Ferrimagnetic nanocrystal assemblies as versatile magnetic particle hyperthermia mediators

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A R T I C L E   I N F O

Article history:
Received 16 March 2015
Received in revised form 14 June 2015
Accepted 12 August 2015
Available online 15 August 2015

Keywords:
Magnetic nanoparticles
Magnetic hyperthermia
Multi-core nanoclusters

A B S T R A C T

Colloidal nanocrystal assemblies (nanoclusters), consisting of 13 nm iron oxide nanocrystals, were synthesized in various sizes (45–98 nm), and were investigated as heating mediators for magnetic particle hyperthermia. The colloidal nanocrystal clusters show enhanced heating efficiency in comparison with their constituent primary iron oxide nanocrystals due to collective magnetic features. The fine tuning of intra-cluster magnetic interactions results to the domination of the hysteresis losses mechanism over the relaxation loss heating contributions and eventually to a versatile magnetic particle hyperthermia mediator.

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1. Introduction

Magnetic nanoparticles have attracted considerable attention in biomedical applications as Magnetic Resonance Imaging (MRI) contrast agents, drug delivery vehicles and heating mediators in Magnetic Particle Hyperthermia (MPH) [1–4]. The ease and cost efficiency of fabrication as well as their biocompatibility have established iron oxide nanoparticles as an important family of nanomaterials for biomedical applications [5,6]. Magnetic nanoparticles can be categorized by their size (total diameter D) and their blocking temperature (TB), which is due to the coherent rotation of all atomic magnetic moments [11].

When magnetic nanoparticles are exposed in an alternating magnetic field (AC), different mechanisms produce heat at the surrounding regions. In the SPM nanoparticles the heat is mainly generated from Néel (related to the fluctuation of magnetization through energy barrier) and Brown (related to the rotation of the entire nanoparticle in the fluid) relaxation mechanisms [10]. Within the ferro(ι) magnetic regime the heat dissipation is mainly interconnected to the hysteresis losses [9]. In the multi-domain case, such an effect arises either from the domain wall motion or the reorientation in the presence of the externally applied field. Specifically, in the single domain state the main loss mechanism is due to the coherent rotation of all atomic magnetic moments [11].

Although various commercial ferrofluids exist already on the market of biomedicine, a worldwide scientific effort is going on further increasing the heating efficiency in nanosystems. Heating response of magnetic nanoparticles depends on intrinsic parameters like particle size, morphology and magnetic characteristics (saturation magnetization and coercivity) as well as on extrinsic parameters like the applied AC magnetic field (frequency and amplitude) [12,13]. Ideally, in order to maximize thermal response of SPM nanoparticles one should either utilize SPM nanoparticles with Néel relaxation time equal to the applied field period (1/f) or FM nanoparticles with anisotropy field matching the applied field amplitude (1/f) [14]. The heating performance of a nanosystem is expressed by the specific loss power (SLP) value, a gauge of the heat conversion efficiency which has to be maximized. The strategy for enhancing SLP is crucial since higher SLP results in better efficiency with a lower dosage level of nanoparticles and milder magnetic field conditions. The side-effects expressed by the 3Ds (Dose, Dimensions and Durability) require carefully addressing during the design of an effective system for such applications. The SLP index is usually proportional to the saturation magnetization of nanoparticles (Ms) while inversely proportional to the size distribution of the nanoparticles (σ). In addition it exhibits a maximum value at a certain particle size (D) and magnetic anisotropy constant (Keff) [15]. Despite the unceasing efforts to achieve the optimum parameters [13,14], such as their size and shape, [16,17] lately there is a tendency to enhance the magnetic profile of hyperthermia agents using other approaches. One such approach is the exploitation of the interparticle interactions of the material, like dipolar and/or exchange coupling...
between or within nanoparticles [18,19] responsible for the enhanced heating response in hard–soft core–shell ferrite nanoparticles [20].

When nanoparticles assemble in secondary structures, the particles interact with each other and collective magnetic features become pronounced. The study of the physical properties of such cluster-like assemblies is very important in order to unravel interconnections between the heating response mechanisms and particle interactions. Enhanced coercivity is observed in the case of a pomegranate-like assembly of hematite particles as its magnetic response is governed by intra–cluster interactions [21]. Meanwhile, in maghemite multi-core nanoparticles, the crystallographic orientation of the consisting particles gives an enhanced magnetization and heating efficiency keeping their SPM character [22]. The assembly of interacting magnetic nanoparticles in controllable cluster–like formation may provide a novel roadmap in enhanced heat–triggered biomedical modalities [23].

