Journal of Magnetism and Magnetic Materials 441 (2017) 310–327

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

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

Research articles

Magnetic hyperthermia in magnetic nanoemulsions: Effects of polydispersity, particle concentration and medium viscosity

B.B. Lahiri, Surojit Ranoo, A.W. Zaibudeen, John Philip *

Smart Materials Section, Physical Metallurgy Division, Metallurgy and Materials Group, Indira Gandhi Centre for Atomic Research, HBNI, Kalpakkam, Tamil Nadu PIN 603102, India

ARTICLE INFO

Article history:
Received 30 March 2017
Received in revised form 24 May 2017
Accepted 25 May 2017
Available online 27 May 2017

Keywords:
Magnetic fluid hyperthermia (MFH)
Magnetic nanoemulsion
Neel & Brown relaxation
Agar gel
Specific absorption rate (SAR)
Linear response theory (LRT)

ABSTRACT

Magnetic fluid hyperthermia (MFH) is a promising cancer treatment modality where alternating magnetic field is used for heating cancerous cells loaded with magnetic nanofluids. Of late, it is realized that magnetic nano-carriers in the size range ~100–200 nm (e.g. magnetic nanocomposites, magnetic liposomes and magnetic nanoemulsions) are ideal candidates for multimodal MFH coupled with drug delivery or photodynamic therapy due to enhanced permeation and retention (EPR) in the leaky vasculature of cancerous tissues. Here, we study the radiofrequency alternating magnetic field induced heating in magnetically polarizable oil-in-water nanoemulsions of hydrodynamic diameter ~200 nm, containing single domain superparamagnetic nanoparticles of average diameter ~10 nm in the oil phase. We probe the effects of size polydispersity of the droplets and medium viscosity on the field induced heating efficiency. The contribution of Neel and Brown relaxation of the magnetic nanoparticles on specific absorption rate (SAR) of the magnetic nanoemulsions, was found to increase linearly with the square of the applied field, with a maximum value of 164.4 ± 4.3 W/g_{Fe}. In magnetic nanoemulsions, the heating is induced by the Neel-Brown relaxation of the MNP over a length scale of 10 nm, and the whole scale Brownian relaxation of the emulsion droplets has over a length scale of 200 nm. The magnetic nanoemulsion sample with lower polydispersity ($\sigma = 0.2$) exhibited a significantly higher SAR value (3.3 times higher) as compared to the sample with larger polydispersity ($\sigma = 0.4$). The SAR values of the samples with 4.6 and 1.7 wt.% of MNP loading with σ values 0.4 a 0.3, respectively were comparable, suggesting a higher heating efficiency in nanofluid containing particles of lower size polydispersity even at lower particle loading. The emulsion droplets, immobilized in an agar matrix (4 wt.%), gave a maximum SAR value of 41.7 ± 2.4 W/g_{Fe} as compared to 111.8 ± 3.4 W/g_{Fe} in the case of droplets dispersed in water, which indicate a ~40–50% drop in SAR due to abrogation of whole scale Brownian relaxation of the emulsion droplets. This suggests the need for improving the heating efficiency during actual therapy in tissues. The residual SAR of the immobilized sample correlates well with the SAR of the magnetic nanofluid, albeit under a lower external field amplitude due to demagnetization effect of the clusters of MNP loaded inside the droplets. The observed heating efficiency of larger sized magnetic nanoemulsion offer new possibilities for multimodal therapy due to availability of large volume for loading anti-cancer drug or photodynamic agents.

