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Magnetic hyperthermia in phosphate coated iron oxide nanofluids

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ABSTRACT

We study the magnetic field induced hyperthermia in water based phosphate coated Fe_3O_4 nanofluids, synthesized by a co-precipitation method using ferrous and ferric salt solutions, ammonia and ortho-phosphoric acid. The specific absorption rate (SAR) values were measured at a fixed frequency of 126 kHz and at extremely low field amplitudes. The SAR values were determined from the initial rate of temperature rise curves under non-adiabatic conditions. It was observed that the SAR initially increases with sample concentration, attains a maximum at an optimum concentration and beyond which SAR decreases. The decrease in SAR values beyond the optimum concentration was attributed to the enhancement of dipolar interaction and agglomeration of the particles. The system independent intrinsic loss power (ILP) values, obtained by normalizing the SAR values with respect to field amplitude and frequency, were found to vary between 158–125 $nHm^2\,kg^{-1}$, which were the highest benchmark values reported in the biologically safe experimental limit of $1.03–0.92 \times 10^8\,Am^{-1}\,s^{-1}$. The very high value of ILP observed in the bio-compatible phosphate coated iron oxide nanofluids may find practical applications for these nanoparticles in tumor targeted hyperthermia treatment.

1. Introduction

In hyperthermia therapeutic procedure, biological tissues are heated above physiological temperature ranges using various stimulus such as phased array microwave heating, radio frequency heating, laser heating and whole body water bath heating. Temperature in the range of 42–46 °C can lead to alteration of protein metabolism of the cancerous cells and can ultimately lead to cellular degradation and apoptosis [1,2]. Moreover, it has been reported that the cancerous cells, above 42 °C, become more susceptible to conventional treatments using, drugs, radiation or chemotherapy [3–5]. In 1957, Gilchrist et al. [6] first reported the use of magnetic nanoparticles for magnetic fluid hyperthermia (MFH) – a therapeutic procedure where the cancerous tissues are heated above their normal physiological temperature ranges, leading to the death of cancerous cells [2]. The cancerous tissues, in general show lower thermal resistance, in comparison to normal tissues, due to poor development of blood vessels and lack of oxygen which enables destruction of cancerous cells by localized heating using MFH, where cell temperature is increased by the heat dissipation of the magnetic nanoparticles which are exposed to a high frequency alternating magnetic field [7–9]. Very high surface area to volume ratio of magnetic nanoparticles and their preferential adsorption in tumor tissues (magnetic nanoparticles conjugated with tumor specific peptides or antibodies) are found to be beneficial for promoting biological contact, *in-vitro* control and escape from vasculature [9,10]. *In vivo* experiments in animal models have shown the efficacy of this methodology for various types of cancers like melanoma, breast tumors and prostate cancer [11–13]. Moreover, magnetic nanoparticles, in the form of stable colloidal suspension, can be easily guided to the cancerous cells via external magnetic field or a variety of drug delivery routes thereby allowing tissue specific localized hyperthermia treatment [2]. The first successful clinical trial of interstitial hyperthermia in the treatment of human cancer using magnetic nanoparticles was attempted by Johannsen et.al [13] in 2005. In recent years, magnetic fluid hyperthermia (MFH) has become a rapidly developing alternate methodology for treatment of cancerous cells [2,14–31].

Superparamagnetic Fe_3O_4 and γ-Fe_2O_3 are the most widely used magnetic system for hyperthermia applications because of their selective heating capacity without damaging healthy tissues, superior bio-compatibility (metabolization through heme oxygenase-1 to form blood hemoglobin [32]), ease of synthesis and long term stability [10,33–38]. Apart from iron ferrite systems, several other spinel ferrites, like cobalt, manganese and nickel ferrites have also been used for hyperthermia studies [14]. To limit the heating beyond the desired limits, Gd based materials with large magnetization values and Curie temperatures around 40–45 °C have been developed and tested [39]. A very high value of specific absorption rate (SAR) was reported in polymer coated iron oxide nano-cubes [40] (SAR=2452 W/g at H=29 kAm^{-1} and f=52 kHz, where H and f are the magnitude and frequency of the applied

