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Magnetic fluid hyperthermia: Focus on superparamagnetic iron oxide nanoparticles

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ABSTRACT

Due to their unique magnetic properties, excellent biocompatibility as well as multi-purpose biomedical potential (e.g., applications in cancer therapy and general drug delivery), superparamagnetic iron oxide nanoparticles (SPIONs) are attracting increasing attention in both pharmaceutical and industrial communities. The precise control of the physiochemical properties of these magnetic systems is crucial for hyperthermia applications, as the induced heat is highly dependent on these properties. In this review, the limitations and recent advances in the development of superparamagnetic iron oxide nanoparticles for hyperthermia are presented.

Contents

1. Introduction

Magnetic nanoparticles (MNP) have found numerous applications in biomedicine, such as magnetic separation, drug delivery, magnetic resonance imaging (MRI), and hyperthermia [1–4]. Due to rapid advances in nanotechnology, novel synthetic routes to nanoparticles (NPs) with the ability to rigorously control the microstructure of the magnetic core (such as size monodispersity and crystallinity) have been described [5–9]. These nanosystems can be made to heat up, which leads to their use as hyperthermia agents, delivering toxic amounts of thermal energy to tumors, or as chemotherapy and radiotherapy enhancement agents, where a moderate degree of tissue warming results in more effective cell destruction [10]. The increasing interest for MNP is due to the discovery of their physical and chemical properties. In particular, it has been shown that the magnetic anisotropy of MNP can be much greater than those of a bulk specimen, while differences in the Curie or Néel temperatures, i.e., the temperatures of spontaneous parallel or antiparallel orientation of spins between MNP and the corresponding microscopic phases, reach hundreds of degrees [11]. In addition, magnetic nanomaterials have been found to possess a number of interesting properties such as giant magnetoresistance or abnormally high magnetocaloric effect.

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Experimental investigations of the application of magnetic materials for hyperthermia date back to 1957 when Gilchrist et al. [12] heated various tissue samples with 20–100 nm size particles of γ-Fe_2O_3 exposed to a 1.2 MHz magnetic field. Since then, there have been numerous publications describing a variety of schemes using different types of magnetic materials, different field strengths and frequencies, and different methods of encapsulation and delivery of the particles [13].

The application of ferrofluids for hyperthermia treatment was investigated in the work of Chan et al. [14] and Jordan et al. [15] in 1993. These studies experimentally prove the high efficiency of a superparamagnetic crystal suspension to absorb the energy of an alternating magnetic field and convert it into heat. Given that tumor cells are more sensitive to a temperature increase than healthy ones [16,17], this property can be used in vivo to increase the temperature of tumor tissue and to destroy the pathological cells by hyperthermia.

Many efforts have been devoted in the last 20 years to improve hyperthermia techniques for clinical applications. Advances in the area of nanotechnology have contributed to the development of magnetic fluid hyperthermia. This technique is a promising technique for cancer treatment because of ease in targeting the cancerous tissue and hence having fewer side effects than chemotherapy and radiotherapy. It is notable that the results of current/ongoing clinical trials show significant reduction in side effects [18].

One of the early magnetic fluid papers for magnetic hyperthermia. They injected 100 mg dextran magnetite into the tail vein of Sprague–Dawley rats, treated with AC magnetic field (12 min, 450 kHz, unknown field and SAR), and saw tumor shrinkage and tissue necrosis. After this, they just published a few patents until 1988 [19]. Flow of embolized carbonyl iron particles under the influence of a magnetic field was evaluated in vitro and in vivo. The magnetic force caused particles to form aggregates, obstructing tubing or vascular beds. In dogs, 0.5 ml of iron particles injected into a renal artery under magnetic control may be helpful in embolic arterial occlusion and localized irradiation, hyperthermia and chemotherapy [20]. Rand et al. [21,22] introduced additional radiofrequency heating up to more than 55 °C on the renal surface of rabbits. In this way, total coagulation necrosis of a renal cancer model could be achieved, possibly more as a result of the hyperthermic treatment than caused by the occlusion. The treated animals survived the procedures and exposure in the magnetic field and to the ferromagnetic compounds without evidence of ill effects.

