had a high transverse relaxivity ($r_2 = 356$ s$^{-1}$ mM$^{-1}$ at 300 K). The latter coating allowed attachment of targeting vectors.

Coating of MnFe$_2$O$_4$ NPs (12 nm) with an aminated non-ionogenic surfactant polysorbitol 80 afforded a polycationic CA under physiological conditions (see Table 1), which was taken up by cells probably through electrostatic interaction with the negatively charged cell membranes [74].

To increase stability and reduce toxicity, MnFe$_2$O$_4$ NPs have also been coated with Au (see Table 1) [116].

3.6. Clustering of manganese ferrite nanoparticles

Synthetic methods to prepare Mn-ferrite NPs, such as solvothermal decomposition of metal complexes and precipitation can be used to prepare NPs with sizes up to about 20 nm. Since the diameter of the NPs is one of the principal parameters that govern the transverse relaxivity, the clustering of these small NPs may be an attractive way to attempt to increase $r_2$. Several ways of clustering Mn-ferrite NPs have been explored, including encapsulating dense clusters of single crystals in an impermeable coating (core–shell systems), embedding in micelles or liposomes, and attachment to solid supports. The resulting clusters all contain substantial amounts of diamagnetic material. Analysis of the literature data on the magnetic properties of such systems is complicated by the non-uniform way in which values of $\sigma_2$ and $r_2$ are expressed in the literature. The magnetizations are expressed either for the whole cluster or for the composing small NPs. In both methods, the mass may be related either to (1) the whole particles (Mn-ferrite + all diamagnetic material), (2) Mn + Fe (+Zn), or (3) Fe. Often mass densities and the Mn-ferrites loading (wt %) of the clusters are not known, which makes interconversion between these unit systems impossible. In addition, the lack of knowledge on the water permeability of the nanoparticles makes it difficult to accurately determine their effective diameters. Relaxivities are expressed in s$^{-1}$ mM$^{-1}$ (Mn + Fe) but sometimes as s$^{-1}$ mM$^{-1}$ (Fe). Moreover, the magnetization may be affected by the clustering, for example by altering the thickness of the dead layer in the constituting single NPs or by oxidation of Mn$^{2+}$ to Mn$^{3+}$ during the cluster preparation.

Monte Carlo simulations have shown that compact clusters induce relaxation enhancements equivalent to similarly-sized single-crystal particles [152]. Therefore, for NPs that are in the MAR, the transverse relaxivity can also be increased by assembly to larger clusters, such as micelles, liposomes, or by embedding them in gels. The cluster can be considered as a particle with a total magnetic moment as determined by Langevin’s law (Eq. (22)). Consequently, the $\sigma_2$-values of the constituting small NPs effectively do not add up but the overall magnetization per weight bare ferrite remains the same, provided that magnetic interactions between the constituent NPs of the cluster are negligible. However, an increase in the number of NPs in a cluster (the loading density) determines the volume fraction $f$, which leads to an increase in $r_2$ [30]. Moreover, the diameter and thus $\sigma_2$ increases upon clustering, which also contributes to an increase in $r_2$. It should be noted the relaxivity increase would look less impressive if it were expressed per unit of mass rather than per mM [153].

At constant $\sigma_2$, $r_2$ will rise with $d$ in the MAR, but after passing the border of the SDR, no further increase in $r_2$ or $r_2^*$ will take place, and when, at even larger $d$, the PRR is reached $r_2$ will decrease, whereas $r_2^*$ remains unchanged. (see Fig. 2). Besides the beneficial effect on the relaxivity, clustering will allow a high payload of paramagnetic ions and/or therapeutic drugs to be delivered to the site of interest, which will lead to an increased local concentration of these ions and therefore a high sensitivity. Another advantage of such an architecture may be the possibility of disintegration by bio-degradation, which may be less harmful to the body [77].

In Table 4, sizes, $\sigma_2$, and $r_2$-values of clustered systems are compiled. From these values, it can be estimated that for the majority of these large particles $T_2^\alpha$ (Mn + Fe) ≥ 1, which implies that they are in the MAR approaching the border with the SDR or in the SDR and, therefore, relatively high $r_2$-values may be expected (see also Figs. 2 and 9). Nevertheless, only a few systems have $r_2$ values higher than 400 s$^{-1}$ mM$^{-1}$ (Mn + Fe). This can be explained by a low loading density or by the fact that the systems are under the PRR and not under the SDR. An easy but seldom performed check to discriminate between SDR and PRR is a comparison of $r_2$ and $r_2^*$. In the SDR these relaxivities are about equal, whereas in the PRR, $r_2^* > r_2$ with a gap between them that is dependent on $T_2^\alpha$. This is nicely illustrated by Tromsdorf et al. for 6 nm Mn-doped ferrites (Mn/Fe = 0.12–0.32) embedded in micelles formed by a lipid (250 nm), which have $r_2 = 122$ and $r_2^* = 825$ s$^{-1}$ mM$^{-1}$ (Fe) [113]. Here, it is evident that the PRR is operative. By contrast, encapsulating the same NPs into an amphiphilic polymer shell with a diameter of about 15 nm afforded $r_2 = 53$ and $r_2^* = 62$ s$^{-1}$ mM$^{-1}$ (Fe).

The dramatic transverse relaxation enhancing effect by the increase in diameter due to clustering is demonstrated in an early example by Lee et al., who clustered spherical 12 nm MnFe$_2$O$_4$ NPs ($\sigma_2 = 79$ A m$^2$ kg$^{-1}$; $r_2 = 358$ s$^{-1}$ mM$^{-1}$) to spherical kernels with a diameter of 47.3 nm that were covered with a layer of SiO$_2$ and subsequently a layer of Au [154]. Due to these coating layers, the resulting NPs had diameters of 120 nm with an $\sigma_2$-value of only about 2 A m$^2$ kg$^{-1}$, which should be expected because $\sigma_2$ reduces with the third power of the diameter increase (see Eq. (25)). After PEGylation, the NPs had an $r_2$ of 465 s$^{-1}$ mM$^{-1}$ at 1.5 T. Based on these NPs a multifunctional targeting theranostic has been developed [154].