In the present work we report on the thermal efficiency of maghemite nanocrystal assemblies named hereafter colloidal nanocrystal clusters (CNCs) comprised of primary iron oxide nanocrystals (PNCs). These assemblies have already shown a remarkable improvement (4–5 times comparing the commercial product Endorem®) of the image contrast in Magnetic Resonance Imaging [24]. Thus, by a careful engineering of dipolar interactions through the nanocrystals’ cluster–packing together with the emerging collective properties and the occurrence of FM, an enhanced heating response may be achieved. Eventually, such systems may be further exploited for combinatorial diagnosis and therapy schemes, classifying them into the group of theranostic agents [15].

2. Materials and methods

2.1. Materials

All reagents were used as received without further purification. Anhydrous iron chloride (FeCl₃, 98%), was purchased from Alfa Aesar. Anhydrous sodium hydroxide (NaOH, 98%), polyacrylic acid (PAA, M₈ = 1800), were purchased from Sigma Aldrich, while diethylene glycol (DEG, (HOCH₂CH₂)₂O) of reagent (≤99.7%) and laboratory (≤99.5%) grades were purchased from Fisher. The absolute Ethanol was purchased from Sigma Aldrich.

2.2. Synthesis

The primary iron oxide nanocrystals and the colloidal nanocrystal clusters of γ-Fe₂O₃ were synthesized using a high–temperature polyol–based chemical protocol with iron chloride (FeCl₃) as precursor, sodium hydroxide (NaOH) as reductive medium and polyacrylic acid (PAA) as capping agent. Details of the synthetic procedure may be sought in Ref. 25. The diameter of the colloidal nanocrystal clusters varies from 45 to 98 nm while the diameter of the primary iron oxide nanocrystals is 13 nm. Sample notation hereafter is S–XX, where XX refers to the average diameter in nm as calculated from TEM images.

2.3. Characterization

2.3.1. Structure and morphology characterization

The shape, morphology and size of colloidal nanocrystal clusters were investigated with conventional and high resolution Transmission Electron Microscopy (TEM) images, using a LaB₆ JEOL 2100 electron microscope operating at an accelerating voltage of 200 kV. All the images were captured by the Gatan ORIUS™ SC 1000 CCD camera. For the purposes of the TEM analysis, a drop of a diluted colloidal nanoparticle aqueous solution was deposited onto a carbon–coated copper TEM grid and then the water was allowed to evaporate. In order to estimate the average size, statistical analysis was carried out on several low–magnification TEM images, with the help of specific software (ImageJ) [26].

2.3.2. Determination of iron concentration

Iron concentration was determined by graphite furnace atomic absorption spectrophotometry using a Perkin Elmer AAnalyst 800 instrument. Prior to analysis, the samples were completely dissolved in HCl.

2.3.3. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was carried out by a SDT Q600 V8.3 Build 101 TG–DTA (TA Instruments) from 20 to 600 °C with a heating rate of 10 °C/min under Ar flow. The volume fraction (φ) of the inorganic (magnetic) phase has been calculated from the weighted fraction according to the formula:

\[ \frac{\rho_{\gamma–Fe₂O₃} \times (1–f_{\gamma–Fe₂O₃})}{\rho_{PAA} \times f_{\gamma–Fe₂O₃}} = \frac{\varphi_{\gamma–Fe₂O₃}}{\varphi_{PAA}} \]

where \( \rho_{\gamma–Fe₂O₃} \) and \( \rho_{PAA} \) are the crystal density, the weight fraction and volume fraction of \( \gamma–Fe₂O₃ \) nanoparticles respectively and \( \varphi_{PAA} \) is the average density of the organic component [27].

