Evaluation of iron-cobalt/ferrite core-shell nanoparticles for cancer thermotherapy

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Magnetic nanoparticles (MNPs) offer promise for local hyperthermia or thermoablative cancer therapy. Magnetic hyperthermia uses MNPs to heat cancerous regions in an rf field. Metallic MNPs have larger magnetic moments than iron oxides, allowing similar heating at lower concentrations. By tuning the magnetic anisotropy in alloys, the heating rate at a particular particle size can be optimized. Fe–Co core-shell MNPs have protective $CoFe_2O_4$ shell which prevents oxidation. The oxide coating also aids in functionalization and improves biocompatibility of the MNPs. We predict the specific loss power (SLP) for FeCo (SLP ~450 W/g) at biocompatible fields to be significantly larger in comparision to oxide materials. The anisotropy of Fe-Co MNPs may be tuned by composition and/or shape variation to achieve the maximum SLP at a desired particle size. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2830975]

INTRODUCTION

Colloidal ferrofluids consisting of nanosized magnetic particles suspended in a fluid medium are increasingly employed in many applications in the biomedical sciences.[1] In recent years, magnetic nanoparticles (MNPs) have generated great interest for application in magnetic targeted drug delivery and in thermotherapy for cancer treatment. In thermotherapies, MNPs dispersed within blood or cellular fluid act as nanosources of heat for temperature enhancement under the influence of an applied high frequency magnetic field. It is desirable to have a high specific loss power (SLP) heat generated per unit mass of MNPs, to achieve the desirable temperature rise enhancement with low MNP concentration.

Thermotherapy for cancer treatment includes hyperthermia and thermoablation. Hyperthermia involves elevating the temperature of tumor region to 42–46 °C for an extended period of time. Thermoablation refers to the process of heating the cancerous cells for a relatively short time period at higher temperatures of up to 56 °C to cause widespread necrosis, coagulation, or carbonization of cancerous tissue. Blood vessels are poorly developed within the cancerous tissues and have a lower thermal resistance than healthy tissue.[2]

Recent efforts have been directed at realizing the ability to selectively apply heat only to cancer cells without damaging normal cells, which is referred to as local hyperthermia.[3] One such means of achieving localized heating is known as magnetic hyperthermia (MH), employing MNPs targeted to the tumor site, which are subsequently heated by subjecting them to nonbioinvasive radio frequency (rf) magnetic field. During MH therapy, MNPs dissipate applied magnetic energy into heat mainly via relaxation loss processes, while eddy currents, hysteresis, and resonance losses do not contribute to heat generation in MNPs employed for MH at therapeutic field amplitudes and frequencies.[4]

In addition to the field parameters, SLPs of MNP dispersions are strongly dependent on particle size, size distribution, anisotropy constant, saturation magnetization, and surface modification.[5] The magnitude of the SLP roughly scales with the saturation magnetization of the magnetic material. Traditionally, iron oxides have been explored for application in hyperthermia due to their biocompatibility and biodegradability. However, the use of materials with larger magnetic anisotropy and larger magnetic moments is desirable, since it would lead to increase in the SLP at smaller particle sizes.

Iron-cobalt alloys exhibit the highest possible saturation magnetization and, hence, the maximum SLP achievable for any material. The magetocrystalline anisotropy of Fe–Co alloys can be tuned over a wide range by varying their composition. The estimation of desired power loss for such particles at small enough sizes demonstrates their feasibility for use in biomedical applications. Fe–Co nanoparticles are known to form core-shell structures with a protective coating

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of cobalt ferrite on their surface. The presence of this oxide would aid in functionalization to improve biocompatibility.

THEORY

In biological applications, tolerable limits of inductive heating of tissues limit the safe range of magnetic field amplitudes and frequency that can be employed for MH therapy. Assuming the MNPs to be superparamagnetic (SPM), the dominant mechanism for power loss in an ac magnetic field is dictated by relaxation.[5] For SPM particles, the barriers for magnetization reversal are comparable to the thermal energy due to small particle volume. The magnetic relaxation of a system of MNPs suspended in a carrier fluid occurs via Néel and Brown mechanisms, relative contribution of which for a particular particle size depends on the magnetic anisotropy of the particles and the viscosity of the fluid.

Néel relaxation refers to the rotation of the magnetic moment within the particle, which occurs when thermal energy exceeds the magnetic anisotropy energy barrier. Brown relaxation occurs due to reorientation of the particle itself as a consequence of thermal agitation against the viscous drag of the carrier fluidn. The characteristic relaxation times τ_N for Néel and τ_B for Brown relaxations are

$$\tau_N = \frac{\sqrt{\pi}}{2}\tau_0\frac{\exp(\Gamma)}{\sqrt{\Gamma}}; \quad \text{where } \Gamma = \frac{KV_M}{k_BT}, \quad \tau_B = \frac{3\eta V_H}{k_BT},$$

where τ_0 is time constant of the order of 10^{-9} s, $k_B = 1.38 \times 10^{-23}$ J/K is the Boltzmann constant, T is the absolute temperature, K is the magnetic anisotropy constant, and V_M is the magnetic particle volume, η is the viscosity of carrier liquid, and V_H is the hydrodynamic volume of the particle.