Mn$_{0.60}$Zn$_{0.40}$Fe$_{1.97}$O$_{4}$ NPs (10 nm diameter) have been encapsulated in silica. The resulting NPs consisted of a 26 nm diameter core of clustered ferrite, surrounded by a 19 nm thick silica coating [131,155]. The final system had a hydrodynamic diameter of 87 nm and $r_2 = 122$ s$^{-1}$ mM$^{-1}$ Mn + Fe at 0.5 T and 310 K. Because the $\sigma_2$ of these NPs showed a linear dependence on the temperature, whereas a quadratic decrease of the transverse relaxivity was observed in the range 70–5 °C, it was concluded that the system is in the MAR. Single particles coated with a monolayer of citrate showed a similar temperature dependency, whereas larger clusters covered with TiO$_2$ (hydrodynamic diameter 157 nm) showed an almost linear trend with the temperature, suggesting
that these particles were close to the SDR regime, which was supported by the relatively high $r_2$ ($329\ s^{-1}\ \text{mM}^{-1}\ \text{Mn + Fe}$ at 0.5 T and 310 K).

MnFe$_2$O$_4$ NPs (8 nm diameter) have been embedded into a gel matrix by coating them with poly(ethylene-glycol)-grafted graphene oxide [157]. The resulting NPs had a diameter of 222 nm with $r_2 = 436.8\ s^{-1}\ \text{mM}^{-1}$ at 4.7 T and room temperature, which is most likely in the PRR. By attachment of negatively charged quantum dots to these positively charged NPs, a bimodal $r_2$-value [75,77,113,156]. The $r_2$ values of these NPs might be operative. The value of $r_2$ was dependent on the shape of the copolymer applied for the encapsulation; comb-shaped copolymers gave rise to higher $r_2$ values than a linear one.

| Composing NPs | Clustered NPs |
|---------------|---------------|
| Mn/Fe | $d_{\text{max}}$ (nm) | Type | Carrier/coating | $d_{\text{mean}}$ (nm) | $d_{\text{trans}}$ (nm) | $\sigma_2$ (A M$^{-1}$ kg$^{-1}$) | $B_0$ (T) | $r_2$ (s$^{-1}$ mM$^{-1}$) |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 8 | M | Star-block copolymer | 12 | 92 | 2 | 3 | 138$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 10 | C | SiO$_2$ | 65$^e$ | 0.5 | 0.5 | 300 | 155$^f$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 15 | C | SiO$_2$ | 40 | 40 | 7.5 | 4.7 | 61 | 162$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 5.78 | S | GO-@OAm | 5.8 | 81 | 9.1 | 9.4 | 106$^d$ | 158$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 10.94 | S | GO-@OAm | 10.9 | 90 | 13.1 | 9.4 | 228$^d$ | 158$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 13.93 | S | GO-@OAm | 13.9 | 82 | 15.7 | 9.4 | 256$^d$ | 158$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 5 | S | GO sheets | 0.5 | 19 | 0.5 | 122$^d$ | 158$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 12 | C | SiO$_2$@Au@PEG-COOH$_{6000}$ | 47.3 | 120 | 2 | 1.5 | 506 | 113$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 7.5 | M | P(ANa-co-DAAm) | 45–65 | 130 | 63 | 11.7 | 153 | 157$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 9 | M | P(ANa-co-DAAm) | 90–100 | 140 | 63 | 11.7 | 153 | 157$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 9 | M | P(MANa-co-DMA) | 90–100 | 140 | 63 | 11.7 | 153 | 157$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 9 | M | P(MANa-co-DMA-co-SDPQ)-g-PNIPAM | 58 | 97 | 64 | 1.5 | 47 | 161$^d$ |
| Mn$_{90}$Zn$_{10}$Fe$_2$O$_4$ | 9 | M | P(MANa-co-DMA-co-SDPQ)-g-PNIPAM | 146 | 48 | 9.4 | 9.4 | 472 | 161$^d$ |

**Table 4**

Diameters, saturation magnetization, and transverse relaxivities of clustered Mn-ferrite NPs.

$^a$ Diameter as determined by TEM.

$^b$ C = capsules or core–shell; M = micelles; NG = nanogel; S = NPs on support.

$^c$ GO-g-OAm = graphene oxide grafted with oleylamine; P(ANa-co-DAAm) = copolymer of poly(sodium acrylate) and dodecyl acrylamide; P(ANa-co-DAAm) = copolymer of poly(sodium acrylate) and dodecyl acrylamide; P(ANa-co-DAAm) = copolymer of poly(sodium acrylate) and dodecyl acrylamide; P(ANa-co-DAAm) = copolymer of poly(sodium acrylate) and dodecyl acrylamide; P(ANa-co-DAAm) = copolymer of poly(sodium acrylate) and dodecyl acrylamide; P(ANa-co-DAAm) = copolymer of poly(sodium acrylate) and dodecyl acrylamide.

$^d$ Hydrodynamic diameter as determined by DLS.

$^e$ Expressed per kg material, unless stated otherwise.

$^f$ Expressed per mM (Fe + Mn) unless stated otherwise. Measured at 298–310 K.

$^g$ Per mM Fe.

$^h$ Liposome membrane: 78.4% 1,2,3-tri-(cis,cis,cis,9,12-octadecadienoyl)glycerol, 19.6% 1,2-diacyl-sn-glycero-3-phosphocholine and 2% 1-acyl-sn-glycero-3-phosphocholine.

$^i$ Per kg MnFe$_2$O$_4$.

$^j$ Thermolabile nanocapsules prepared from hexadecanediol, toluene-2,4-diisocyanate, and 2,2’-Azobis[2-(1-(2-hydroxyethyl)-2-imidazolin-2-yl)propane] dihydrochloride.

$^k$ Measured on composing single NPs.

$^l$ Depending to the number of composing NPs in the cluster.

$^m$ Per kg (Fe + Mn).

$^n$ Amphiphilic star-block polymer. For structure see Ref. [157], supporting information.

$^o$ Diameter of resulting silica embedded ferrite clusters with cluster diameter of 26 nm.
shells: a fluorescent silica shell doped with rhodamine-B-isothiocyanate and a silica shell, without dye, to prevent photo-bleaching and to enhance the photo-stability. The resulting NPs have diameters of 60–80 nm with \( \sigma_t = 62.45 \text{ A m}^2 \text{ kg}^{-1} \), which likely is in the SDR (see Fig. 9) and therefore, has a rather high \( r_2 \) (598 s\(^{-1}\) mM\(^{-1}\)). This material has potential as dual \( T_2/T_1 \) optical imaging CA and also has good hyperthermia capabilities [73].