2.3.4. Magnetic characterization

Magnetic measurements were carried out with a Superconducting Quantum Interference Device (SQUID) magnetometer – MPMS, at 5 and 300 K. The measurements have been performed in powder samples inside gelatin capsules. Minor hysteresis loops of the same samples were recorded with Vibrating Sample Magnetometer (VSM) at room temperature, under a maximum applied field equal to the applied field strength of hyperthermia experiments (20 and 25 kA/m) after the full demagnetization of samples. Hysteresis losses were then, estimated and may serve as a conservative estimation of the heating efficiency lower bound (as described in Supplementary Data section).

2.3.5. Hyperthermia measurements

For hyperthermia measurements, solutions were prepared in varying concentrations (1–4 mg/mL) of all samples, using deionized water as solvent. The colloidal solutions were exposed first to an applied magnetic field of 20 and 25 kA/m at 765 kHz for 900 s, and subsequently were cooled down with the AC field turned off again for 900 s. The solution temperature was recorded with an optic fiber at steps of 0.4 s. It should be mentioned here that despite the use of a relatively high frequency (765 kHz), analogous frequencies have been utilized in-vitro studies to overcome the limited heating efficiency [3,13]. Specifically, in applications where nanoparticles are involved, nanoscale tissue regions may tolerate larger field–frequency products if we account additional parameters that affect nanoscale tissue heating [28].

To quantify and compare the heating response, the SLP values were calculated from hyperthermia data based on the adiabatic correction, as described in detail in previous works, [29,30] in order to provide reliable SLP values, by avoiding overestimations due to non-magnetic origins. The goal of such procedure is to evaluate the actual temperature rise provoked solely by the magnetic field effect on the magnetic primary iron oxide nanocrystals or colloidal nanocrystal clusters overriding additional non-magnetic heating contributions such as heat–exchange with the surroundings and eddy–current heat losses. A schematic representation of magnetic particle hyperthermia experiment together with its principle of operation is depicted in Supplementary Data section (Fig. S3).

3. Results and discussion

3.1. Magneto-structural characteristics

Colloidal nanocrystal clusters are practically agglomerates of single–core particles assembled in a controllable way that prevents further changes to the number of cores per cluster with time. These complex
multicomponent magnetic particle systems require detailed methods to be analyzed. Morphological characterization, via TEM investigation, revealed the cluster type formation of all resulted samples, consisting of primary nanocrystals. Fig. 1 depicts representative images of primary iron oxide nanocrystals and colloidal nanocrystal clusters as well. One can distinguish the primary nanocrystals of ~13 nm iron-oxide nanoparticles with roughly spherical shape (Fig. 1a) building the nanoclusters (Fig. 1b–f).

The CNCs average diameters (d) vary from 45 to 98 nm as calculated from low-magnification TEM images (Table 1). Since each nanocluster is composed of a magnetic (inorganic) and an organic phase (surfactant) the magnetic volume fraction (φ) may be calculated as described in Section 2.3.3.

The case of the colloidal nanocrystal clusters against the primary nanocrystals is more complex. The spatial arrangement of magnetic cores per cluster is determined by the number of cores participating, their size (both the core’s and the cluster’s together with the corresponding size distributions), the distances between them, and the subsequent magnetic interactions between the cores due to their close proximity. From the volume fraction (φ = 0.47) of the PNCs, it seems that for a single particle, the magnetic content is eventually ~47% while the rest 53% corresponds to the capping layer. Depending on cluster size, PNCs are forming clusters starting from a loose packing (ψ = 0.30 for the 45 nm clusters) and ending to a much denser one for the biggest clusters (ψ = 0.75 for the 98 nm clusters) as shown in Table 1. Volume fraction, ψ, and hence the magnetic phase generally increases with the diameter of the nanoclusters, against to the organic (PAA) content [25].

A typical lower magnification image from sample S-86 is presented in Fig. 2, along with the size distribution histogram. The Fast Fourier Transformation (FFT) analysis of High Resolution TEM images of similar clusters revealed that these nanoparticle ensembles consist of