Néel and Brown relaxation processes occur in parallel, with an effective relaxation time τ for the system. A crossover between Néel and Brown regimes occurs at a particle size that depends on the anisotropy constant and the viscosity. The Néel relaxation time increases exponentially with the particle volume and the Brown relaxation time increases linearly. Thus, effective relaxation time versus the particle size shows an exponential behavior for small particles which changes to a linear behavior beyond a critical size.

The volumetric power dissipation in an ac magnetic field of amplitude H and frequency f is

$$P = \pi\mu_0\chi''H^2f,$$

where $\mu_0 = 4\pi \times 10^{-7}$ and χ'' is the imaginary part of the magnetic susceptibility χ. In the Debye model, the magnetic susceptibility for relaxation of magnetization with a characteristic time τ and angular frequency $\omega = 2\pi f$,

$$\chi = \frac{\chi_0}{(1 + i\omega\tau)}, \quad \chi'' = \frac{\omega\tau}{1 + (\omega\tau)^2}\chi_0,$$

and χ is the loss component of susceptibilitywhere χ_0 is the static susceptibility, which for small field amplitudes can be approximated by a Langevin relationship,

$$\chi_0 = \chi_i\frac{3}{\xi}\left(\coth\xi - \frac{1}{\xi}\right), \quad \xi = \frac{\mu_0 M_d H V_M}{k_BT},$$

where is ξ the Langevin parameter and χ_i the initial susceptibility is determined from the differentiation of the Langevin relationship with M_d as the domain magnetization of MNPs.

The effective power loss is evaluated:

$$\tilde{P} = \int_0^\infty Pf(D)dD, \quad \frac{\Delta T}{\Delta t} = \frac{P}{\rho c_p},$$

and $f(D)$ is a lognormal particle size distribution, ρ is the weighted density and c_p is the weighted specific heat capacity. However, this expression for the linear temperature increase ΔT is valid only in an adiabatic system.

RESULTS AND DISCUSSION

The losses arising in a dispersion of MNPs in a fluid medium when exposed to an ac field are not only dependent on the amplitude and frequency of the magnetic field, but also depend on the physical and magnetic properties of the MNP and the material parameters of the carrier fluid. The primary loss mechanism for dissipation of magnetic energy into heat is governed by the relaxation processes. The relaxation time determines the maximum loss power achievable.

The imaginary part of the magnetic susceptibility has a maximum at $\omega\tau = 1$. For $\omega\tau \ll 1$, the losses increase with square of frequency, while for $\omega\tau \sim 1$ they are linear with frequency. For $\omega\tau \gg 1$, the power loss approaches a frequency independent saturation value. The power loss increases with increasing field amplitude with a square law behavior for small amplitudes.

Apart from the field parameters, the power loss is related to the susceptibility of the MNPs, which is determined by the saturation magnetization of the material, the particle volume, and the field amplitude. In comparison to oxides, metallic systems have higher saturation magnetization and one can achieve higher heating rates for same concentration of MNP or, otherwise, attain similar temperature rise at smaller MNPs concentrations. This has significance for MH applications, where the power loss in the currently studied materials has not been sufficiently high at reasonable concentrations to target small tumors. The ability to achieve temperature rise at lower concentrations allows for novel means of MNP delivery to the tumor site by intravenous injection and subsequent magnetic field gradient targeting or via functionalization with specific tumor binding antibodies.

Metallic nanoparticles have not been explored for use in MH treatments due to the fact that they easily oxidize when exposed to air or aqueous mediaum. In order to form stable aqueous dispersions, it is typically required to coat them with a protective coating.[6,7] Recently, Maenosono and Saita discussed the feasibility of exploiting FePt nanoparticles for MH applications.[8] We extend on their analysis and explore the viability of using Fe–Co alloy based nanoparticles for MH applications. In Fig. 1, we show the power loss dependence on the particle size for magnetite ($M_d = 446$ kA/m, $K = 9$ kJ/m^3), maghemite ($M_d = 414$ kA/m, $K = 4.7$ kJ/m^3), FePt ($M_d = 1140$ kA/m, $K = 206$ kJ/m^3), FeCo (M_d