A spinel Mn-ferrite (with Fe/Mn ratio 10, diameter 14 nm) has been deposited on graphene oxide sheets (GO) which were grafted with oleicamine. After covalent attachment of mPEG\(_{5000}\)-NH\(_2\), the NPs with a hydrodynamic size of 82 nm had an \( r_2 \) value as high as 256 s\(^{-1}\) mM\(^{-1}\) (Fe at room temperature) [158]. A hybrid of GO (width: 50–500 nm, thickness: 0.8–1.1 nm) and MnFe\(_2\)O\(_4\) spinels with a Fe/Mn ratio of about 2 showed a saturation magnetization \( \sigma_t \) close to 19.0 emu g\(^{-1}\) and \( r_2 = 8.4 \) and \( r_2 = 81.3 \) s\(^{-1}\) mM\(^{-1}\) (Fe + Mn, 0.5 T, 36°C). Thanks to the graphene oxide support this material also has strong optical absorbance in the near-infrared (NIR) region and good photothermal stability, which can be exploited for photothermal ablation of cancer cells. Furthermore, GO@MnFe\(_2\)O\(_4\) nanohybrids loaded with doxorubicin have potential as theranostic in chemotherapy [159].

A tumor-targeting \( T_2 \) CA has been prepared by encapsulating 11.7 nm MnFe\(_2\)O\(_4\) NPs into L-\( \alpha \)-phosphatidylethanolamine-hyper branched polyglycidol (PE–HBPG) bioconjugates covalently functionalized with folic acid (FA). The NPs had a \( \sigma_0 \) of 59 A m\(^2\) kg\(^{-1}\) and after the clustering they had an \( r_2 \) value of 141 s\(^{-1}\) mM\(^{-1}\) [68]. Attachment of 12 nm MnFe\(_2\)O\(_4\) NPs to adenovirus resulted in hybrid systems, which are promising for in vivo MR tracking of targeted viral gene delivery therapies [56]. Fluorescent polyethyleneimine-cation-coated MnFe\(_2\)O\(_4\) NPs (74 nm diameter) have been suggested for dual-mode human mesenchymal stem cell tracking [160]. The positively charged coated NPs are supposed to interact with the negatively charged cell surface and, in this way, to promote uptake of the NPs.

A different approach to contrast enhancement was taken by Choo et al., who encapsulated uniform octahedral MnFe\(_2\)O\(_4\) NPs (diameter 18.4 nm) in polymeric nanospheres [161]. The superparamagnetic gel particles (hydrodynamic diameters 132–175 nm) showed separate \( ^1H \) resonances of the bulk water and water inside the gel particles with an induced shift difference that was 3.2 ppm irrespective of the amount of MnFe\(_2\)O\(_4\) NPs inside the gel particles. This shift difference could be exploited for MRI at an offset frequency from the main water peak. In this way, the background interference by water was effectively eliminated and hence, the regions affected by the nanospheres would be exclusively detectable. The gel particles had also impressive \( r_2 \) values (191.9–632.6 s\(^{-1}\) mM\(^{-1}\) at 9.4 T, 298 K, depending on the hydrodynamic diameter and the loading with MnFe\(_2\)O\(_4\)).

Vanvakidis et al. constructed bi-magnetic clusters of the soft magnetic MnFe\(_2\)O\(_4\) NPs (9 nm, \( \sigma_0 = 66 \) emu g\(^{-1}\) and \( H_C = 150 \) Oe at 300 K) and the hard CoFe\(_2\)O\(_4\) NPs (9 nm, \( \sigma_0 = 85 \) emu g\(^{-1}\) and \( H_C = 250 \) Oe at 300 K), covered by sodium dodecyl sulfate [84]. A synergetic magnetic interaction of these species leads to clusters with a hydrodynamic diameter of 105 nm with both a high \( \sigma_0 \) and \( H_C (90 \) emu g\(^{-1}\) and 250 Oe at 300 K), respectively. This makes these clusters promising for application as MRI CAs (\( r_2 = 81.8 \) s\(^{-1}\)–1.5 T) and magnetic hyperthermic therapy. More recently, the same group encapsulated solvothermally prepared 9 nm MnFe\(_2\)O\(_4\) NPs in grafted co-polymers endowed with multifunctional and responsive characteristics, such as thermo-responsive shrinking upon heating just above body temperature which has potential for drug delivery initiated by magnetic heating [71].

3.7. Manganese ferrites as \( T_1 \) MRI contrast agent

The longitudinal \( ^1H \) NMRD profiles reported for Mn\(_{1.5}\)Fe\(_{1.5}\)O\(_4\) \((d = 3–6 \) nm, see Fig. 15) exhibit a shape as predicted for a low anisotropy model (see Fig. 1) [125]. Only Mn-ferrite NPs with a high \( r_1/r_2 \) value are suitable for application as \( T_1 \) MRI CA. From Fig. 1 it can be concluded that for magnetic field strengths at which the currently most used clinical MRI scanners operate (0.5–1.5 T), a high \( \sigma_0 \) and a small \( d <10 \) nm) are favorable to reach high \( r_1 \) values. This combination of requirements makes it necessary to avoid a large dead layer of the favorable ultra-small NPs by using a careful synthetic protocol. At the same time, the value of \( r_2 \) should be minimized, which also requires very small NPs but now with large dead and/or paramagnetic layers. Usually, the outer sphere mechanism is dominant, which implies that \( r_1 \) is proportional to \( \sigma_0 \) (see Eq. (1)). It should be noted that the relative contribution of the inner sphere mechanism increases with a decrease in the diameter of NPs because of the increase of the number of paramagnetic atoms at the surface that are in direct contact with water protons relative to the inaccessible core atoms. Furthermore, coating with a compound rich in exchangeable protons may give rise to an additional large second sphere contribution.

