Simple and fast evaluation of relaxation parameters of magnetic nanoparticles

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Abstract

The efficacy of magnetic hyperthermia treatment depends on the optimal available magnetic nanoparticles (MNPs) that are excited in a given alternating magnetic field and viscosity of the region of interest. In this regard, assessing the relevant relaxation parameters is of upmost importance and could improve the speed of development of efficient applications. Here, we demonstrate how to deduce all relevant magnetic parameters from fast, independent, and simple experimental measurements such as dynamic light scattering, vibrating sample magnetometer, and lock-in thermography. We study the thermal behaviour of two MNPs with different forms, i.e. spherical and cubical, synthesized in-house by thermal decomposition and coated with 4 different surface agents. By determination of specific absorption rate (SAR) values, hydrodynamic diameters and $M-H$ curves it is possible to compute the magnetic particle volume, dominant relaxation time and magnetocrystalline anisotropy constant. The calculated SAR values derived from these parameters, show good agreement with the experimental determined SAR data, demonstrating the applicability of the reported procedure. Additionally, our results indicate that surface coatings can have minor impacts on the thermal dissipation of Néel relaxation dominated MNPs.

1. Introduction

Magnetic nanoparticles (MNPs) gained much attention in recent years, due to their biocompatibility [1], biodegradability [2,3], superparamagnetic properties [4], and ability to convert magnetic energy into heat [5,6,7]. The conversion of magnetic energy, generated by an alternating magnetic field (AMF), into thermal energy is based on relaxation mechanisms, which can be categorized into Brownian and Néel relaxations [7]. In short, Brownian relaxation describes the complete rotation of the entire particle towards the direction of the applied external magnetic field and generates heat via rotational friction [8], while in Néel relaxation only the magnetic moment inside the particles follows the magnetic field direction and the magnetic energy is dissipated as heat [7]. The efficiency of this conversion is dictated by external parameters including magnetic field frequency [9] and amplitude [10], as well as by several intrinsic particle properties, such as crystallinity [11], surface coating [6], polydispersity index [12], colloidal stability [13], and size [14]. In addition, the latter factor, particle size, determines to a large extent the effective relaxation mechanism [7,14]. Even though the effective relaxation is a combination of both, it is widely accepted that in small MNPs Néel relaxation is the dominant mechanism, while Brownian relaxation dominates for particles with a size above a certain threshold [14]. This value can vary from batch to batch depending upon the magnetocrystalline anisotropy constant, which can be described as the energy needed to change the direction of the dipole moment from the easy axis of magnetization [15]. In short, the higher the magnetocrystalline anisotropy constant for a given particle, the smaller is the nanoparticle size for which the transition from Néel- to Brownian-dominated relaxation occurs [7]. To achieve efficient magnetic hyperthermia treatment, it is of upmost importance to know which is the dominant relaxation mechanism, since Brownian relaxation is hindered at high viscosities and will not dissipate sufficient heat to alter the cells [16]. Hence, the intended area of application and the used magnetic field frequency dictates which relaxation particle type is favored to yield maximum heat dissipation [7]. However, assessing the dominant relaxation mechanism and magnetocrystalline anisotropy constant are challenging and require a combination of several characterization techniques. Brownian relaxation is related to the viscosity

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coefficient \( \eta \) of the surrounding fluid, the absolute temperature \( T \), and the hydrodynamic volume of the nanoparticle \( V_p \) [14]. While viscosity and temperature are easy to determine, the hydrodynamic particle volume requires more elaborated measurement techniques, e.g., dynamic light scattering (DLS) or Taylor dispersion analysis (TDA) [17,18]. In contrast, the characteristic Néel relaxation time is given by the characteristic internal relaxation time, which is often approximated as \( \tau_{BN} \approx 10^{-6} \text{ s} \) [20], the magnetic particle volume can be estimated from the magnetization \( (M-H) \) curve [21], while \( \tau_N \) requires more complex experiments and/or calculations based on susceptibility measurements or \( M-H \) curves of MNPs samples, since its values for nanofluids often differs substantially from the corresponding bulk material values [22,23].