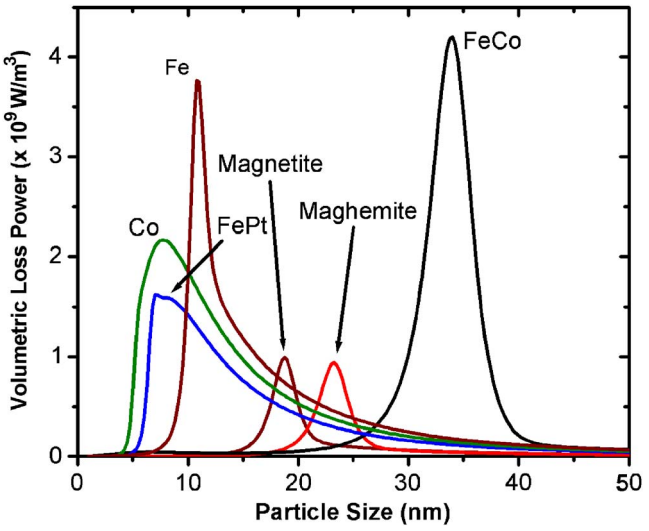

FIG. 1. (Color online) Volumetric power loss for various magnetic materials at 300 kHz and 50 mT ac field in aqueous dispersion with 10% particle concentration.

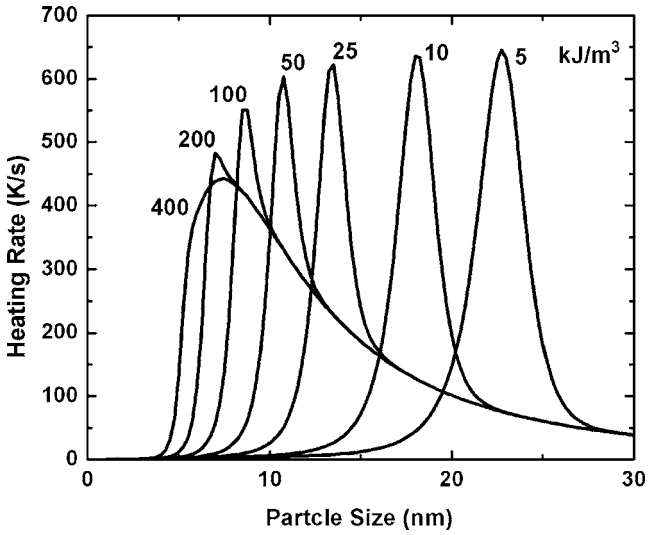

FIG. 2. Variation in heating rates for FeCo MNP with change in anisotropy constant.

$=1790$ kA/m, $K=1.5$ kJ/m^3), Co ($M_d=1440$ kA/m, $K=412$ kJ/m^3), and Fe ($M_d=1750$ kA/m, $K=48$ kJ/m^3) MNP aqueous monodispersions. The values of magnetic parameter for magnetite, maghemite, FePt, and FeCo are taken from Ref. 8, while for Fe and Co, the data have been obtained from Ref. 9. The field amplitude and frequency were taken to be 50 mT and 300 kHz. The maximum power loss achievable for a material scales with its saturation magnetization and the particle size at which maximum occurs is inversely related to the magnetic anisotropy. For a given frequency, the Brown contribution to losses attains a maximum at a particular particle size for all materials. The Néel relaxation time is exponentially dependent on the product of magnetic anisotropy constant and the particle volume; therefore, with increasing anisotropy, the particle size which satisfies the maximum loss criterion decreases.

The power losses in metallic nanoparticles far exceed those in oxides. The power loss for Fe–Co MNPs is the highest of the materials. However, the maximum power loss occurs at particle sizes which are considered unsuitable for MH application, because larger particles will quickly be endocytosed by macrophages and removed from the body. FeCo particles offer an advantage by forming a core-shell structure with a protective layer of cobalt ferrite, which prevents the oxidation of the bulk material, and aids in the functionalization of the particle. Further, interfacial anisotropy contribution increase the magnetic anisotropy and reduce the particle size where the maximum power loss occurs. In iron-cobalt alloy system, it is possible to tune the anisotropy over a wide range by compositional variation while retaining high saturation magnetization. One may further enhance the anisotropy by considering shape anisotropy for acicular particles.

The heating rates for dispersion of FeCo MNPs ($\rho_{\mathrm{FeCo}}=8900$ kg/m^3, $c_{p(\mathrm{FeCo})}=172$ J/kg K) in water ($\rho_{\mathrm{H2O}}=1000$ kg/m^3, $c_{p(\mathrm{H2O})}=4148$ J/kg K) with different anisotropy values are shown in Fig. 2. For increasing anisotropy, the particle size at which the maximum heating rate occurs decreases, while the peak heating rate itself is not significantly affected. Above a certain value, increases in the anisotropy gives no significant change in the heating rate dependence on the particle size since the Néel relaxation ceases to occur. The remaining Brown relaxation is independent of materials parameters and only depends on the particle size. Hence, one can achieve high heating rate at desirable sizes.

When cells are exposed to elevated temperatures, they undergo a heat shock response and release heat shock proteins (HSPs). Use of HSP inhibitors as anticancer drugs in conjunction with hyperthermia is a novel treatment for cancer. Hyperthermia damages the tumor cell's proteins and the HSP inhibitor prevents a cell from refolding its proteins. This combined treatment would increase the efficacy of either treatment alone.

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