The synthesis of small particles requires control of their composition and size. Using a co-precipitation procedure, this can be achieved by burst precipitation in the presence of multidentate polymeric ligands to avoid crystal growth. For example, Li et al. have prepared ultrasmall MnFe\(_2\)O\(_4\) NPs by co-precipitation in the presence of poly(methacrylic acid) pentaerythritol tetrakis (3-mercaptopropionate) [163]. The obtained NPs...
in a range decreasing from 4.9 to 2.2 nm showed a decrease in $\sigma_2$ from 11.6 to 0.22 A m$^2$ kg$^{-1}$ at 300 K. The smallest NPs had an almost linear $\sigma$-H curve, which suggests a very disordered structure that was almost exclusively paramagnetic of nature. XPS spectra indicated that Mn$^{3+}$ was partially oxidized to Mn$^{4+}$, which may have further reduced $\sigma_2$. All in all, it made this material a good $T_1$ CA ($r_1 = 6.61$ s$^{-1}$ mM$^{-1}$, $r_2 = 35.92$ s$^{-1}$ mM$^{-1}$ at 4.7 T and 300 K).

Thermal decomposition of metal complexes may be the preparation of choice. It is then important that the metal complexes exhibit simultaneous decomposition dynamics, which guarantees an initial burst of seeds with the correct stoichiometry. Zhang et al. have designed a procedure with a combination of Fe-erucarate (decomposition temperature 584 K) and Mn-oleate (decomposition temperature 599 K) that allowed the controlled synthesis of ultrasmall Mn-ferrite NPs with diameters of less than 4 nm [86]. With this procedure, MnFe$_2$O$_4$ NPs were prepared with diameters between 2 and 3.9 nm, which showed, after coating with phosphorylated mPEG$_{2000}$, $r_1$ values between 8.43 and 6.98 at 3 T with $r_2/r_1$ ratios below 3.

Miao et al. have optimized 3 nm Mn$_{3}$Fe$_{2-x}$O$_{4}$ NPs prepared by a solvothermal procedure [119]. The highest $r_2$ values were obtained for NPs with a mPEG$_{1000}$ coating for $x = 0.4-0.8$, and the optimal $r_1$ ($10.35$ s$^{-1}$ mM$^{-1}$ at 3 T; $r_2/r_1 = 2.29$) and ratio $r_2/r_1$ for $x = 0.75$. A series of samples of Mn$_{2-x}$Fe$_{x}$O$_{4}$ NPs with different shapes (cubes, octapods, and plates) that were coated with citrate showed an increase in $r_1$ with an increase in $x$ from 0 to 0.5. The $\sigma_2$-values for NPs with $x = 0.5$ having these shapes were 67.3, 64.8, and 40.5 A m$^2$ kg$^{-1}$, respectively [143]. The $r_1$ values of these NPs showed a similar trend (57.8, 62.1, and 22.4 s$^{-1}$ mM$^{-1}$, respectively at 0.5 T).

Ultrasmall MnFe$_2$O$_4$ NPs (diameter 3.9 nm) were coated with dihydrocycasinic acid and subsequently with the tumor-targeting peptide CREKA (cys-arg-glu-lys-ala) [118]. The resulting system had an $r_1$ value of 6.79 s$^{-1}$ mM$^{-1}$ at 7 T and 313 K. These NPs exhibited an enzyme-like response to the acidic and redox conditions in tumors by releasing Mn$^{2+}$, which resulted in amplification of the contrast enhancement. In this way, a metastasis with a diameter of only 0.39 mm was detected.

3.8. Manganese ferrites as dual $T_1$-$T_2$ MRI contrast agent

Quenching of longitudinal relaxation due to the high magnetization of Mn-ferrite NPs is a common problem. Choi et al. have tackled this by constructing core–shell particles separated by a silica layer [164]. The 15 nm core consisted of MnFe$_{2O_4}$ prepared by solvothermal decomposition of metal acetylacetonates, which served as a $T_2$ CA, whereas a thin outer layer (1.5 nm) of Gd$^{3+}$-carbonate was used as a $T_1$ CA. Direct contact between water and the Gd$^{3+}$ ions at the surface provided optimal longitudinal relaxation enhancement. The quenching of the $r_1$ by the magnetization of the core was minimized by tuning the thickness of the intermediate silica layer. Optimum values were obtained for MnFe$_2$O$_4@$SiO$_2@Gd_2O_3(CO_3)_{2}$ NPs having a 16 nm thick SiO$_2$ layer, which were coated with poly(ethylene glycol) methyl ether methacrylate ($r_1 = 33.1$ s$^{-1}$ mM$^{-1}$, $r_2 = 274$ s$^{-1}$ mM$^{-1}$ at 4.7 T).

Another separation of the $T_1$ and $T_2$ enhancing functionalities was achieved with acorn like shaped Janus NPs MnFe$_2$O$_4@$MnO that were stabilized with PEG$_{2000}$ [165]. The MnO side of these NPs has a relatively large amount of Mn$^{3+}$ ions on its surface that boost the $T_1$ relaxation, whereas the MnFe$_2$O$_4$ side provides a magnetization ($\sigma_2 = 2.25$ A m$^2$ kg$^{-1}$ at room temperature) for enhancement of the $T_2$ relaxation. The ratio $r_2/r_1$ for these NPs was 10 at 1.41 T and room temperature.

The $\sigma_2$ values of manganese ferrite NPs coated with gallol-PEG (MW = 3 kDa) have been shown to increase with the particle diameter [81]. The longitudinal relaxivities appear to be almost independent of the size, whereas the transversal relaxivities strongly increased with the particle size. This allowed tuning these NPs through their size for application as dual $T_1$-$T_2$ CA. Thanks to the PEG coating, these particles showed prolonged circulation times in vivo.