<table>
<thead>
<tr>
<th>Sample</th>
<th>d (nm)</th>
<th>SD %</th>
<th>ψ</th>
<th>Ms (Am²/kg)</th>
<th>Hc (kA/m)</th>
<th>H.L. (W/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-13 (PNCs)</td>
<td>12.7 ± 3.0</td>
<td>24.0</td>
<td>0.47</td>
<td>57.8</td>
<td>7.6</td>
<td>110</td>
</tr>
<tr>
<td>S-45 (CNCs)</td>
<td>44.8 ± 7.5</td>
<td>16.7</td>
<td>0.30</td>
<td>60.7</td>
<td>8.0</td>
<td>218</td>
</tr>
<tr>
<td>S-50 (CNCs)</td>
<td>50.2 ± 5.4</td>
<td>10.8</td>
<td></td>
<td>71.1</td>
<td>8.3</td>
<td>259</td>
</tr>
<tr>
<td>S-62 (CNCs)</td>
<td>61.7 ± 13.4</td>
<td>21.7</td>
<td>0.56</td>
<td>65.4</td>
<td>9.6</td>
<td>225</td>
</tr>
<tr>
<td>S-86 (CNCs)</td>
<td>85.6 ± 13.3</td>
<td>15.5</td>
<td>0.72</td>
<td>73.9</td>
<td>4.0</td>
<td>186</td>
</tr>
<tr>
<td>S-98 (CNCs)</td>
<td>97.7 ± 13.6</td>
<td>13.9</td>
<td>0.75</td>
<td>75.7</td>
<td>4.7</td>
<td>206</td>
</tr>
</tbody>
</table>

* Single particle case: 1 particle per cluster.

Table 1: Properties and features of primary iron-oxide nanocrystals and colloidal nanocrystal clusters: d is the average diameter of the PNCs or the CNCs, SD is the size standard deviation, ψ the volume fraction of the inorganic (magnetic) phase, Ms the saturation magnetization at room temperature, Hc the coercivity at room temperature, and H.L. the estimated hysteresis losses.

Fig. 1. Representative TEM images of S-13 (a), S-45 (b), S-50 (c), S-62 (d), S-86 (e) and S-98 (f), as well the volume fractions (ψ) and the average diameters of the particles (Ø) also coding sample names.
individual nanoparticles coalescing and sharing the same crystallographic orientation [25] with relatively homogeneous size distributions (Fig. S1 in Supplementary Data).

In Fig. 3 the inner hysteresis loop corresponds to the minor loop recorded under a field equal to hyperthermia field amplitude (25 kA/m) and is used to estimate the hysteresis losses (energy product in W/g shown in last column of Table 1). Magnetization curves recorded at room temperature reveal the ferrimagnetic behavior (non-zero coercive field) of all the CNCs’ samples (Fig. 3, blue curve is a representative case for sample S-50 while hysteresis loops for all samples appear in Fig. S2 in Supplementary Data). The latter is in agreement with the study of the same samples with Mössbauer spectroscopy and AC magnetometry reported earlier indicating a collective magnetic behavior [25]. In such systems the magnetic behavior is strongly dependent on factors affecting their constituent nanoparticles’ magnetic anisotropy as well as their possible intra and inter-particle interactions in the clusters. The existence of dipolar interactions in nanoclusters, results to the increase of saturation magnetization and modulation of coercivity values when compared to that of individual nanoparticles as shown in Fig. S2 and corresponding values of Table 1.

Saturation magnetization is gradually increasing, as expected, with cluster size since it is directly connected with the numbers of magnetic moments within the cluster entity. On the other hand, Hc is more sensitive to interactions within the cluster and seems to have an increasing trend up to 62 nm cluster size and for bigger sizes, where PNCs are densely packed seems to deteriorate. We have to consider here, the fact that several magnetic cores fit inside each cluster so that there are two markedly different dimension scales, the size of the cluster and the size of the constituent PNC which govern the CNC formation and the strength of the collective features. One might expect that since stronger interparticle interactions lead to an increased effective magnetic anisotropy energy barrier in the system, higher hysteretic power losses, and more intense magnetic heating should appear. Contrary, as recently presented, for the case of core–shell ferromagnetic particles, [9] the solution concentration increase (followed by stronger dipolar interactions) has a positive influence up to a point where the dipolar interaction strength becomes comparable with the anisotropy field, while further increase leads to attenuation of both the coercive field and the magnetic heating effect. Similar cases of multi-core particles, where the interactions assist or hinder the magnetic heating via the effective anisotropy are also present both in experiment [31] and theory [32,33]. Similar to our system, dipolar interactions may act in both ways (either in favor or against heating efficiency), depending on the system parameters. In other words, magnetically softer particles (single-core: smaller concentration, multi-core: smaller volume fraction), can profit from the dipolar interaction which increases the effective anisotropy energy barrier and thus improves the SLP. On the other hand, magnetically harder particles (single-core: larger concentration, multi-core: larger volume fraction) are seen to be further hampered by increasing the dipolar interaction due to a larger freezing of the magnetic spins. Eventually, the collective magnetic state of such systems is getting even more complex if we consider spin glass features and surface spin disorder that come into play [25,34,35].

