Journal of Magnetism and Magnetic Materials 387 (2015) 96–106

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

Impact of magnetic field parameters and iron oxide nanoparticle properties on heat generation for use in magnetic hyperthermia

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ARTICLE INFO

Article history:
Received 5 March 2014
Received in revised form
2 September 2014
Accepted 25 March 2015
Available online 30 March 2015

Keywords:
Magnetic fluid hyperthermia
Iron oxide nanoparticles
Magnetic field strength
Magnetic field frequency
Specific absorption rate

ABSTRACT

Heating of nanoparticles (NPs) using an AC magnetic field depends on several factors, and optimization of these parameters can improve the efficiency of heat generation for effective cancer therapy while administering a low NP treatment dose. This study investigated magnetic field strength and frequency, NP size, NP concentration, and solution viscosity as important parameters that impact the heating efficiency of iron oxide NPs with magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) crystal structures. Heating efficiencies were determined for each experimental setting, with specific absorption rates (SARs) ranging from 3.7 to 325.9 W/g Fe. Magnetic heating was conducted on iron oxide NPs synthesized in our laboratories (with average core sizes of 8, 11, 13, and 18 nm), as well as commercially-available iron oxides (with average core sizes of 8, 9, and 16 nm). The experimental magnetic coil system made it possible to isolate the effect of magnetic field parameters and independently study the effect on heat generation. The highest SAR values were found for the 18 nm synthesized particles and the maghemite nanopowder. Magnetic field strengths were applied in the range of 15.1–47.7 kA/m, with field frequencies ranging from 123 to 430 kHz. The best heating was observed for the highest field strengths and frequencies tested, with results following trends predicted by the Rosensweig equation. An increase in solution viscosity led to lower heating rates in nanoparticle solutions, which can have significant implications for the application of magnetic fluid hyperthermia *in vivo*.

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1. Introduction

Magnetic fluid hyperthermia (MFH) using localized iron oxide NPs offers a significant benefit over whole body and regional hyperthermia, which can lead to several vascular and cardiac disorders [1–3]. MFH has also been shown to kill cells faster as compared to traditional hyperthermia methods, which can play an essential role in reducing the therapy administration time for cancer treatment [4]. MFH can reduce side effects in patients while amplifying treatment of cancer using superparamagnetic NPs, which can be specifically targeted using antibodies or peptide sequences [5, 6] and directed to cancerous tissue through the enhanced permeation and retention (EPR) effect [7]. Magnetic fields in the kHz to MHz range have been investigated for heat generation in various MFH systems using superparamagnetic and ferromagnetic iron oxide NPs [8, 9]. To be used effectively for cancer treatment, the least possible dose of NPs should be introduced in the human body to avoid possible side-effects and bioaccumulation. Thus, it is essential to understand the factors that affect heat generation in NP dispersions to maximize the therapeutic effectiveness of MFH.

Some NPs based on iron oxide have been approved for medical use by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [6]. While magnetic NPs that contain cobalt ferrites and nickel ferrites may have better magnetic properties for heat generation, the medical use of these materials is generally infeasible. NPs made of nickel ferrite have been shown to have an adverse effect on cell viability and replication, while it was demonstrated that cobalt ferrite NPs can be toxic to mammalian cells at concentrations needed for cancer hyperthermia treatment [10–12]. In addition to their acceptability for medical use, iron oxide NPs feature good colloidal stability when coated with appropriate surfactants or polymers which can also provide a linkage to cell-targeting moieties [13]. Iron oxide NPs have been widely investigated for magnetic heating, and have also proven to be useful as MRI contrast agents [6, 14]. These properties make iron oxide NPs attractive for use in cancer theranostics.

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http://dx.doi.org/10.1016/j.jmmm.2015.03.085
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To characterize the heating of magnetic nanoparticles under AC magnetic field exposure, specific absorption rate (SAR) values are determined from temperature–time profiles and computed as heat generation per mass of NPs or iron (Fe) content of NPs in W/g [15–18]. NPs with high SAR are largely favored for cancer treatment as administration of NPs to patients can be kept to a minimum while using brief durations of magnetic field exposure that still achieve the temperature rise essential to induce cell death. SAR is calculated as:

$$SAR\ (W/g) = \frac{m_s * c_p}{m_{np}} * \left(\frac{\Delta T}{\Delta t}\right) \quad (1)$$

Here m_s is the mass of solution, m_{np} is either the mass of NPs or the mass of Fe in the NPs, c_p is the heat capacity of the solution, and $(\Delta T/\Delta t)$ is the initial slope of the temperature rise vs. time curve for NP heating. The SAR value serves as guidance for comparing the heating rates of NPs with different compositions and concentrations, at different magnetic field settings.