1. Introduction

Single domain superparamagnetic nanoparticles have been a topic of intense research during the last few decades due to their unique properties and diverse applications, especially in the biomedical field. Such single domain magnetic nanoparticles (MNP) in a host medium (viscous or viscoelastic) generate heat, under a high frequency alternating magnetic field, mainly due to the relaxation (Neel-Brownian) losses. The targeted and controlled field induced heating by MNPs have several applications in the field of biological sciences, e.g. enhanced drug release in the region of interest [1–3], magnetic fluid hyperthermia (MFH) [4–6], theranostic applications [7] and enhanced destruction of cancerous cells using combined therapies like photodynamic or chemotherapy paired with MFH [8–10]. MFH as a therapeutic procedure was first reported by Gilchrist et al. in 1957 [11], where a fluid containing MNP was injected into a tissue containing cancerous cells and thereafter exposed to a radio frequency (RF) alternating magnetic field which caused an increase in the fluid temperature beyond 42 °C (known as hyperthermia limit) that lead to cellular degradation and apoptosis [12]. Reports also suggest that cancerous cells

---

* Corresponding author.
E-mail address: philip@igcar.gov.in (J. Philip).

http://dx.doi.org/10.1016/j.jmmm.2017.05.076
0304-8853/© 2017 Elsevier B.V. All rights reserved.

exposed to the hyperthermia limit becomes more susceptible to conventional treatment methods like radiotherapy or chemotherapy [13,14]. The high surface area to volume ratio of the MNP is found to be beneficial for promoting biological contact along with several other advantages like easy escape from vasculature, preferential conjugation with tumor cells for surface modified MNP and external magnetic field guided drug delivery. *In vivo* studies show good efficacy of MFH in curing various cancer modes like melanoma, breast tumors and prostate cancer [15–17]. Owing to its immense clinical benefits, MFH is being actively pursued as an alternative cancer treatment modality [18–29]. The field induced heating of magnetic nanoparticles is quantified in terms of a dosimetric quantity known as specific absorption rate (SAR) which is defined as the heat generated per unit mass (W/g). Experimentally, SAR is evaluated from the initial rate of temperature rise during the field induced heating in non-adiabatic limit where the increase in sample temperature is measured as a function of time using a suitable radio-frequency immune probe like fiber optic temperature sensor, liquid thermometer, infrared point thermometers and infrared thermography (IRT) [30–32].

Though numerous types of spinel ferrites, like cobalt, nickel, manganese, zinc, lanthanum, and strontium are used for MFH studies, the most widely used candidates for MFH applications are iron oxides (magnetite: Fe_3O_4 or maghemite: γ-Fe_2O_3); primarily due to their inherent biocompatibility (heme oxygenase-1 mediated metabolism) and ease of synthesis. These materials are used without or with inorganic/organic bio-compatible coatings. Recently, Kumar and Mohammed [33] broadened the definition of MFH to include magnetically modulated drug delivery, which opened up several interesting opportunities to use comparatively larger sized (~ 200 nm diameter) nano-systems like, magnetic nano-composites [34,35] and magnetic nanoemulsions. Such approaches are designed to make these system multifunctional, for e.g. specific anticancer drugs (like doxorubicin, paclitaxel or daunorubicin) attached to these materials for magnetically controlled drug delivery along with MFH [1] or use of photoactive chloroaluminum phthalocyanine (ClAlPc) agents with the MNP to combine photodynamic therapy and MFH [8,36,37]. Though superparamagnetic nanoparticles (SPM) are used in the most of the MFH studies, larger size nanoparticles are favorable for many applications, especially for multimodal applications [38,39].

Studies show that nano-carriers loaded with anticancer drugs in the size range ~100–200 nm, are beneficial for enhanced permeation and retention (EPR) in the local environment (consisting of leaky vasculature) of cancerous cells and to avoid uptake by macrophages, filtration at spleen or liver and human complement system which enhances the immunity against damaged cells and foreign inclusions [34,40,41]. Win and Feng [42] reported higher cellular uptake of the larger sized nanoparticles, which was found to be beneficial to increase the drug delivery ratio to the affected cells. A higher SAR for ~200 nm sized ultra-magnetic liposomes particles has been reported by Bealle et al. [43]. It has been reported that for doxorubicin loaded (loading efficiency ~80%) polyethylene glycol coated and carboxyl enriched mesoporous $MgFe_2O_4$ samples, MFH in combination with drug therapy results in ~90% cell deaths *in vitro* as compared to MFH only [44]. Paula et al. reported a 70% increase in cell death during simultaneous application of photodynamic therapy and MFH [8]. The above studies show that comparatively larger sized nano-carriers are essential for achieving synergistic multimodal therapy. Recent studies indicate that high macroscopic temperature rise is not a prerequisite for MFH induced drug delivery thereby opening up the possibilities of using nano-carriers with even lower concentration of magnetic phases as multi-modal MFH agents [45].