By direct comparison of hysteresis loops presented in Fig. S2, one can see that Mf and Hf reach the optimum values for S-50, a typical case of relatively large cores (~13 nm) in a relatively small ensemble (~50 nm) for a fine tuning of collective magnetic behavior. This is also reflected to the minor loops (inner hysteresis loops) where the maximum magnetization value is attained again for S-50 (the only case of intersection between major and minor loop). Since the PNCs within the cluster are in close proximity, magnetic interaction between them could be significant and contribute to enhance Tb. The increase of the cluster size results in the gradual increase of the blocking temperature as shown in Fig. 8c of Ref. [25] where the ZFC-FC curves for samples S-13, S-50 are depicted. Moreover, the broad peak observed at Tb in the MZFC curve for the three samples may also be attributed to increasing strength of magnetic coupling between PNCs as the cluster size increases while size distribution of PNCs may also play a role. Another interesting feature of corresponding M(T) curves is that MZF flattens out below Tb suggesting the presence of collective magnetic state due to magnetic interactions among the nanocrystals either in single- or in multi-core form while in non-interacting magnetic nanoparticles, the MZF should continuously increase as the temperature decreases [36]. Eventually, we may surmise that each nanocluster behaves as a ferrimagnetic coherent region of aligned correlated particles whose magnetic moment follows the external magnetic field with tunable convenience [37]. What follows is how

Fig. 2. Low magnification TEM image (a) for a colloidal nanocrystal cluster sample S-86 along with its size distribution histogram (b).

Fig. 3. Hysteresis loop (outermost: blue) and minor loop (red) of the CNC sample S-50 at room temperature, recorded under a maximum applied field of 800 and 25 kA/m respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
these magneto-structural features of colloidal nanocrystal clusters correlate with magnetic hyperthermia measurements.

3.2. The influence of the magnetic-related characteristics on the heating efficiency

In order to study the heating efficiency of the nanocrystal assemblies, typical sets of magnetic hyperthermia measurements under 20, 25 kA/m at 765 kHz have been performed (Fig. 4a for the sample S-50 and Fig. S4 in Supplementary Data Section for the rest of samples). The curve for 1 mgFe/mL (green) is a typical hyperthermia profile showing a sharp increase of temperature up to ~200 s which then slows down and attains a plateau with time. The more concentrated samples (2, 4 mgFe/mL) exhibit more abrupt inclination at initial heating stage, a first hint for enhanced hyperthermia efficiency. Analogous thermal behavior has been observed for all nanoclusters and individual nanocrystal samples and for variable solution concentrations (Fig. S4 in Supplementary Data Section).

The SLP was studied as a function of magnetic field strength for the nanocrystal clusters of varied diameter (50, 86, 98 nm) and compared with those obtained for PNCs (Fig. 4b). A systematic increasing trend of thermal response for all CNCs samples compared to thermal response of the individual PNCs is observed, with the S–50 being the more effective. The same behavior is observed for both magnetic field strengths and the SLP values increase with the magnetic field strength. This is expected as the SLP values are found to be proportional to $H^2$, depending on size and magnetic profile [12, 38]. The sample S–50 can be considered as an effective hyperthermia mediator since the temperature of the surrounding medium rises and not only reaches the desired hyperthermia levels (shaded yellow band area in Fig. 4a, denoting temperature region between 41 and 45 °C) at time intervals less than 220 s but also surpasses them for all measurement sequences.