While it was just recently reported how to evaluate \( \tau_N \), \( V_p \), and \( \tau_0 \) using the \( M-H \) curve and AC susceptibility of immobilized and suspended MNPs [24], we present here a straightforward way to assess the same parameters using simple measurement techniques. In detail, by determining the hydrodynamic diameters via DLS, the \( M-H \) curves via vibrating sample magnetometer (VSM), and the specific absorbance rate (SAR) values via lock-in thermography (LIT), we were able to deduce the above-mentioned properties. For that purpose, we synthesized 2 different MNPs batches by thermal decomposition method, transferred them to water, coated each particle batch with 4 different surface agents, and subsequently analysed the most common particle characteristics using simple and fast measurement techniques. The validity of this approach is shown by the good agreement between experimental and modelled SAR values. Furthermore, our results indicate that surface coatings have little impact on the heating efficiency of Néel relaxation dominated MNPs.

2. Materials and methods

2.1. Spions synthesis and coating

Cubic and spherical superparamagnetic iron oxide nanoparticles (SPIONs) were synthesized by thermal decomposition method described elsewhere [11,25,26]. Cubic morphology was achieved by introducing sodium oleate into the reaction [11,27]. The obtained particles were transferred into an aqueous environment by a ligand exchange with citric acid (CA) [28]. Catechol-conjugated (Cat-) polymer (Polyethylene glycol, PEG and Polyvinyl alcohol, PVA) was synthesized following a published procedure [29] and dissolved in Milli-Q water. Catechol-PEG was synthesized by a modified procedure from ref. 29. In brief, 6 mL of dry dimethylformamide (DMF) and 3 mL of dichloromethane (DCM) were introduced into a balloon. The liquids were degassed with argon and 500 mg PEG-NHS was added to the solution. Subsequently, 95 mg dopamine hydrochloride and trimethylamine were added and the reaction was stirred overnight at RT. CA coated SPIONs were added (10 molecules polymer/nm² nanoparticle surface) and the mixtures were sonicated at room temperature overnight. No further purification was done thus keeping the iron concentration constant at 4 mg/mL for all applied coatings. This procedure was performed for both morphologies and resulted in Cat-PEG 5 kDa, Cat-PEG 2 kDa, and Cat-PVA 5 kDa coated SPIONs.

2.2. Particle analysis

The iron content of CA coated SPIONs was analysed according to a procedure published elsewhere [12] using a PerkinElmer Avio 200 inductively coupled plasma optical emission spectroscopy (ICP-OES). Diluted samples of CA-coated cubic and spherical SPIONs were prepared for transmission electron microscopy (TEM) by a reported procedure [30]. In brief, by mixing MNPs with a defined concentration of bovine serum albumin (BSA), the individual particles get stabilized against aggregation and drying artefacts are avoided. TEM images were collected with a side-mounted Olympus Veleta CCD camera using a FEI Tecnai Spirit, operating at a voltage of 120 kV. X-ray diffraughtograms (XRD) were collected with an Ultima IV X-Ray diffractometer from Rigaku. The dried samples were measured between 20° and 80° and the resulting diffraughtograms were normalized to show the same maximum peak height. Zeta potential measurements were estimated via the Henry equation using the Smoluchowski approximation and measured at 25 °C in a Milli-Q water/PBS mixture using a Brookhaven ZetaPALS. Dynamic light scattering (DLS) experiments were carried out on a 3D LS spectrometer of LS Instruments at 25 °C as described elsewhere [11]. To assess the magnetic properties, coated nanoparticle suspensions were deposited onto hydrophobic cotton pellets and dried. Vibrating sample magnetometer (VSM) measurements were carried out on a Model 3900 VSM of Princeton Measurements Corporation. Magnetization curves were measured at room temperature and normalized by the dried sample mass of iron. All thermal measurements of nanoparticle dispersions were conducted with an in-house developed lock-in thermal (LIT) imaging set-up [31,32]. MNP heating was induced in an alternating magnetic field of 523 kHz – 10.45 mT, 331 kHz – 7.62 mT, 173 kHz – 6.04 mT, and 110 kHz – 5.97 mT, respectively, and recorded with an infrared camera. VSM and LIT data were analysed by the Shapiro–Wilk normality test and their significance level determined using the two-sample t-test.