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alternating magnetic field, respectively) and for maghemite nanopartilces [41] (SAR=1650 W/g at $H=24.8\ \mathrm{kAm^{-1}}$ and $f=700$ kHz). On the other hand, bacterial magnetosomes yielded a SAR value of 960 W/g (at $H=10\ \mathrm{kAm^{-1}}$ and $f=410$ kHz) which was attributed to the relatively narrow size distribution of the particles [42,43]. Among other magnetic systems, highest SAR values were reported as 1661 W/g (at $H=23.9\ \mathrm{kAm^{-1}}$ and $f=717$ kHz) for manganese ferrite [44] and 720 W/g (at $H=10\ \mathrm{kAm^{-1}}$ and $f=410$ kHz) for metallic cobalt nanoparticles [45]. In general, to ensure biocompatibility, the magnetic nanoparticles are often coated with various organic or inorganic species like polyethylene glycol, dextran, chitosan, gold, silica, etc [14]. Theoretically, SAR values dramatically increases with increasing magnitude or frequency of the applied alternating magnetic field, which is due to the quadratic and linear dependence of the heating power with magnitude and frequency of the applied field, respectively. Monotonic increase of SAR value by increasing the field parameters is restricted due to biological constraints [2,24]. Apart from the beneficial heating, the applied alternating magnetic field also induces significant heating of the healthy tissues due to eddy current and the heating power (P) is proportional to the square of the product of H, f and induced current loop diameter (D) [24], i.e. $P\sim(\mathrm{H.f.D})^2$. Considering a current loop diameter of 30 cm, Brezovich [46] proposed a safety limit of $\mathrm{H.f}<4.85\times10^8\ \mathrm{Am^{-1}\ s^{-1}}$ for magnetic nanoparticle hyperthermia based cancer treatment. Nevertheless, the optimum field conditions and material properties are still being studied, as the SAR values vary, often non-linearly and interdependently, with several parameters like particle size, morphology, size distribution, concentration, dispersion medium, saturation magnetization, magnetic anisotropy, etc. [2,14]. Considering the immense clinical benefits, it is important to enhance the heating efficiency of the magnetic nanoparticles which will minimize the ferrofluid dose and related toxicity effects [10,33] thereby enabling MFH readily adaptable for cancer treatments.

To make MFH as a standard therapeutic procedure, further systematic studies are necessary to understand the effects of material properties, frequency-dependent magnetic response and the subsequent heating rate along with the safety and efficacy of magnetic nanoparticles inside tumor cells. Further, magnetic nanoparticle suspensions with statistically distributed properties makes the quantification of heating efficiency calculations difficult, though it is very important from practical application point of view [47]. Many of the reported results are on materials that are not bio-compatible, concentrations much above the desired concentrations limits and at field-frequency products much above the biological safety limit. To adopt MFH as a routine tumour therapy for thermoablation, systematic studies on the above aspects in biocompatible and stable nanofluids are prerequisite. In this paper, we investigate the MFH of water based phosphate coated Fe_3O_4 nanoparticles which are synthesized in our laboratory using a single step co-precipitation method [48]. The two important questions we address from our studies are the following: (a) Can we achieve the desired heating efficiencies at low magnetic field and frequency (H.f) values in appropriate water based biologically suitable magnetic nanofluids? (b) What is the role of particle concentration and aggregation on hyperthermia efficiency in such magnetic fluids? The SAR values are experimentally measured at a fixed frequency of 126 kHz and for low field magnitudes in the range of 0.36–0.82 $\mathrm{kAm^{-1}}$. We find a very high value of heating efficiency with an extremely low value of magnetic field-frequency product (H.f), which is found to be ideal for practical applications. The effect of particle concentration on SAR is also studied.