In Ref. 25 working on similar CNCs and supported by Monte Carlo simulation dipolar energy strength gets maximized for the sample S–50, in comparison to bigger nanocluster sample S–86. This may lead to the assumption that S–50 indeed is the sample with the best heating response due to the fine tuning of dipolar interactions. Moreover, C. Haase and U. Nowak present a theoretical simulation of the correlation of dipole interactions of nanoparticles ensembles with hyperthermia results [39]. In that work authors conclude that there is an optimum-hyperthermia density of nanoparticles within a cluster, as it seems to be in our case of 50 nm (S–50). Furthermore, the optimized heating response for the specific size of ferromagnetic nanoparticles was also experimentally confirmed by B. Mehdaoui et al., while for bigger sizes within the multi-domain state coercive field and heating efficiency decrease are observed [40].

Although, both theoretical and experimental investigations [22, 31–33, 36] have shown that densely packed three dimensional nanoassemblies experience strong dipolar as well as exchange coupling between the nanoparticles, the answer how this effect is optimized under certain conditions is not straightforward. Enhanced heating efficiency compared to that of the individual subunits has been found in iron oxide cluster-like nanoassemblies by P. Hugounenq et al. [41]. The more enhanced SLP values exhibited may be attributed to variations of magneto-structural characteristics such as different morphology and different degree of magnetic moments’ alignment. In our case, one possible explanation for the superior magnetic heating effect of S–50 could be that nanocrystals in this ensemble are better crystallographically aligned with respect to the other CNCs samples. Furthermore, the arrangement of nanocrystals could also show slightly differences which could result in different dipolar interaction strengths. Thus, under the influence of AC field, a relatively more coherent magnetization direction reversal as well as a shorter spin relaxation takes place. The PNCs within the CNCs are in close proximity and hence magnetic coupling at the nanocrystals’ interfaces is expected. The findings from the magnetic characterization confirm the enhancement of $M_r$ value and the presence of collective magnetic dynamics as shown by $H_k$ trends. So, we believe that the increase of heating efficiency is practically facilitated by the proper tuning of cluster/particle ($D_{DCNC}/D_{DPNC}$) size ratio as far as the nanocrystal alignment which provides the conditions for a high particle magnetic moment together with effective anisotropy barrier increase via dipolar interaction strength tuning.

3.3. The effect of concentration and the role of the hysteresis losses on heating efficiency

The SLP values for aqueous solutions of the PNCs and CNCs have been calculated for three different concentrations. The concentration dependence of the SLP value is shown in Fig. 5a. The increase of the SLP with the concentration for the sample S–50 is worth noting contrary to the typical trend for maghemite-based ferrofluids [42] shown by the other three samples (S–13, S–86, S–98). Depending on the nanoparticle interactions, the SLP value may increase for superparamagnetic or weakly interacting nanoparticles but also the opposite tendency may also occur when the magnetic interactions become strong [19]. The different thermal behavior of the sample S–50 implied the competitive
complexity of heating contributions rather than the simple occurrence of a single heating mechanism.

In order to clarify the existence of magnetic interactions and their role in the heat generation, the hysteresis losses have been calculated through the minor loops at room temperature (Fig. 3, Fig. S2, Supplementary Data, last column of Table 1). The appearance of the room temperature ferrimagnetism of the CNCs indicates that the hysteresis losses might play a significant role in the heat generation [16,43]. The results (Fig. 4b) show the increased heating efficiency of nanocrystal clusters compared to that of constituent PNCs. It is known that magnetic nanoparticles in the superparamagnetic regime produce heat via two basic mechanisms, Neél and Brown relaxation while as reported by Dutz et al., when the magnetic nanoparticles injected in human tissue, the Browninan relaxation mechanism may be safely considered negligible and not accounted to the total thermal response [44]. Additionally, the gradual development of room temperature ferrimagnetism modulated by magneto-structural features resulting in measurable hysteresis at room temperature, also intrigues the enhanced heating response due to hysteresis losses. The evolution of heating performance, which arises from clustering (as potentially confirmed by the evolution of the volume fractions, Table 1) and reorganization of the magnetic grains, further confirm the intra-cluster interactions among incorporated subunits. These interactions are the main reasons of heating efficiency in similar systems, either in the form of dipole–dipole interactions within a cluster or as exchange interactions at the nanocrystal interfaces [21]. In addition to the latter, the S-50 nanocrystal cluster sample with the higher SLP value have also shown enhanced hysteresis losses outlining the connection between magneto-structural characteristics with magnetic heating. It seems that this material yields the optimum hyperthermia conditions both from structural ($\phi$, $D_{xyc}/D_{xyc}$) and magnetic ($M_s$, $H_c$, $K_{app}$) point of view under the certain field conditions ($f$, $H_o$).