4. Conclusions

During the last two decades, much progress has been made in the understanding of the magnetic properties of Mn-ferrites. This allows the design of NPs with relaxivities tuned for optimal performance as MRI CAs. The Mn-ferrites are particularly efficient in enhancing the transverse relaxivities. The highest $r_2$ values can be obtained with Mn$_{0.6}$Zn$_{0.4}$Fe$_2$O$_4$ and Mn$_{0.8}$Fe$_{2.8}$O$_4$ NPs with diameters of about 20 nm. A minimal magnetically dead layer is necessary to reach maximal relaxivities, which seems to be achievable by a carefully performed solvothermal synthesis eventually followed by a seed growth procedure. The as-synthesized NPs are hydrophobic and consequently, they need to be made water-dispersible by covering with a hydrophilic coating for application as MRI CAs. Minimal thickness of the coating generally is favorable to achieve high relaxivities. NPs of less than 20 nm are generally in the MAR. The highest $r_2$ values are obtained near the border with the SDR. In principle, higher $r_2$-values would be possible by clustering to NPs with larger diameters but then passing the border of SDR and PRR should be avoided if $T_2$ CAs are needed because then $r_2$-values decrease with increasing diameter in the PRR, whereas $r_2^*$ remains constant. The magnetization of these systems generally are saturated at magnetic field strengths higher than about 0.5 T, and consequently, the $r_2$ values are then independent of the magnetic field strength $r_2$. Values up to about 600–800 s$^{-1}$ mM$^{-1}$ at room temperature can be reached. The $r_2$ values are higher than those reported for commercial iron oxide NPs, which exhibit $r_2 < 120$ s$^{-1}$ mM$^{-1}$ [18].

The transverse relaxation of Mn-ferrites is generally much faster than the longitudinal relaxation, which may lead to signal loss in $T_1$-weighted MRI. This effect becomes more serious upon an increase of the magnetic field strength because the longitudinal relaxation rates decrease significantly upon an increase of the magnetic field strength, whereas the transverse relaxation rates are about constant above 0.5–1 T. Sufficiently low ratios $r_2/r_1$ for application as MRI $T_1$ CAs are only possible with ultrasmall NPs (<10 nm). With these systems, $r_1$ values up to about 60 have been reported.

Many factors other than relaxivity determine whether a particular nanoparticulate material is suitable as an MRI CA, including its biodistribution and toxicity [166], which are both dependent on the size of the NPs and the nature of the coatings. Many publications in this field report on pre-clinical tests, such as cytotoxicity tests and studies on various cell lines. Many in vivo studies have been reported mainly on mice, sometimes with implanted tumors. These are not discussed in detail as this review focuses on the relaxivity characteristics of these agents. To the best of my knowledge, no clinical studies on humans have been performed with these agents. At present, the extremely high costs of clinical trials of MRI CAs are a major obstacle to the introduction of new agents, especially as the expected market of these agents is small compared to that of more profitable blockbuster pharmaceuticals applied for wide-spread chronic diseases [6]. However, due to the trend toward personalized medicine, there is an increasing interest in new theranostics. The manganese ferrites are very promising in this regard, because they can act as efficient agents for magnetic hyperthermic therapy as well as diagnostic agents.
Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

I am grateful to Dr. Kristina Djanashvili for her helpful comments on this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] P.C. Lauterbur, Image Formation by Induced local interactions: examples employing nuclear magnetic resonance, Nature 242 (1973) 190–191, https://doi.org/10.1038/242190a0.
[2] J. Lohrke, T. Frenzel, J. Endrikat, F.C. Alves, T.M. Grist, M. Law, J.M. Lee, T. Johnson, P. Caravan, J.J. Ellison, T.J. McMurry, R.B. Lauffer, Gadolinium(III) chelates as contrast agents in medical magnetic resonance imaging, second ed., John Wiley & Sons, Ltd, Chichester (UK, 2013), https://doi.org/10.1002/9781118190366.ch1.
[3] P. Caravan, J.J. Ellison, T.J. McMurry, B.R. Lauffer, Gadolinium(III) chelates as MRI contrast agents: structure, dynamics, and applications, Chem. Rev. 119 (2019) 957–1057, https://doi.org/10.1021/acs.chemrev.8b00363.
[4] A.G. Bleicher, E. Kanal, Assessment of adverse reaction rates to a newly approved MRI contrast agent: review of 23,553 administrations of gadobenate dimeglumine, Am. J. Roentgenol. 198 (2007) W207–W211, https://doi.org/10.2214/AJR.06.00071.
[5] Z. Baranyai, E. Brücher, F. Uggeri, A. Maiocchi, I. Tóth, M. András, M. Gáspár, L. Zékány, S. Aime, The role of equilibrium and kinetic properties in the dissociation of Gd[DTPA-bis(methylamide)] (Omniscan) at near to physiological conditions, Chem. Eur. J. 21 (2015) 4789–4799, https://doi.org/10.1002/chem.201500527.
[6] Q.L. Vuong, P. Goussin, P. Gillis, On $T_1$-shortening by weakly magnetized particles: the chemical exchange model, Magn. Reson. Med. 45 (2001) 1014–1020, https://doi.org/10.1002/1522-2598(200104)45:4<1014::AID-MRM13>3.0.CO;2-C.
[7] R.S. Brown, Distribution of fields from randomly placed dipoles: free-precession signal decay as result of magnetic grachts, Phys. Rev. 121 (1961) 1379–1382, https://doi.org/10.1103/PhysRev.121.1379.
[8] D.A. Yablonskiy, E.M. Haacke, Theory of NMR signal behavior in magnetically inhomogeneous tissues: the static dephasing regime, Magn. Reson. Med. 32 (1994) 749–763, https://doi.org/10.1002/mrm.19130320609.
[9] P. Gillis, F. Mouny, P. Goussin, On $T_1$-shortening by strongly magnetized spheres: a partial refocusing model, Magn. Reson. Med. 47 (2002) 257–263, https://doi.org/10.1002/mrm.10105.
[10] Y. Gossuin, T. Orlando, M. Basini, A. Lascialfari, C. Mattea, S. Stapf, Q.L. Vuong, NMR relaxation induced by iron oxide particles: testing theoretical models, Nanotechnology 27 (2016), 155706, https://doi.org/10.1088/0957-4484/27/15/155706.
[11] A. Roch, R.N. Muller, P. Gillis, Theory of proton relaxation induced by superparamagnetic particles, J. Chem. Phys. 110 (1999) 5403–5411, https://doi.org/10.1063/1.4787262.
[12] H.W. de Haan, Mechanisms of proton spin dephasing in a system of magnetic nanoparticles, Magn. Reson. Med. 66 (2011) 1748–1758, https://doi.org/10.1002/mrm.22966.
[13] Q.L. Vuong, J.F. Berret, J. Fresnais, Y. Goussin, O. Sandre, A universal scaling law to predict the efficiency of magnetic nanoparticles as MRI $T_2$-contrast agents, Adv. Healthcare Mater. 1 (2012) 502–512, https://doi.org/10.1002/adhm.201100078.
[14] Q.L. Vuong, P. Goussin, P. Gillis, S. Delangre, New simulation approach using classical formalism to water nuclear magnetic relaxation dispersions in presence of superparamagnetic particles used as MRI contrast agents, J. Chem. Phys. 137 (2012), 114505, https://doi.org/10.1063/1.4751442.
[15] Y. Gossuin, T. Orlando, M. Basini, D. Henrard, A. Lascialfari, C. Mattea, S. Stapf, Q.L. Vuong, Nuclear relaxation induced by iron oxide particles: testing theoretical models, Nanotechnology 27 (2016), 155706, https://doi.org/10.1088/0957-4484/27/15/155706.
[16] R.A. Brooks, F. Mouny, P. Gillis, On $T_1$-shortening by weakly magnetized particles: the chemical exchange model, Magn. Reson. Med. 45 (2001) 1014–1020, https://doi.org/10.1002/1522-2598(200104)45:4<1014::AID-MRM13>3.0.CO;2-C.
[17] R.S. Brown, Distribution of fields from randomly placed dipoles: free-precession signal decay as result of magnetic grachts, Phys. Rev. 121 (1961) 1379–1382, https://doi.org/10.1103/PhysRev.121.1379.
[18] A. Roch, Y. Goussin, R.N. Muller, P. Gillis, Superparamagnetic colloid suspensions: water magnetic relaxation and clustering, J. Magn. Mater. 293 (2005) 532–539, https://doi.org/10.1016/j.jmmm.2005.01.070.
[19] G. Della, T. Klapuri, S.M. Himmelstein, H.P. Schlegel, C.H. Ziener, Theoretical model of the simple spin-echo relaxation time for spherical magnetic perturbers, Magn. Reson. Med. 71 (2014) 1888–1895, https://doi.org/10.1002/mrm.25196.
[20] L.C. Pinho, G.A. Pereira, P. Voisin, J. Kassem, V. Bouchaud, L. Etienne, J.A. Peters, L. Carlos, S. Moneet, C.F.C. Gearelds, J. Rocha, M.-H. Delville, Fine tuning of the relaxometry of $\gamma$-Fe$_2$O$_3$@SiO$_2$ nanoparticles by tweaking the silica coating thickness, ACS Nano 4 (2010) 5339–5349, https://doi.org/10.1021/nn101125w.
X.-Z. Tang, C.M. Sorensen, K.J. Klabunde, G.C. Hadjipanayis, Size-dependent Curie temperature in nanoscale MnFe₂O₄ particles, Phys. Rev. Lett. 67 (1991) 3023–3025.

