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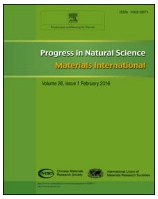

Review

Structural effects on the magnetic hyperthermia properties of iron oxide nanoparticles☆

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ABSTRACT

Magnetic iron oxide nanoparticles (IONPs) are heavily explored as diagnostic and therapeutic agents due to their low cost, tunable properties, and biocompatibility. In particular, upon excitation with an alternating current (AC) magnetic field, the NPs generate localized heat that can be exploited for therapeutic hyperthermia treatment of diseased cells or pathogenic microbes. In this review, we focus on how structural changes and inter-particle interactions affect the heating efficiency of iron oxide-based magnetic NPs. Moreover, we present an overview of the different approaches to evaluate the heating performance of IONPs and introduce a new theranostic modality based on magnetic imaging guided–hyperthermia.

1. Introduction

Iron oxide nanoparticles (IONPs) are widely investigated due to their tunable magnetic properties and potential as diagnostic (i.e. as magnetic resonance imaging contrast agents and magnetic particle imaging tracers) and therapeutic (e.g. drug and gene delivery, hyperthermia) agents [1–23]. Upon excitation with an AC field, these unique materials can transform electromagnetic energy to heat, and the heat generated can be utilized to destroy cancer cells or pathogenic microbes. In magnetic hyperthermia, the heating can occur by any of the three mechanisms: (1) eddy current heating due to the effects of induction from the application of an alternating pulsed magnetic field; (2) frictional heating induced by the interaction between the NPs and the surrounding medium, and (3) relaxation and hysteretic losses of the magnetic NPs [24].

The use of IONPs for magnetic hyperthermia treatment of cancers was first demonstrated by Gilchrist et al. in 1957 [25]. Following this seminal work, various groups have investigated the important operational parameters to effectively carry out the use of magnetic hyperthermia in cancer therapy [26–28]. In 2004, the first clinical magnetic hyperthermia treatment system was developed at Charité – Medical University of Berlin [29], and a few years later, *Magforce*® obtained European regulatory approval to treat patients with brain tumor using magnetic hyperthermia [30]. Over the years, the utility of magnetic hyperthermia has been extended to other applications including heat triggered drug delivery [31–34], biofilm inactivation [35,36], and fabrication of smart heat responsive materials [37].

While magnetic hyperthermia has been clinically approved for brain tumor treatment in Europe, it is still not widely utilized in the clinic. Particularly, magnetic hyperthermia has not been approved as a treatment approach in hospitals in the USA and other parts of the world. The lack of widespread adaptation of this treatment modality can be partly attributed to gaps in the development of optimized magnetic NP hyperthermia agents.

Shown in Fig. 1 is a schematic representation of the important parameters (i.e. optimization of the magneto-structural properties of magnetic NPs, magnetic dipolar interaction effects, reliability of the methods used in magnetic hyperthermia measurements) that need to be addressed in designing IONPs with optimized heating efficiency for various magnetic hyperthermia applications (e.g. magnetic imaging-guided hyperthermia, magnetic actuated drug delivery, thermal cancer therapy, biofilm eradication). To date, several excellent review articles have been published, which focused on the different synthetic routes that have been developed to prepare IONPs with different morphologies and surface chemistries [4,9–12,15,17,22,38–40], while some articles have detailed the different heat release mechanisms in magnetic hyperthermia [41,42]. In this review article, we will center the discussion on how the different structural motifs such as NP size, composition, morphology, and nano-assemblies (i.e. clustering and chaining) affect the magnetic hyperthermia properties and heating

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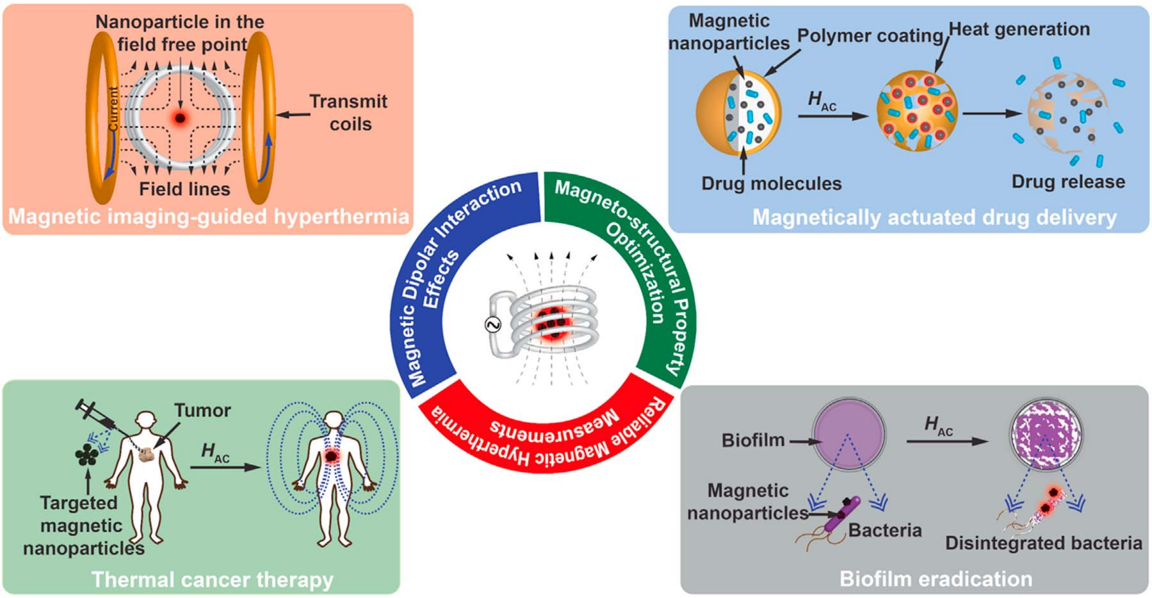