2.3. Modelling of heat dissipation

Linear response theory (LRT) was used to interpret the heat generated by SPIONs exposed to an alternating magnetic field. According to this theory, the power \( P \) generated per unit mass of particles exposed to a magnetic field with an amplitude \( H_0 \), frequency \( f \):

\[
P = \frac{\mu_0}{2\pi} H_0^2 \frac{\tau_{BN}}{\eta} \int \frac{\sin(\omega t) + \frac{\omega \tau_{BN}^2}{2}}{\left( 1 + \frac{\omega \tau_{BN}^2}{2} \right)^2} dt
\]

\[
\tau_N = \frac{2}{3} \frac{V_p}{\eta}
\]

\[
\sigma = \frac{k}{T} \exp(-\frac{\Delta H}{RT})
\]

In the above equation, \( M_s \) is the saturation magnetization of particles, which is obtained from magnetization data, \( V_p \) is the particle magnetic volume, \( k \) is Boltzmann constant, \( \mu_0 \) is the vacuum magnetic permeability, \( T \) is the absolute temperature, \( \tau \) is the overall relaxation time (combination of Brownian and Néel relaxation times), \( \tau_B \) is the characteristic internal relaxation time of the material, which is often assumed to be \( -10^{-9} \text{ s} \), \( \tau_N \) is the hydrodynamic volume of particles, \( \eta \) is the viscosity of the solution, \( \xi \) is the magnetocryalline anisotropy constant and \( \rho \) is the particle density. While the hydrodynamic volume of the particles is determined from DLS data, the magnetic volume can only be determined by looking at magnetization curves. As already suggested in the literature, we have assumed that, in spite of the narrow size distribution of particles as seen from TEM images, the prepared SPIONs can still have a broader distribution of magnetic size, and consequently of magnetic volumes, due to defects in the crystalline structure and to the existence of magnetic dead layer. Therefore, we have assumed that it is possible to describe the magnetic size distribution by means of the lognormal function. We have further assumed that each particle volume has a magnetization behaviour that can be described by means of a Langevin function. Therefore, the magnetization curve of the particles can be described as follow:
Table 1. As can be expected, the respective hydrodynamic diameters
tion. The success of each individual coating process is displayed in
coated SPIONs, represent the results obtained after overnight sonica-
dispersions, performed all coatings at the same time using the exact
comparable results, we choose the same particle concentration in all
solutions and sonicated at room temperature overnight. To ensure
cubic and spherical SPIONs, respectively, were added to the polymer
catechol-conjugated polymers were dissolved in Milli-Q water and
the starting point for all further functionalization. For that purpose,
Cubes Citric Acid
−26.4 ± 0.6 19.2 ± 0.2 1.10^{-9} 4587
Catechol-PEG 2 kDa
−4.5 ± 1.1 19.0 ± 0.2 1.10^{-9} 3595
Catechol-PEG 5 kDa
−6.6 ± 0.6 32.4 ± 0.8 1.10^{-9} 3919
Catechol-PVA 5 kDa
−4.7 ± 0.6 27.8 ± 0.4 1.10^{-9} 3527
Catechol-PVA 2 kDa
−27.2 ± 0.8 23.0 ± 0.2 6.10^{-9} 6205
Catechol-PEG 2 kDa
−4.4 ± 0.9 23.2 ± 0.2 6.10^{-9} 5007
Catechol-PEG 5 kDa
−5.2 ± 0.5 34.0 ± 2.4 6.10^{-9} 6137
Catechol-PVA 5 kDa
−4.3 ± 1.4 31.2 ± 0.2 6.10^{-9} 5749

In the above equation, B is the intensity of the applied magnetic
field, \( g(r) \) is the lognormal magnetic particle size distribution, with \( s \) and \( m \) being the mean and standard deviation of the natural logarithm
of the size \( r \). A fitting of the magnetization curves, allowing us to re-
trieve the two parameters \( s \) and \( m \) for the each SPIONs sample, is shown in
the supporting information (Fig. S3).