A. Banerjee, B. Blasiak, E. Pasquier, B. Tomanek, S. Trudel, Synthesis, characterization, and evaluation of PEGLyated first-row transition metal ferrite nanoparticle as T₂ contrast agents for high-field MRI, RSC Adv. 7 (2017) 38121–38125, https://doi.org/10.1039/C7RA07049A.

The reported plots were digitized with WebPlotDigitizer, https://automeris.io/WebPlotDigitizer/ (last accessed: 30-06-2020).

R. Augustine, H.R. Lee, H. Kim, Y. Zhang, I. Kim, Hyperbranched lipopolysaccharide-stabilized magnetic nanoparticle for the water-soluble targeted MRI contrast agent, React. Funct. Polym. 44 (1999) 299–305, https://doi.org/10.1016/S0924-861X(99)00001-1.

Y. Du, X. Liu, Q. Liang, X.-J. Liang, J. Tian, Optimization and design of magnetic ferrite magnetic nanoparticles for highly sensitive MRI/MR Performance and improved magnetic hyperthermia therapy, Nano Lett. 19 (2019) 3618–3626, https://doi.org/10.1021/acs.nanolett.9b00630.

M. Günay, H. Ederer, A. Baykal, H. Süzeri, M.S. Toprak, Triethylene glycol stabilized MnFe₂O₄ nanoparticle: synthesis, magnetic and electrical characterization, Mater. Res. Bull. 48 (2013) 1057–1064, https://doi.org/10.1016/j.materresbull.2012.11.097.

Z. Iatridi, K. Vamvakidis, I. Tsougos, K. Vassiou, C. Dendrinos-Samaras, G. Bokias, Multifunctional polymeric platform of magnetic ferrite colloidal superparticles for luminescence, imaging, and hyperthermia applications, ACS Appl. Mater. Interfaces 8 (2016) 35059–35070, https://doi.org/10.1021/acsami.6b00835.

D. Kim, Y.T. Thai, D.E. Nikles, C.S. Brael, Heating of aqueous dispersions containing MnFe₂O₄ nanoparticles by radio-frequency magnetic field induction, IEEE Trans. Magn. 45 (2009) 64–70, https://doi.org/10.1109/TMAG.2009.2013161.

S. Kumar, A. Daverey, V. Khalidzhal-Sharghi, N.K. Sahu, S. Kidambi, S.F. Othman, D. Bahadur, Theranostic fluorescent silica encapsulated magnetic nanomaterials for in vitro MRI imaging and hyperthermia, RSC Adv. 5 (2015) 53180–53188, https://doi.org/10.1039/C5RA07532C.

E.-K. Lim, J. Yang, J.-S. Suh, Y.-M. Huh, S. Haam, Self-labeled nanoprobe using tri-aminated polysorbate 80 for detection of human mesenchymal stem cells, J. Mater. Chem. 19 (2009) 8958–8963, https://doi.org/10.1039/b912149H.

J. Lu, S. Ma, J. Sun, C. Xia, J. Cui, Z. Wang, X. Zhao, F. Gao, Q. Gong, B. Song, X. Shuai, H. Ai, Z. Gu, Magnetic nanoparticle micelles as MRI contrast agent for liver imaging, Biomaterials 30 (2009) 2919–2928, https://doi.org/10.1016/j.biomaterials.2009.02.001.

E. Mazario, J. Sánchez-Marcos, N. Menéndez, M. Callefe, A. Mayoral, S. Rivera-Fernández, J.M. de la Fuente, P. Herrasti, High specific absorption rate and transverse relaxivity effects in magnetic nanoparticle micelles obtained by an electrochemical route, J. Phys. Chem. C 119 (2015) 6828–6834, https://doi.org/10.1021/acs.jpcc.5b00373.