The parameters that govern power loss in magnetic hyperthermia are defined by the Rosensweig equation [19], where the power generation (P) in iron oxide NPs when subjected to an AC magnetic field is defined as:

$$P = \pi\mu_o\chi_o H^2 f \frac{2\pi f\tau}{1 + (2\pi f\tau)^2} \quad (2)$$

Here, μ_o is the permeability constant of free space ($4\pi * 10^{-7}$ T-m/A), χ_o is the magnetic susceptibility of the particles, H is the magnetic field strength, f is magnetic field frequency, and τ is the relaxation time for reorientation of magnetic moments in NPs, either through whole NP motion (Brownian relaxation) or spin relaxation (Néel relaxation) [19]. The power generated through application of an AC magnetic field results in thermal energy, and for a given set of superparamagnetic NPs the quantity of heating is a function of the square of magnetic field strength when all other factors are held constant. Frequency can also be used to tune the heat generation, as the power generation reaches an asymptote when frequency is increased. The application of the Rosensweig equation, and contribution of different relaxation mechanisms to MFH has been well described [19–24], and further relationships between magnetic heating and NP properties are manifest in the magnetic susceptibility and relaxation time.

By changing the properties of the applied magnetic field (through field intensity and frequency), heating in superparamagnetic NPs can be optimized. The power input by the magnetic field can also be tuned by adjusting the time course of field application. The field can be applied for different durations of time or using variable field intensity, for example through the use of a feedback control loop where the field is adjusted to maintain a fixed temperature. One such system has been proposed by Tseng et al. using a thermocouple and a temperature processing unit to maintain a constant hyperthermia temperature [25]. A number of studies have investigated MFH to determine preferred parameters that lead to high SAR values [26–31]. In most published studies, MFH magnetic field frequencies are applied in the range of 80–700 kHz, while field strength usually lies between 1 and 50 kA/m [15, 26–31]. A wide range of SAR values have been reported for NPs of different compositions, sizes, and size distributions, for many different field strengths and frequencies which are often fixed by the geometry and electrical configuration of the magnetic coils. Additional complications that make comparison of experimental results between groups challenging include the reliability of NP characterization and differences in SAR reporting, which is normalized by either NP mass or the mass of Fe in the NPs, but is often not clearly reported due to difficulties in distinguishing the oxidation state of Fe in the NPs. These variables make it difficult to reach conclusions about optimal NP structures and magnetic field parameters to achieve effective heating. SAR values for commercial and custom-synthesized iron oxide NPs have been reported covering a range from lower than 10 W/g Fe to higher than 2000 W/g Fe [15, 26–31]. Some of the highest reported SAR values of 2452 W/g of Fe for cubic iron oxide NPs and 1650 W/g for spherical iron oxide NPs were obtained by Guardia et al. and Fortin et al., respectively [26, 27].

Heat generation in magnetic NPs under application of a high frequency magnetic field is governed by Néel relaxation, Brownian relaxation, and a hysteresis loss mechanism [19]. Néel relaxation occurs due to the flipping of magnetic moments inside each NP, whereas Brownian relaxation occurs due to the rotation of entire particles along with the magnetic moment. Néel and Brownian relaxations are theorized to be the dominant heat loss mechanisms for particles that are superparamagnetic in nature, while hysteresis losses that occur due to movement of domain walls under application of magnetic field are responsible for heating in larger sized ferromagnetic particles [19]. There is, however, disagreement over the maximum size for single domain NPs, and where this transition occurs. The critical NP size range separating superparamagnetic and ferromagnetic domain varies based on structure and composition of NPs. In a study by Bakoglidis et al. where NPs investigated were a mixture of maghemite and magnetite, it has been suggested that particles beyond 13 nm in size lie in the ferromagnetic domain, whereas smaller particles lie in the superparamagnetic domain [32]. Krishnan has determined by mathematical modeling that the maximum size for a particle to be single domain and superparamagnetic is in the range of around 35 nm for maghemite and 25 nm for magnetite, while that for being single domain and ferromagnetic is approximately 90 nm for maghemite and slightly larger than 80 nm for magnetite [22]. Vergés et al. surveyed the results of other researchers and reported that the transition range from single domain to multi domain is around 50 nm for magnetite NPs [33]. Thus, while the mechanism of heating is expected to depend largely on particle size, there are two complicating factors that make attributing heat generation to a particular heating mechanism difficult: (1) the particles may have single or multiple crystal domains, and (2) the size distribution of NPs can be widely disperse for a given sample.

The viscosity surrounding NPs can also impact magnetic heating, primarily through increasing the relaxation time for Brownian relaxation, which reduces the Brownian contribution to heat generation. As most experimental investigations of MFH are done on aqueous dispersions of NPs with no significant additives to alter viscosity, the applicability of data to more complex *in vivo* environments may not be accurately estimated. For example, many applications of magnetic NPs involve the deployment of NPs in blood or tissue, where they will be surrounded by proteins [34], or in the core of a drug delivery device where the free motion of NPs is impeded by a polymer [13]. One recent study has shown that when a mixture of 13.9 nm magnetite and maghemite NPs was subjected to increasing solution viscosity from 0.9 cP to 43.2 cP at a magnetic frequency of 215 kHz and amplitude of 3.8 kA/m, the SAR value decreased to 70% of the original value [35]. Since the environment surrounding NP for medical uses will likely be significantly more viscous than water, experiments to determine the effect of viscosity on SAR are needed to predict heating *in vivo*. Thus, this phenomenon can affect the overall feasibility of MFH, particularly if Brownian relaxation is responsible for much of the heating.

While many research groups have contributed to the understanding of MFH, it is difficult to compare SAR values from different groups, as the magnetic induction coils in each laboratory often have fixed or narrow operational frequency ranges. Also in many research studies multiple factors affecting the NP heating

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