2. Theory of field induced heating and heating efficiency

Alternating magnetic field can induce heating in magnetic materials by four independent heating mechanisms, viz. eddy current, hysteresis loss, Neel relaxation and Brownian relaxation. Eddy current losses are insignificant for magnetic nanoparticles and hence, the remaining three mechanisms are only responsible for MFH [2]. Hysteresis loss can be expressed as the product of the frequency and area of the hysteresis loop and this mechanism is prominent for large single domain or multi domain magnetic nanoparticles [2]. For superparamagnetic nanoparticles the heating is mainly achieved through Neel or Brownian relaxation methods. In the case of Neel relaxation, the magnetic moments of the individual particles follow the oscillating external magnetic field by rotating against the anisotropic energy barrier within the particle itself and assuming uniaxial anisotropy, the Neel relaxation time (τ_N) can be expressed by the following equation [49,50].

$$\tau_N = \frac{\tau_0}{2}\sqrt{\frac{\pi}{\sigma}}e^{\sigma} \tag{1}$$

Here, τ_0 is the attempt frequency and can be expressed as $\tau_0=\frac{M_s}{2\gamma_0 K}\frac{(1+\alpha^2)}{\alpha}$, where M_s is the saturation magnetization, γ_0 is the electron gyromagnetic ratio, K is the effective uniaxial magnetic anisotropy energy density and α is the damping factor (in the linear response regime) [51]. σ is a dimensionless factor and it is defined as the ratio of the magnetic anisotropy energy to thermal energy: $\sigma=KV_p/k_BT$, where, V_p is the volume of the nanoparticle, k_B is the Boltzmann's constant and T is the system temperature in absolute scale [50]. In absence of an external magnetic field the magnetic moments of the individual superparamagnetic nanoparticles are randomly oriented along their individual easy magnetic axes which are primarily determined by the magnetocrystalline or shape anisotropy [2]. The applied external magnetic field may however, provide sufficient energy to reorient the magnetic moments away from their preferred direction and the magnetic energy is stored internally in the process. Relaxation of the magnetic moments towards their easy direction releases the stored energy thereby causing heating through Neel relaxation. It has been recently reported that heating through hysteresis mode is also caused through Neel relaxation [25,52].

On the other hand, in Brownian relaxation the magnetic nanoparticle itself rotates within the base fluid and the magnetic moments remain fixed with respect to the crystal axes. Under such conditions the heating is achieved by the shear action in the surrounding base fluid. Brownian relaxation time is expressed by the following equation [2].

$$\tau_B = \frac{3\eta V_h}{k_B T} \tag{2}$$

Here, η is the viscosity of the base fluid and V_h is the hydrodynamic volume of the dispersed nanoparticles. Both the relaxation mechanisms are independent and in reality occur in parallel, resulting in an effective relaxation time (τ) which is expressed as $\tau^{-1}=\tau_N^{-1}+\tau_B^{-1}$. This shows that the effective relaxation time scales with the lower component and Neel relaxation time dominates for smaller particles and viscous media whereas, Brownian relaxation is prominent for larger particles in low viscosity media [2].

When an alternating magnetic field, $H(t)=H_0\cos(\omega t)$ is applied on a magnetic nanofluid with complex susceptibility ($\chi=\chi'-i\chi''$), the resultant magnetization $M(t)$ can be expressed as $M(t)=H_0[\chi'\cos(\omega t)+\chi''\sin(\omega t)]$ [53]. χ'' is the out of phase component of the susceptibility which indicates magnetic loss. For a motionless fluid in an oscillatory magnetic field, $\chi''=\chi_0\frac{\omega\tau}{1+\omega^2\tau^2}$, where χ_0 is the ensemble averaged equilibrium susceptibility, ω is the cyclic frequency ($\omega=2\pi f$) and τ is the effective relaxation time