M. Menelaou, Z. Iatridi, I. Tsougos, K. Vassiou, C. Dendrinos-Samaras, G. Bokias, Magnetic colloids of Co, Mn, and Ni ferrite featured with comb-type and/or linear amphiphilic polyelectrolytes, NMR and MRI relaxometry, Dalton Trans. 44 (2015) 10980–10990, https://doi.org/10.1039/C5DT00372E.

R. Banerjee, A. Bishkata, A. Dave, D. Bahadur, M. Aslam, Surface controlled synthesis of MnFe₂O₄ (M = Mn, Fe Co, Mn and Zn) nanoparticles and their magnetic characteristics, CrystEngComm 15 (2013) 524–532, https://doi.org/10.1039/C2CE26957E.

V. N. Dwivedi, S.R. Ryo, S. Kathal, M. De, S.S. Chou, P.V. Prasad, V.P. Dravid, Engineered theranostic magnetic nanostructures: role of composition and surface coating on magnetic relaxivity imaging contrast and thermal activation, ACS Appl. Mater. Interfaces 8 (2016) 6953–6961, https://doi.org/10.1021/acsamatm.5b03177.

J. Park, B. Kang, B. Kim, J.-S. Suh, Y.-M. Huh, S. Haam, A systematic study of core size and coating thickness on manganese-doped nanocrystals for high T₂ relaxivity as magnetic resonance contrast agent, Nano Converg. 2 (2015) 31–38, https://doi.org/10.1186/s40574-014-0020-5.

M. Pernia Leal, S. Rivera-Fernández, J.M. Franco, D. Pozo, J.M. de la Fuente, L. García-Martín, Long-circulating PEGLyated manganese ferrite nanoparticles for MRI-based molecular imaging, Nanoscale 7 (2015) 2050–2059, https://doi.org/10.1039/C5NR02783F.

R. Banerjee, A. Bishkata, A. Dave, D. Bahadur, M. Aslam, Surface controlled synthesis of MnFe₂O₄ (M = Mn, Fe Co, Mn and Zn) nanoparticles and their characteristic properties, CrystEngComm 15 (2013) 524–532, https://doi.org/10.1039/C2CE26957E.

V. N. Dwivedi, S.R. Ryo, S. Kathal, M. De, S.S. Chou, P.V. Prasad, V.P. Dravid, Engineered theranostic magnetic nanostructures: role of composition and surface coating on magnetic relaxivity imaging contrast and thermal activation, ACS Appl. Mater. Interfaces 8 (2016) 6953–6961, https://doi.org/10.1021/acsamatm.5b03177.

J. Park, B. Kang, B. Kim, J.-S. Suh, Y.-M. Huh, S. Haam, A systematic study of core size and coating thickness on manganese-doped nanocrystals for high T₂ relaxivity as magnetic resonance contrast agent, Nano Converg. 2 (2015) 31–38, https://doi.org/10.1186/s40574-014-0020-5.

M. Pernia Leal, S. Rivera-Fernández, J.M. Franco, D. Pozo, J.M. de la Fuente, L. García-Martín, Long-circulating PEGLyated manganese ferrite nanoparticles for MRI-based molecular imaging, Nanoscale 7 (2015) 2050–2059, https://doi.org/10.1039/C5NR02783F.

R. Banerjee, A. Bishkata, A. Dave, D. Bahadur, M. Aslam, Surface controlled synthesis of MnFe₂O₄ (M = Mn, Fe Co, Mn and Zn) nanoparticles and their characteristic properties, CrystEngComm 15 (2013) 524–532, https://doi.org/10.1039/C2CE26957E.
2+ substitution on relaxation induced by clusters of nanoparticles for magnetic properties in nanosize Mn–Zn ferrite, J. Appl. Phys. 91 (2002) 2211–2215, https://doi.org/10.1063/1.1432474.

C. Rath, N.C. Mishra, S. Anand, R.P. Das, K.K. Sahu, C. Upadhyaya, H.C. Verma, Appearance of superparamagnetic on heating nanosize MnO 0.65Zn0.35Fe 2O 4, Appl. Phys. Lett. 76 (2000) 475–477, https://doi.org/10.1063/1.1052792.

L.D. Ding, L.C. Xue, Z.Z. Li, L.D. Wang, W.H. Qi, L.Q. Wu, X.S. Ge, Study of cation distributions in spinel ferrites Mn 1-x Fe x O 4 and Mn 2x/3 Fe x/3 O 4, J. Magn. Magn. Mater. 332 (2010) 157–162, https://doi.org/10.1016/j.jmmm.2010.12.005.

O. Kaman, J. Kuličková, V. Herynek, J. Kotkan, M. Marytko, T. Dědouková, K. Knížek, Z. Jiráí, Preparation of Mn–Zn ferrite nanoparticles and their silica-coated clusters: Magnetic properties, and transverse relaxivity, J. Magn. Magn. Mater. 427 (2017) 251–257, https://doi.org/10.1016/j.jmmm.2016.10.095.

J. Amighian, E. Karimzadeh, M. Mozaffari, The effect of Mn 2+ substitution on magnetic properties of MnFe 2 O 4 nanoparticles prepared by coprecipitation method, J. Magn. Magn. Mater. 332 (2013) 157–162, https://doi.org/10.1016/j.jmmm.2012.12.005.

J.-H. Lee, J.-T. Jung, J.-S. Choi, S.H. Moon, S.-H. Noh, J.-W. Kim, J.-G. Kim, I.-S. Kim, K.I. Park, J. Cheon, Exchange-coupled magnetic nanoparticles for efficient heat induction, Nat. Nanotechnol. 6 (2011) 418–422, https://doi.org/10.1038/nnano.2011.173.

T.-J. Yoon, H. Lee, H. Shao, R. Weissleder, Highly magnetic core–shell nanoparticles with a unique magnetization mechanism, Angew. Chem., Int. Ed. 50 (2011) 4659–4662, https://doi.org/10.1002/anie.201100101.

Y. Matsumoto, A. Jasanoff, T2 relaxation induced by clusters of superparamagnetic nanoparticles: Monte Carlo simulations, Magn. Reson. Imaging 26 (2008) 994–998, https://doi.org/10.1016/j.mri.2008.01.039.