Magnetic nanoemulsions is an ideal model candidate for larger sized nano-carriers due to its structural and dimensional similarities with encapsulated ultra-magnetic liposomes (UML) [34,43]. Magnetically polarizable nanoemulsions have been used as smart sensors for non-enzymatic glucose detection [46], nanoscale mechanical probes and actuators in complex fluids and biological systems [47] and magnetic resonance imaging [48]. Iron oxide modified oil-in-water magnetic nanoemulsion, with the magnetic particles distributed in the water phase and the oil phase containing photodynamic agents like chloroaluminum phthalocyanine or Zn(II)-phthalocyanine were used for simultaneous photodynamic therapy and MFH [8,36,37]. Hu et al. [49] reported the use of bio-compatible core-shell, water-in-oil-in-water double emulsion, where poly vinyl alcohol and magnetic iron oxide nanoparticles were used as surfactant and stabilizing agent, respectively as a dual-drug carrier with controlled drug release.

Although field induced heating of magnetic nanoemulsions have been demonstrated previously, to the best of our knowledge, systematic studies on the field induced heating efficiency of magnetic nanoemulsions were not carried out earlier, in spite of having tremendous potential for multimodal MFH agents. Though the field induced heating in MNP based nanofluid is well studied, several challenges still exist in the basic understanding of the heating mechanism in magnetic nanoemulsions and magnetic clusters. Despite the fact that the role of polydispersity [23,50], demagnetizing field [51,52] and dipole-dipole interactions [20,53] on heating efficiency is studied theoretically (analytically or numerically), the experimental work, which is essential for practical applications, on these aspects in model colloidal system consisting of magnetic nanoemulsion is scarce. In magnetic nanoemulsion, both the MNP's (10 nm) and the droplets (20 times bigger at ~200 nm) acts as heat generators. Due to larger size of the emulsion droplets, Brownian relaxation is the dominant heating mechanism, whereas in the case of MNP, both Neel and Brownian contributions are present. The size and polydispersity of the droplets play a crucial role in heat generation through Brownian relaxation. The effect of demagnetizing field and inter-particle interaction also needs to be understood well for effective utilization of MFH towards cancer treatment. Finally, the role of interfacial thermal resistance and dispersion medium viscosity on the heat transfer from the droplets to the dispersion medium needs to be understood clearly.

The main aim of this work was to systematically study the field induced heating of an oil-in-water magnetic nanoemulsions of size ~200 nm containing MNPs (~10 nm). The second objective was to probe the role of polydispersity of the oil droplets (with same size and concentrations of the loaded MNP) on the heating efficiency of the nanoemulsions. The third objective was to compare the heating efficiency with and without Brownian relaxation mechanism (studied by immobilizing of the emulsion droplets in tissue mimicking agar gel) and to study the effect of demagnetizing field on heating efficiency. We also probe the morphological consistency of the emulsion droplets immobilized in agar gel. The experimentally obtained data were also compared with theoretical results obtained under linear response regime.

2. Theoretical background

2.1. Mechanism of field induced heating in magnetic nanoparticle (MNP) dispersions

Alternating magnetic field can induce heating in MNP via three major heating mechanisms, viz. hysteresis loss (for large single domain or multi domain MNP) and Neel-Brown relaxation mechanisms (for SPM MNP) [12,23]. In the case of hysteresis loss, power dissipated (P) can be expressed as $P = A.f$, where A and f indicate hysteresis loop area (in general, minor loops for MFH applications) and frequency of the applied magnetic field, respectively. On the