Fig. 1. Schematic diagram illustrating the important parameters affecting the efficiency of magnetic hyperthermia treatment and the different types of biomedical magnetic hyperthermia applications.

efficiency of iron oxide-based NPs.

2. Basic principles and measurements in magnetic hyperthermia

2.1. Magnetic behavior of single domain nanoparticles

The Stoner-Wohlfarth (SW) model describes the magnetic behavior of a single domain NP (Fig. 2a) [43]. The total energy (E) of such a system is defined by both the anisotropy energy (E_A) and the Zeeman energy (E_z):

$$E = E_A + E_z = KVsin^2\theta - HVM_s\cos(\theta-\phi) \tag{1}$$

where, K is the uniaxial magnetic anisotropy, H is the applied field, V is the NP volume, M_s is the saturation magnetization, θ is the angle between the easy axis and the NP magnetization, and ϕ is the angle between the easy axis and the applied magnetic field. At $H = 0$, the energy barrier is equivalent to KV and for systems wherein the anisotropy energy barrier is comparable to the thermal activation energy ($KV \sim k_BT$), magnetic moment switching becomes feasible leading to superparamagnetic behavior.

Superparamagnetism involves the thermal activated switching of the magnetic moment of a NP. This occurs above the so-called blocking temperature (T_B), which is described by the equation,

$$T_B = \frac{KV}{k_B ln(\tau_m/\tau_0)} \tag{2}$$

where, k_B is the Boltzmann constant, τ_m is the measurement time, and τ_0 is the attempt time, which is typically approximated as 10^{-9} s. For magnetite (Fe_3O_4) NPs, superparamagnetic behavior at room temperature typically occurs at particle sizes smaller than 25 nm in diameter [16].

2.2. Heating of magnetic nanoparticles in an AC field

Various models and experimental data have been employed to better understand the heating process in magnetic hyperthermia [41–47]. In 2002, Rosensweig developed the linear response theory (LRT) to explain the heating of colloidal magnetic fluids subjected to an alternating magnetic field [44]. In his formulation, it was assumed that the heat generation was only due to the rotational relaxation of non-interacting single domain NPs, and the magnetization of the NPs varies linearly with the applied magnetic field. From the LRT model, an expression for the power dissipation (P) was derived as follows [44]:

$$P=\mu_0\pi\chi''fH^2 \tag{3}$$

where, H and f are the amplitude and frequency of the AC magnetic field, respectively, μ_0 represents the permeability of free space, and χ'' is the out-of-phase component of the colloidal magnetic fluid AC susceptibility. In turn, χ'' can be expressed as:

$$\chi''=\frac{\omega\tau}{1+(\omega\tau)^2}\chi_0 \tag{4}$$

where, $\omega = 2\pi f$, χ_0 is the actual susceptibility, and τ is the effective

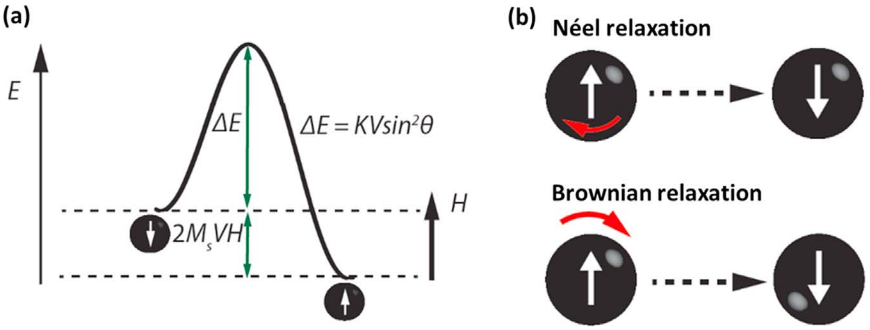

Fig. 2. (a) Representation of the energy barriers governing single domain particles. (b) Relaxation processes that influence the heating properties of magnetic nanoparticles.