The first clinical patient trials [23] were started by the research group of Jordan [24–38]. They built a hyperthermia-generating prototype instrument which is able to generate variable magnetic fields in the range of 0–15 kA/m at a frequency of 100 kHz. At the same time, the machine allows for real time patient temperature measurements to ensure that neither the upper limit of the therapeutic temperature threshold is exceeded, thus preventing thermal ablation, nor the lower, ineffective limit is crossed. This prototype is capable of treating tumors placed in any region of the body (e.g., prostate cancer, brain tumors).

Currently, only local hyperthermia is considered for magnetic fluid hyperthermia. For this purpose, MNP in a carrier fluid are placed inside the tumor through direct injection or tumor specific antibody targeting, after which the tumor is exposed to an alternating magnetic field. This field makes the particles generate heat by magnetic relaxation mechanisms. For hyperthermia treatments knowing the temperature profile obtained in the tissues is of utmost importance. The ideal temperature profile is one where the body temperature in healthy tissue is maintained, while the therapeutic temperature of 45 °C inside the tumor is reached immediately and maintained constant. In reality these temperature profiles are not flat, neither in the tumor nor in normal tissue, because of thermal diffusion.

In this review, we will focus on the basic concepts of magnetism and review the physics of the hyperthermia process.

2. Physics of magnetism

When a magnetic material is placed in a magnetic field of strength H, the individual atomic moments in the material contribute to its overall response; the magnetic induction is given by Eq. (1):

$$B = \mu_0(H + M) \tag{1}$$

where μ_0 is the permeability in vacuum and M is the magnetic moment per volume. The magnetic materials may be conveniently classified in terms of their volumetric magnetic susceptibility, χ (with $M = \chi H$). Most materials display magnetism only in the presence of an applied field. They are classified as paramagnets, with χ in the range of 10^{-6}–10^{-1}, or diamagnets with a negative χ. However, some materials exhibit ordered magnetic states and are magnetic without requiring a magnetic field; these are classified as ferromagnets, and ferrimagnets [40]. The coupling interaction between magnetic moments within the material can give rise to large spontaneous magnetizations.

In 1930, Frenkel and Dorfman [41] showed on the basis of energy considerations that particles of a sufficiently small size should be single-domain. In the mid-20th century, the theory of single-domain particles started to be actively developed [42–45] and the related phenomena were studied experimentally [46–53]. These studies identified a substantial increase in the coercive force of a ferromagnet on passing from a multi-domain to the single-domain structure, which is important for the creation of permanent magnets. The calculated critical diameter (at room temperature) of a single-domain spherical particle with axial magnetic anisotropy varies in a broad range. The upper values are 128 nm for Fe_3O_4 and 166 nm for γ-Fe_2O_3 [54] and the lower values are around 80 nm for magnetite [55]. The latter data were confirmed experimentally for particles consisting of solid solutions of maghemite and magnetite [56]. Experimental determination of the critical diameter above which a single-domain particle becomes multi-domain is a complicated task, although it has recently become possible to observe this transition directly through a magnetic force microscope [57,58] or a quantum magnetic interferometer (m-SQUID) [59–61] or indirectly by means of the analysis of the magnetic properties.

The term 'single-domain' does not require a uniform magnetization throughout the whole particle bulk but only implies the absence of domain walls. The specific properties of MNP start to be manifested at sizes much smaller than the 'single-domain limit'.

One more remarkable property of MNP, which allowed their experimental discovery in the mid-20th century, is their superparamagnetism. The model of an ideal superparamagnetic material was proposed in the early 1960s [62], but is still under development [63,64]. The simplest variant of this model considers a system of N non-interacting identical particles with the magnetic moment μ_{ef}. Since the magnetic moment of the particle is assumed to be large, its interaction with the magnetic field H is calculated without taking into account the quantum effects. In the case of isotropic particles, the equilibrium magnetization of the [M] system can be described by the Langevin equation (Eq. (2)):

$$\langle M \rangle = N\mu_{ef}\left[cth\left(\frac{\mu_{ef}H}{k_BT}\right) - \frac{k_BT}{\mu_{ef}H}\right] \tag{2}$$

Eq. (2) has been derived with the assumption that single particles are magnetically isotropic, i.e., all directions of their magnetic moments are energetically equivalent, but this condition is hardly ever fulfilled. If the particles are magnetically anisotropic, the calculation of the equilibrium magnetization becomes more complicated. According to the nature of factors giving rise to the non-equivalence of the directions of magnetic moments, one can distinguish the magnetically crystalline anisotropy,