The comparison between calorimetric (SLP values estimated via hyperthermia procedure) and hysteresis losses (arising from DC magnetic measurements) is clearly seen in Fig. 5b. From this figure we can conclude that hysteresis losses are in accordance to the SLP magnitudes. As it is discussed in the previous section, the optimization of magneto-structural features occurring for S-50 sample arises from the interplay of dipolar interactions as governed by the nanocrystal arrangement or crystallographic alignment combining multiple heating contributions in a beneficiary way.

The hysteresis losses of the ferrimagnetic nanoclusters can be affected by the anisotropy of the system (surface anisotropy or/and surface spin disorder), the alignment and the size/magnetization of the incorporated particles into the nanoclusters as well as of the emerged dipolar interactions among them. All the above parameters that affect the hysteresis losses may explain the SLP decrease as the volume fraction increases for nanocluster sizes above that of 50 nm (Fig. 5b).

In the pursuit of optimized magnetic nanostructures we demonstrated that the internal collective organization of three dimensional cluster-like architectures can modulate their magnetic properties in such a way as to critically enhance their hyperthermia efficiency. Iron oxide based nanoparticles remain among the best candidates for adapting magnetic hyperthermia in humans not only for their heating efficiency records but also for their good iron metabolism in the organism without toxic effects [45]. The colloidal, chemical and magnetic stability in aqueous and biological media is surmised also by the fact that maghemite is the fully oxidized state of iron oxide. These nanocrystal clusters having previously shown an enhanced relaxivity, $r_2$ together with low cytotoxicity [24] appear to be an adequate model system for studying the magneto-structural parameters that affect on their thermal response. The fact that all colloidal nanocrystal clusters proved to be ferrimagnetic and so their thermal response is dominated by hysteresis losses is proven to be advantageous with respect to superparamagnetic candidate nanoparticles as hyperthermia mediators.

4. Conclusions

We have discussed the properties of colloidal ferrimagnetic nanoclusters which are composed of similar-size primary maghemite nanocrystals. The ferrimagnetism at room temperature and the evolution of the magnetic properties upon the increasing volume fraction suggest that the hysteresis losses in the case of the nanoclusters are an additional and the main heating mechanism in comparison with usual relaxation loss mechanisms (Neél and Brown). The heating generation as expressed by the SLP value is enhanced compared to those of individual nanocrystals with similar size with those in the nanoclusters. Furthermore, it increases with the size of the nanoclusters and the magnetic material volume fraction ($\phi$) while it decreases for nanoclusters with diameter larger than 50 nm. Hysteresis losses analysis demonstrated the existence of a particular cluster size for which magnetic heating generation becomes prominent. Furthermore, we observe that the intra-cluster volume fraction together with the surface spin disorder of the constituent nanoparticles may be manipulated with the applied magnetic field parameters (e.g. field amplitude) in order to have optimum conditions for heat dissipation.

This study illustrates how the knowledge and the contribution of the dipolar interactions, the alignment of the particles and/or the nanocrystal arrangement in the nanoclusters are necessary for the development of tuneable hyperthermia mediators. The design of such nanoparticle-assembled materials, with optimum magneto-structural characteristics
appears to have potentiality for combining efficiently the functions of thermally-triggered applications. These may span from magnetic hyperthermia and go through thermally assisted drug delivery, together with image-guided hyperthermia.

Acknowledgments

This work was supported by the European Commission through the Marie-Curie Transfer of Knowledge program NANOTAIL (Grant no. MTKD-CT-2006-042459).

This work has been performed in part under the framework of the PROENYL and BIOSYS research projects, Action KRIIPS, project numbers MIS-448305 (2013E01380034) and 448301 (2013E01380036) that were funded by the General Secretariat for Research and Technology, Ministry of Education, Greece and the European Regional Development Fund (Sectoral Operational Programme: Competitiveness and Entrepreneurship, NSRF 2007–2013)/European Commission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.msec.2015.08.023.

References
