Materials Science and Engineering C 68 (2016) 18–29

Contents lists available at ScienceDirect

Materials Science and Engineering C

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

Determining iron oxide nanoparticle heating efficiency and elucidating local nanoparticle temperature for application in agarose gel-based tumor model

Rhythm R. Shah [a], Alexander R. Dombrowsky [a], Abigail L. Paulson [b], Margaret P. Johnson [b], David E. Nikles [b], Christopher S. Brazel [a,*]

[a] The University of Alabama, Department of Chemical and Biological Engineering, Tuscaloosa, AL, United States
[b] The University of Alabama, Department of Chemistry, Tuscaloosa, AL, United States

ARTICLE INFO

Article history:
Received 13 January 2016
Received in revised form 8 April 2016
Accepted 19 May 2016
Available online 21 May 2016

Keywords:
Hyperthermia
Magnetic heating
Iron oxide nanoparticles
Magnetic field
Power generation
Specific absorption rate
Local nanoparticle temperature
Agarose gel tumor model

ABSTRACT

Magnetic iron oxide nanoparticles (MNPs) have been developed for magnetic fluid hyperthermia (MFH) cancer therapy, where cancer cells are treated through the heat generated by application of a high frequency magnetic field. This heat has also been proposed as a mechanism to trigger release of chemotherapy agents. In each of these cases, MNPs with optimal heating performance can be used to maximize therapeutic effect while minimizing the required dosage of MNPs. In this study, the heating efficiencies (or specific absorption rate, SAR) of two types of MNPs were evaluated experimentally and then predicted from their magnetic properties. MNPs were also incorporated in the core of poly(ethylene glycol-*b*-caprolactone) micelles, co-localized with rhodamine B fluorescent dye attached to polycaprolactone to monitor local, nanoscale temperatures during magnetic heating. Despite a relatively high SAR produced by these MNPs, no significant temperature rise beyond that observed in the bulk solution was measured by fluorescence in the core of the magnetic micelles. MNPs were also incorporated into a macro-scale agarose gel system that mimicked a tumor targeted by MNPs and surrounded by healthy tissues. The agarose-based tumor models showed that targeted MNPs can reach hyperthermia temperatures inside a tumor with a sufficient MNP concentration, while causing minimal temperature rise in the healthy tissue surrounding the tumor.

1. Introduction

The use of magnetic nanoparticles (MNPs) is progressively increasing for theranostics of life-threatening diseases such as cancer [1–8]. With proper design, MNPs can be employed in cancer therapy due to their ability to generate heat when exposed to a high frequency magnetic field. This treatment, known as magnetic fluid hyperthermia (MFH), aims to provide an effective treatment which has minimal side effects when targeted to tumors [1–8]. The ability of these MNPs to generate heat also makes them candidates for use in thermally-triggered nanoscale drug release systems. These systems can then provide dual therapy in forms of MFH and chemotherapy which increases the therapeutic effectiveness compared to either of the treatments administered individually [8]. Recently, many of the MFH systems have been successfully utilized in vivo to cause a reduction in tumor mass, and demonstrate the potential of MFH to treat cancer using animal models [9–11]. MFH has also been used to target and reduce cancer stem cell populations in the body to minimize proliferation and metastasis of tumor cells [12,13]. The efficiency of MFH treatment and the novel therapeutic options facilitated by this therapy depend on the heating efficiency of MNPs used in such treatments; hence it is essential to investigate the phenomenon of heat generation in MNPs under application of alternating magnetic field to develop MNPs that maximize the generation of heat.

