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Superparamagnetic iron oxide nanodiscs for hyperthermia therapy: Does size matter?

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ABSTRACT

For the final realization of magnetic nanoparticles (MNPs) mediated hyperthermia as a viable clinical therapy for cancer treatment, it is necessary to devise novel approaches in order to improve the heating efficiency or Specific Loss Parameter (SLP) of these MNPs. Recently, it has been shown that magnetic nanodiscs with enhanced shape anisotropy, diameters around 200 nm (25 nm thick), and vortex magnetic domain structure exhibit very high SLP values. Despite their high heating efficiency, biomedical applications of these nanodiscs could not be hassle-free due to their relatively big size. Therefore, in this work, we have studied how the heating efficiency of the nanodiscs changes upon size reduction (~12 nm diameter and ~3 nm thickness). In addition, we have compared these results with those obtained for more typically studied spherical nanoparticles of similar volume. Transmission Electron microscopy, Atomic Force Microscopy and X-ray Diffraction confirm the disc shape of our MNPs and that they are mostly composed of iron oxide (Fe_3O_4 or γ-Fe_2O_3) phase. Magnetometry indicates that the nanodiscs do not exhibit a vortex magnetic domain structure, but still present a superparamagnetic-like behavior, with zero magnetization in the absence of field at room temperature (ideal for biomedical applications) and enhanced effective anisotropy as compared to the spherical nanoparticles. Finally, calorimetric methods based magnetic hyperthermia experiments indicate that the SLP values for these small nanodiscs are much lower than those reported for the bigger disc-shaped nanoparticles, but these superparamagnetic nanodiscs act as better heating mediators than the spherical nanoparticles of similar volume.

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1. Introduction

Magnetic nanoparticles (MNPs) mediated hyperthermia is one of the most promising techniques for cancer treatment [1–3]. This technique essentially comprises the following steps: injecting MNPs into the human body, delivering them to the tumor area, and once the MNPs are disseminated inside the tumor, an external AC magnetic field is applied, and the nanoparticles transform the electromagnetic radiation into heat [4]. The generated heat rises the temperature in the tumor area and, in this way, damages or even kills and eradicates cancerous cells with minimally affecting the healthy ones, because healthy cells present a better resistance to high temperature than cancer cells [5,6]. In this way, the patient can receive a localized and highly efficient cancer therapy, without suffering from the collateral damage associated with other more commonly employed treatments, such as chemotherapy or radiotherapy. Despite the many promising aspects of this therapy, the current status of the clinical application of magnetic hyperthermia therapy is still very preliminary [3]. Only in a few places in the world, including Germany, Japan, and China, clinical trials have been carried out [7]. For example, ferrite core-based magnetic nanoparticles are being used for clinical cancer treatment (MagForce Nanotechnologies AG, Berlin, Germany) with a magnetic field strength of up to 225 Oe at 100 kHz, in combination with radiotherapy [8]. The results indicate an increase in the median survival time of the patients, but unfortunately no full recovery has been achieved yet.

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There are several limitations that negatively affect the efficiency of the magnetic hyperthermia treatment and therefore hinder its clinical realization [9]. These include problems in the delivery of the nanoparticles to the tumor area, restrictions in the maximum field and frequency that can be applied within the safety limits, low performance of the nanoparticles once inside the tumor, etc. [10]. In particular, the limitations related to the low heating efficiency of the commonly employed iron oxide (Fe_3O_4 or γ-Fe_2O_3) nanoparticles have received great attention in the last few years. Superparamagnetic iron oxide nanoparticles (SPIONs) were initially considered as the ideal MNPs for a wide range of biomedical applications, including magnetic hyperthermia, due to the excellent biocompatibility of the material and the small tendency to agglomeration, thanks to their superparamagnetic nature [11,12]. However, results have shown that these MNPs present a rather limited heating efficiency or Specific Loss Power (SLP), as it is denominated in the context of magnetic hyperthermia [13,14]. The SLP of the MNPs is directly related to their hysteresis losses [15], and therefore to their AC hysteresis loop area: the bigger the area under a certain applied AC field, the better the heating efficiency. Therefore, despite their good biocompatible characteristics, SPIONs generally present relatively low saturation magnetization (M_S) and coercivity (H_C), which diminish their heating efficiency, and therefore, deter their applicability.

Different strategies have been proposed in order to overcome this limitation [16]. These include changing the magnetic material by other with higher M_S (Fe, FeCo, …) [17,18]; tuning the size of the nanoparticles in order to optimize the hysteresis losses [19]; increasing the coercivity (anisotropy) of the nanoparticles through exchange coupling or doping [17,18,20–22] or changing the morphology (aspect ratio, shape) of the MNPs [23,24]. In this way, different shapes of MNPs other than the typical spheres have been proposed in order to tune their anisotropy and improve their heating efficiency: cubes, octopods, octahedral, cube-octahedral [23,25,26,46,47].

In this regard, disc shaped magnetic particles have attracted much attention in biomedicine [27–29,48]. Thanks to their large surface area, they can attach several bio-substances at once; their disc shape also increases their effective anisotropy; and at bigger sizes, they develop a vortex magnetic domain structure that ensures null magnetization in absence of magnetic field, reducing the problem of particle agglomeration [24,27]. As an example, it has been reported that bio-functionalized magnetic-vortex microdiscs (60-nm-thick, 1-μm-diameter 20:80% iron-nickel (perm-alloy discs) can oscillate in the presence of an alternating magnetic field, destroying the cancerous cells directly by mechanical force [31].