3. Results and discussion

Cubic and spherical SPIONs were synthesized in house following the
well-known thermal decomposition method [11,25,26] and subse-
sequently transferred to water by ligand exchange with CA [28]. Fig. 1 shows that the particles are well dispersed after the ligand exchange
and are entirely composed of magnetite/maghemite. The diameter was
found to be 14.3 ± 2.0 nm for the cubes and 18.7 ± 2.4 nm for the spheres (determined using ImageJ particle sizing software, \( n > 1000 \)
nanoparticles).

Furthermore, zeta potential and DLS measurements confirm the
colloidal stability of the CA coated particles (Table 1) and hence, were
the starting point for all further functionalization. For that purpose,
catechol-conjugated polymers were dissolved in Milli-Q water and
cubic and spherical SPIONs, respectively, were added to the polymer
solutions and sonicated at room temperature overnight. To ensure
comparable results, we choose the same particle concentration in all
dispersions, performed all coatings at the same time using the exact
same parameters and also included the CA coated SPIONs into the so-
nication process. All data presented in this work, including the CA
coated SPIONs, represent the results obtained after overnight sonica-
tion. The success of each individual coating process is displayed in
Table 1. As can be expected, the respective hydrodynamic diameters
increase upon coating the particles with the 5 kDa polymers, whereas
the shorter 2 kDa PEG resulted in hydrodynamic sizes comparable to CA
SPIONs. However, the increased zeta potential proves successful
coating since the strongly negative citric acid is partially replaced by
the grafted (neutral) polymer. Additionally, DLS shows that no ag-
gregation occurred upon polymer coating (Fig. S1, supplementary in-
formation), which allowed us to study the effect of different coatings of
single MNPs on heating.

In a second step, we analysed the MNPs’ magnetic and thermal
properties (Fig. 2). All particles display superparamagnetic behaviour and no hysteresis could be detected in the \( M–H \) curve (Fig. S2). Fig. 2 shows that the normalized (by iron mass) magnetization of spherical
particles is lower than the magnetization of cubic MNPs. This can be explained with shape effects, resulting in an increased magnetic core
volume and a lowered surface to volume ratio for quasi-cubic particles
[33], as well as the synthesis process, which leads to paramagnetic
impurities in larger particles [34]. Nonetheless, regarding the effect of
coating, no significant difference in magnetization can be observed,
neither between the 4 different coated cubic particles nor between the
spherical particles coatings which is in good agreement with previous
reported results [35]. In contrast, the SAR values for all three polymer
coated spheres were found to be statistically significant lower than the
SAR value of the CA spheres. This behaviour was only partially ob-
servable for the cubes, where the Catechol-PEG 5 kDa show a sig-
nificant decrease in SAR to CA coated cubes, while Catechol-PEG 2 kDa
and Catechol-PVA 5 kDa are not significantly different. These small
changes might be attributed to the overall lower SAR values of the
cubes due to their smaller size [12].

In order to obtain a better understanding of the heating behaviour of
cubic and spherical MNPs, we decided to investigate the heat dissipa-
tion mechanism in more detail. We used linear response theory [14] in
order to compute the heat generated by the MNPs. It is well known that
the magnetic particle size distribution plays a central role in the heat
generated. Therefore, we first used magnetization data to estimate the
magnetic particle size distribution, which is different from the crystal-
lite size distribution determined via TEM. The calculation has been