Heat generation in superparamagnetic MNPs occurs by two main mechanisms known as Néel relaxation and Brownian relaxation, as described by the linear response theory (LRT) [14–16]. LRT has been used to theoretically calculate the amount of heat generated by MNPs, but it has several limitations and it is essential to note that under most circumstances LRT is valid only when $\xi < 1$ (Eq. (1)), and $\mu_0 H_{max} \ll \mu_0 H_k$ [16,17] where:

$$\xi = \frac{\mu_0 M_d H V_m}{kT} \tag{1}$$

Here, μ_0 is the permeability of free space ($4\pi * 10^{-7}$ T-m/A), M_d is domain magnetization of magnetic material used, H is the maximum

* Corresponding author.
E-mail addresses: rrshah@crimson.ua.edu (R.R. Shah), ardombrowsky@crimson.ua.edu (A.R. Dombrowsky), alpaulson@crimson.ua.edu (A.L. Paulson), mpjohnson1@crimson.ua.edu (M.P. Johnson), dnikles@mint.ua.edu (D.E. Nikles), cbrazel@eng.ua.edu (C.S. Brazel).

http://dx.doi.org/10.1016/j.msec.2016.05.086
0928-4931/

applied field strength, V_m is the magnetic volume of nanoparticles, k is the Boltzmann constant, T is the absolute temperature, and H_k is the anisotropy field.

Despite the limitations of LRT, it can prove to be useful to calculate power generation in MNPs under certain situations, where the magnetization of the MNP system shows a linear response to applied magnetic field. For the MNPs that fall within the LRT domain, heat is generated by both Brownian and Néel relaxation processes. Brownian relaxation occurs by nanoparticle rotation leading to the motion of MNPs against the viscous forces in the fluid dispersion, while Néel relaxation occurs due to re-orientation of the magnetic moment inside the MNP in response to the alternating magnetic field. These relaxation processes are facilitated by thermal fluctuations as opposed to just the energy provided by an applied alternating magnetic field [16,18]. Based on the assumption of linear response, Rosensweig [14] has related power generation (P), and thus heat generation, to various field and material parameters (Eq. (2)):

$$P = \pi\mu_0\chi_0 H^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2} \tag{2}$$

Here, χ_0 is the magnetic susceptibility of the particles, H is the field strength of the applied magnetic field, f is magnetic field frequency, and τ is the relaxation time for reorientation of magnetic moments in MNPs [14]. Usually Néel relaxation dominates for smaller MNPs, while larger MNPs generate more heat due to Brownian relaxation [14]. Brownian relaxation time (τ_B) depends on the viscosity (η) of the medium, hydrodynamic volume of MNPs (V_H), absolute temperature (T), and the Boltzmann constant (k) (Eq. (3)):

$$\tau_B = \frac{3\eta V_H}{kT} \tag{3}$$

Thus, an increase in the viscosity of the medium surrounding the MNPs can increase the Brownian relaxation time and reduce its contribution to magnetic heating. For in vivo applications, the viscosity of protein-containing interstitial fluids, or the rigidity of materials surrounding the MNPs inside a drug delivery vehicle can significantly reduce the temperature rise due to magnetic heating. Experimental validation of this situation has been conducted by researchers, where SAR of MNPs is reduced to 47% of the original value when the iron oxide MNPs dispersed in water are transferred to a rigid silicon-based organic polymer [19]. In addition to these factors, magnetic heating strongly depends on the MNP magnetic properties and magnetic field parameters.

Rosensweig's equation demonstrates a clear relationship between power generation and magnetic field strength, frequency, and magnetic properties of MNPs (Eq. (2)), and these relationships have been verified by experimental studies. Several studies have demonstrated that power generation increases with an increase in the field strength applied for MFH [20–25]. Although it is harder to test the effect of frequency at a constant field strength, some studies have shown that MFH at higher frequencies can produce heat quite efficiently [23,25]. In addition to the ability to tune heating by selecting magnetic field parameters, the magnetic properties of MNPs and the procedures used to synthesize and disperse MNPs can also affect the heating efficiency of MNPs [24,26,27]. Additionally, several experimental and theoretical studies have determined the relationship between optimal size for iron-oxide MNPs and their ability to generate heat for use in MFH [21–24,28–30].