Despite this growing interest, in the field of magnetic hyperthermia for cancer treatment there have been only a few articles on the heating properties of magnetic nanodiscs. Recently Yang et al. [30] have reported that Fe_3O_4 nanodiscs (225 nm diameter; 26 nm thickness) exhibit much better hyperthermia performance than isotropic nanoparticles (SLP_{max} = 4400 W/g at 600 Oe and 488 kHz), attributed to the parallel alignment of nanodiscs with respect to the AC field. Previously, Ma et al. [32] had reported that their nanodiscs (150–200 nm diameter; 10–15 nm thickness) presented a SLP value of 253 W/g (12 Oe and 180 kHz), higher than those typically reported for spherical MNPs. Despite these remarkable results, the average size of the nanodiscs that have been investigated is much bigger than that of MNPs typically used in hyperthermia therapy (5–100 nm) [33]. Their large size could restrict their capacity for being internalized by cancerous cells, decrease their average lifetime in blood and lead to potential negative agglomeration effects [34].

Therefore, in this work, we have synthesized smaller iron oxide nanodiscs (~12 nm diameter, ~3 nm thickness) and compared their heating properties with those of the much bigger nanodiscs reported in the literature [28] and with spherical MNPs of similar volume synthesized by us. The results indicate that the reduction in the size of the nanodiscs deters their heating efficiency but still, the heating results obtained are better than those measured for the spherical MNPs of similar volume. Our study indicates that in order to continue with the development of nanodiscs for magnetic hyperthermia, the size needs to be carefully tuned in order to improve their "in-vivo" properties (kinetics, internalization, dissemination, agglomeration …) while still obtaining a significant heating efficiency.

2. Experimental methods

For this study, we have prepared one sample composed of disc shaped MNPs and one sample formed by spherical MNPs. Iron oxide (Fe_3O_4 or γ-Fe_2O_3) disc-shaped MNPs were synthesized via the soft template-assisted synthesis [35,36] in a binary system of H_2O/Cetyltrimethylammonium bromide (CTAB), 77/23 g at room temperature. This mixture forms a hexagonal lyotropic liquid crystalline phase. $Fe(acac)_3$ in H_2O/CTAB goes through a cascade of reduction-hydrolysis reactions in the presence of aqueous $NaBH_4$. $Fe(OH)_x$, where x is 1, 2 and 3 are formed as intermediately until Magnetite (Fe_3O_4) is formed via nucleation reactions of $Fe(OH)_2$ and Fe(OH) [37]. In a 3-neck round bottom flask, $Fe(acac)_3$ (2 mmol) was dissolved in a mixture of 77 g of degassed DI water and 23 g of CTAB. 10 mmol of $NaBH_4$ was then mixed with 3 mL of degassed DI water and added to the above mixture. The vessel was under constant flow of nitrogen as well as vigorous mechanical stirring (500 rpm) at room temperature. The reaction resulted in two products, the froth and the gel after 5 h, and the disc shaped MNPs were retrieved from the formed gel. In order to isolate the particles from the surfactant, the gel was washed several times with $50°C$ water and centrifuged at 5000 rpm and was eventually dried out.

On the other hand, we also produced iron oxide spherical MNPs by using non-hydrolytic thermal decomposition. Details of the synthesis route have been given previously (see Ref. [38]). Briefly, a three neck flask was charged with 1,2 hexadecane diol, Benzyl ether (98%), Oleylamine (70%), Oleic acid (90%), and Iron (III) acetylacetonate, which was used as the precursor. The mixture was stirred magnetically under a flow of nitrogen gas for 2 h at 200 °C. Temperature was raised subsequently to 300 °C for 1 h. After reflux the sample was cooled down to room temperature. Finally, the spherical MNPs were coated with tetramethylammonium hydroxide (TMAH) to make them water dispersible.

A Bruker AXS D8 X-ray diffractometer (Cu -K_α radiation, 0.15418 nm) was used to analyze the crystalline structure of the disc and spherical shaped MNPs, and an FEI Morgagni 268 transmission electron microscope (TEM), operating at 60 kV, was used to obtain information about their size distribution and morphology. Both X-ray diffraction and selected area electron diffraction were utilized to further investigate the sample's crystalline structure. The thickness of the nanodiscs was determined by using Atomic Force Microscopy (AFM) in tapping mode (DSP Classic model, Nanotec). Magnetic measurements were carried out using a Physical Property Measurement System (PPMS) from Quantum Design, with a vibrating sample magnetometer (VSM) option. The zero-field-cooling/field-cooling (ZFC/FC) curves were measured between 5 and 350 K, with an applied field of 50 Oe, while the hysteresis loops were measured at room temperature, 300 K, applying fields up to 50 kOe. Magnetic hyperthermia measurements were carried out using calorimetric methods, with a 4.2-kW Ambrell Easyheat Li3542 system. A suspension of 1 mg/ml of nanoparticles in water was used for measurements and the AC magnetic field was tuned from 0 to 800 Oe, at a constant frequency of 310 kHz.

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