![Fig. 1. TEM micrographs of CA coated SPIONs and corresponding x-ray diffractograms. Scale bar = 200 nm, insets = 50 nm.](http://doc.rero.ch)
made under the assumption that the magnetization curve of particles with a given magnetic size follows the Langevin equation. By assuming that the magnetic size distribution can be described effectively by a lognormal distribution, the two parameters of the distribution have been obtained by fitting the magnetization data. With the knowledge of the magnetic size distribution, we have performed calculation using LRT, and used the magnetocrystalline anisotropy constant and the relaxation time constant $\tau_0$ as adjustable parameters to fit the experimental SAR data. In order to minimize the uncertainty in these parameters and precisely determine which the dominant relaxation mechanism is, we have performed for all the spherical samples SAR measurements at four different field frequency values. We have found that the small dependence of the SAR value to the change in surface coatings shown in Fig. 2 can only be explained by assuming that Brownian relaxation is not the dominant mechanism of heat dissipation in our system. However, Néel relaxation is the prevailing mechanism, which is supported by the low value of the magnetocrystalline anisotropy constant (Table 1) that can be used to model the experimental SAR data. The corresponding values of the relaxation time $\tau_0$ are for all samples of spherical particles about $6 \times 10^{-9}$ s. With these values, the heating behaviour of all spherical SPIONs can be quantitatively accounted for, as shown in Fig. 3.

In the case of cubes, a similar analysis can be carried out. Because their size regime is in the area of Néel dominated relaxation time, we determined SAR values at only one frequency to show the simplicity of this approach. It is found that using relaxation time value of $10^{-9}$ s, values of the magnetocrystalline anisotropy constant are ca. $3500–4500$ $\text{J/m}^3$, depending on the type of coating, to lead to results in good agreement with the experimental data.

In conclusions, the results of our calculations indicate that the low magnetocrystalline anisotropy constant values found for all nanoparticles cause Néel relaxation to be the dominant heat dissipation mechanism, which explains the small differences in SAR values observed for all particles. In addition, the small differences in SAR values appear to be related to the little differences in the magnetocrystalline anisotropy values for the particles bearing different coatings.

One important aspect should be noted, however. There is a significant difference between the SAR values of particles measured a day after preparation at a frequency of $523$ kHz, reported in Fig. 2, and the same particles measured a few weeks after preparation at various frequencies (including $523$ kHz), reported in Fig. 3. This suggests that the SAR values decrease in time after preparation, and the calculations indicate that the magnetocrystalline anisotropy constant is lower directly after preparation ($K_v = 1700–2100$ $\text{J/m}^3$) than after a few weeks ($K_v = 5000–6200$ $\text{J/m}^3$). Such change might be attributed to aging of MNPs in the presence of oxygen, resulting in oxidation of magnetite to maghemite even inside the nanoparticle core [36,37].

4. Conclusions

We have presented the derivation of the magnetocrystalline anisotropy constant and effective relaxation mechanism of MNPs from simple, independent, and fast measurement techniques. We demonstrated the applicability of this approach using two SPIONs batches, synthesized in-house by thermal decomposition method, and applied four different surface coatings. By acquiring their $M–H$ curves, SAR values, and hydrodynamic diameters it is possible to calculate all relevant parameters needed to assess the magnetic properties which are imperative for magnetic hyperthermia. Hence, a simple and reliable quantification of the dominant relaxation time and magnetocrystalline anisotropy constant can be useful for a better understanding of the areas of application and could facilitate the development of more efficient magnetic hyperthermia treatments. Additionally, our results demonstrate the influence of surface coatings on the heating efficiency of Néel relaxation dominated MNPs. Minor changes in SAR values attributed to the different coatings can be observed, based on changed magnetocrystalline anisotropy constants.

Declaration of Competing Interest

There is no conflict of interest.

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Fig. 3. Comparison between experimental and computed SAR data of spheres as a function of applied coating and the magnetic field frequency.

Geosciences of the University of Fribourg.

Appendix A. Supplementary data

Supplementary data to this article can be found online

References

[31] C.A. Monnier, et al., Lock-in thermography as an analytical tool for magnetic