Carrey et al., have provided a clear understanding of the domain of validity of LRT, and other theories based on the Stoner-Wohlfarth (SW) model that can be used to calculate MNP SAR based on MNP magnetic properties as well as the magnitude of the applied magnetic field. For single-domain, randomly oriented ferromagnetic MNPs where $\mu_0 H_{max} > 2\mu_0 H_c$ (where H_c is the coercivity of MNPs determined from a magnetic hysteresis loop), SW-based theories are used to predict SAR for MNPs [16,17], which relate power generation by MNPs to the area of the magnetic hysteresis loop (A) and the frequency of the applied magnetic field (f) as follows:

$$P = A * f \tag{4}$$

To compare the power generation or heating efficiency of the MNPs, specific absorption rate (SAR) values are determined from MNP heating profiles to normalize the power generated by MNPs by the mass of MNPs or iron content of MNPs (W/g_{MNPs} or W/g_{Fe}) [23–31]. MNPs with high SAR are largely favored for cancer treatment as the MNP dose can be kept minimum, while also reducing the time required for patient exposure to a magnetic field. SAR is calculated from the magnetic heating data as:

$$SAR(W/g) = \frac{m_s * c_p}{m_{np}} * \left(\frac{\Delta T}{\Delta t}\right) \tag{5}$$

Here m_s is the mass of solution, m_{np} is the mass of MNPs, c_p is the heat capacity of the solution, and $(\Delta T/\Delta t)$ is the initial slope of temperature rise vs. time curve for MNP heating. The SAR value serves as guidance for comparing the heating rates of MNPs with different compositions and concentrations, or different magnetic field settings. SAR values depend strongly on MNP size and other factors discussed previously.

The optimal MNP size and effect of magnetic properties of MNPs on heating efficiency can be predicted by estimating the effective relaxation time (τ, which depends on Néel relaxation time τ_N, and Brownian relaxation time, τ_B) of MNPs and magnetic susceptibility (χ_0) to determine the power generated by MNPs when the MNP core diameter is varied (Eqs. (1), (6)–(9)).

$$\frac{1}{\tau} = \frac{1}{\tau_N} + \frac{1}{\tau_B} \tag{6}$$

$$\chi_0 = \chi_i \frac{3}{\xi}\left(\coth\xi - \frac{1}{\xi}\right) \tag{7}$$

$$\text{where, } \xi = \frac{\mu_0 M_s H V_m}{kT}, \text{ and} \tag{8}$$

$$\chi_i = \frac{\mu_0 \Phi M_d^2 V_m}{3kT} \tag{9}$$

For determining the magnitude of relaxation time and susceptibility, values of domain magnetization (M_d), magnetic volume (V_m), hydrodynamic volume (V_H), effective nanoparticle anisotropy (K), and the volume fraction of MNPs in solution (Φ) are required. Since, we investigated MNPs that were predominantly maghemite (γ-Fe_2O_3) for purposes of predicting SAR [32–34], we utilized anisotropy values for maghemite in nanoparticle form. For superparamagnetic maghemite MNPs, the domain magnetization of single domain superparamagnetic MNPs is equal to the saturation magnetization of MNPs at room temperature (using data from magnetization curves) [35], and the effective anisotropy value ranges from 4.7 kJ/m^3 (for bulk maghemite) to 47 kJ/m^3 (for nanoscale maghemite) as reported in the literature [14,36,37].

For the larger-sized ferromagnetic particles, where $\mu_0 H_{max} > 2\mu_0 H_c$ and $\xi > 1$, LRT is no longer valid and SW-based theories are utilized to estimate SAR. In this scenario, the effective anisotropy of these nanoparticles could be calculated by simultaneously solving Eqs. (10) and (11), as described by Shokhufar and Afghahi [17],

$$2\,\mu_0 H_{c(T=0\,K)} M_s > 1.92\, K_{eff} \tag{10}$$

$$\frac{H_{c\ (T=0\ K)}}{H_{c\ (T=298\ K)}} = \frac{1-\left(\frac{k_b T_1}{K_{eff} V}\right) * \left(\ln\left(\frac{1}{f\tau_0}\right)\right)^{3/4}}{1-\left(\frac{k_b T_2}{K_{eff} V}\right) * \left(\ln\left(\frac{1}{f\tau_0}\right)\right)^{3/4}} \tag{11}$$