J. Ramirez, E. Karimzadeh, M. Mozaffari, T. Zeinali, M. Mozaffari, A. Raluf, High relaxivity confined to a small molecular space: a metallosurfacer-based, potential MRI contrast agent, Angew. Chem., Int. Ed. 44 (2005) 1480–1484, https://doi.org/10.1002/anie.200461875.

L. Lee, J. Yang, H. Cho, J. Kang, J. Son, K. Lee, S.W. Lee, H.G. Yoon, J.S. Yuh, M. Huh, S. Haam, Multifunctional magnetic gold nanocomposites: human epithelial cancer detection via magnetic resonance imaging and localized synchronous therapy, Adv. Funct. Mater. 18 (2008) 258–264, https://doi.org/10.1002/adfm.200700482.

O. Kaman, V. Herynek, P. Veverka, L. Kůblíčková, J. Jiráí, Transverse relaxivity of nanoparticle contrast agents for MRI: different magnetic cores and coatings, IEEE Trans. Magn. 54 (2018), 5304045, https://doi.org/10.1109/tmag.2018.2844253.

H.M. Kim, H. Lee, K.S. Hong, M.Y. Cho, M.-H. Sung, H. Poo, Y.T. Lim, Synthesis and high performance of magnetofluorescent polyethylene glycol nanocomposites as MR/near-infrared multimodal cellular imaging nanoparticles, ACS Nano 5 (2011) 8230–8240, https://doi.org/10.1021/nn202912b.

J. Leng, J. Li, J. Ren, L. Deng, C. Lin, Star-block copolymer micellar nanocomposites with Mn–Zn–doped nano-ferrite as superparamagnetic MRI contrast agent for tumor imaging, Mater. Lett. 152 (2015) 185–188, https://doi.org/10.1016/j.matlet.2015.01.120.

E. Peng, E.S.G. Choo, P. Chandrasekaran, C.-T. Yang, J. Ding, K.-H. Chuang, J.M. Xue, Synthesis of manganese ferrite/graphene oxide nanocomposites for biomedical applications, Small 8 (2012) 3620–3630, https://doi.org/10.1002/smll.201201047.

Y. Yang, H. Shi, Y. Wang, B. Shi, L. Guo, S. Yang, H. Wu, D. Wu, Graphene oxide/manganese ferrite nanohybrids for magnetic resonance imaging, photothermal therapy and drug delivery, J. Biomater. Appl. 30 (2016) 810–822, https://doi.org/10.1177/0885328216651926.

S.-R. Seo, J. Yang, E.S.-E. Lee, Y. Jung, K. Kim, S.-Y. Lee, K. Ding, J.-S. Yuh, M.-H. Haam, Nanohybrids vs. polymeric-based nanoremediation method for dual-mode detection of human mesenchymal stem cells, J. Mater. Chem. 18 (2008) 4402–4407, https://doi.org/10.1039/b804544e.

E.S.G. Choo, E. Peng, R. Rajendran, P. Chandrasekaran, C.-T. Yang, J. Ding, K.-H. Chuang, J. Xue, Superparamagnetic nanofillers for off-resonance magnetic resonance spectroscopic imaging, Adv. Funct. Mater. 23 (2013) 496–505, https://doi.org/10.1002/adfm.201202025.

A. Ahmad, H. Bae, I. Rhee, Highly stable silica-coated manganese ferrite nanoparticles for hyperthermia and drug delivery, J. Mater. Chem. 18 (2008) 4588–4593, https://doi.org/10.1039/b714090k.

J.-H. Lee, J.-T. Jung, J.-S. Choi, S.H. Moon, S.-H. Noh, J.-W. Kim, J.-G. Kim, I.-S. Kim, K.I. Park, J. Cheon, Exchange-coupled magnetic nanoparticles for efficient heat induction, Nat. Nanotechnol. 6 (2011) 418–422, https://doi.org/10.1038/nnano.2011.173.
TEM: transmission electron microscopy
XAFS: X-ray absorption fine structure
XANES: X-ray absorption near edge structure
XPS: X-ray photoelectron spectroscopy
XRD: X-ray powder diffraction
\( n_{NP} \): number of NPs per \( m^3 \)
d: diameter
\( D_L \): thickness of dead layer
\( H \): magnetic field strength
\( f \): volume fraction of NPs
\( i \): degree of inversion
\( J_A \): Ayant spectral density
\( J_F \): Freed spectral density
\( K \): anisotropy constant
\( k_B \): Boltzmann constant
\( L(x) \): Langevin function; \( L(x) = \coth x - x^{-1} \) with \( x = m_{NP} H / k_B T \)

\( LF \): Larmor Frequency
\( m_{NP} \): magnetization of a nanoparticle
\( M \): magnetization per volume unit
\( N \): number of NPs per kg
\( n \): number of formula units per NP
\( R_L \): longitudinal relaxation rate
\( R_T \): transverse relaxation rate
\( R_T^* \): observed rate constant of the free induction NMR signal
\( T \): absolute temperature

\( T_B \): blocking temperature
\( T_C \): Curie temperature
\( T_1 \): longitudinal relaxation time
\( T_2 \): transverse relaxation time
\( T_2^* \): observed time constant of the free induction NMR signal
\( V \): volume

\( \gamma_H \): gyromagnetic ratio of the \( ^1H \) nucleus
\( \Delta \omega \): the Larmor frequency of water protons at the particle’s surface as compared to those at infinity
\( \mu \): spin only magnetic moment
\( \mu_B \): Bohr magneton
\( \mu_0 \): the permeability of a vacuum
\( \mu_{mol} \): magnetic moment per formula unit
\( \eta \): dynamic viscosity
\( \rho \): density

\( \sigma \): magnetization per mass unit

\( \tau_0 \): correlation time of the Brownian rotation
\( \tau_{CD} \): half the time interval between successive 180° pulses in a Carr-Purcell-Meiboom-Gill pulse sequence
\( \tau_D \): diffusion correlation time
\( \tau_S \): correlation time defining the border between SDR and PRR
\( \tau_N \): Néel correlation time

\( \omega_H \): angular precession frequency of proton
\( \omega_E \): angular precession frequency of an electron