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Optimization of synthesis and peptization steps to obtain iron oxide nanoparticles with high energy dissipation rates

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ABSTRACT

Magnetic Fluid Hyperthermia (MFH) uses heat generated by magnetic nanoparticles exposed to alternating magnetic fields to cause a temperature increase in tumors to the hyperthermia range (43–47 °C), inducing apoptotic cancer cell death. As with all cancer nanomedicines, one of the most significant challenges with MFH is achieving high nanoparticle accumulation at the tumor site. This motivates development of synthesis strategies that maximize the rate of energy dissipation of iron oxide magnetic nanoparticles, preferable due to their intrinsic biocompatibility. This has led to development of synthesis strategies that, although attractive from the point of view of chemical elegance, may not be suitable for scale-up to quantities necessary for clinical use. On the other hand, to date the aqueous co-precipitation synthesis, which readily yields gram quantities of nanoparticles, has only been reported to yield sufficiently high specific absorption rates after laborious size selective fractionation. This work focuses on improvements to the aqueous co-precipitation of iron oxide nanoparticles to increase the specific absorption rate (SAR), by optimizing synthesis conditions and the subsequent peptization step. Heating efficiencies up to 1048 W/g_{Fe} (36.5 kA/m, 341 kHz; ILP = 2.3 nH m^2 kg^{-1}) were obtained, which represent one of the highest values reported for iron oxide particles synthesized by co-precipitation without size-selective fractionation. Furthermore, particles reached SAR values of up to 719 W/g_{Fe} (36.5 kA/m, 341 kHz; ILP = 1.6 nH m^2 kg^{-1}) when in a solid matrix, demonstrating they were capable of significant rates of energy dissipation even when restricted from physical rotation. Reduction in energy dissipation rate due to immobilization has been identified as an obstacle to clinical translation of MFH. Hence, particles obtained with the conditions reported here have great potential for application in nanoscale thermal cancer therapy.

1. Introduction

Magnetic Fluid Hyperthermia (MFH) as a cancer treatment uses the heat that results from exposing magnetic nanoparticles to alternating magnetic fields. The objective in this approach is to achieve a temperature rise to 43–47 °C in small regions affected by cancer where nanoparticles have been deposited [1]. As a cancer therapy, MFH takes advantage of the increased sensitivity of cancer cells to heat, compared to their healthy counterparts [2]. Recent studies explain how vascularization of tumors can be stimulated by heat, improving the efficiency of chemotherapy and radiotherapy [3]. Although promising, there are still significant challenges to achieving the potential of MFH in treating cancer, of which the most pressing appear to be improving nanoparticle accumulation in tumor sites, achieving controlled and uniform temperature rise throughout the tumor tissue, and obtaining nanoparticles with predictable performance in the tumor environment [1,4]. Recently, various groups have reported efforts to improve the heat dissipation rates of magnetic nanoparticles, in an effort to reduce the amount of particles needed to achieve a desired temperature rise in tumors in vivo. In these studies, the energy dissipation rate performance of the nanoparticles is

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typically reported as the specific absorption rate (SAR), which depends on the amplitude and frequency of the magnetic field used during actuation. In order to avoid ambiguity, the SAR value can be normalized with respect to the frequency and intensity of the applied magnetic field, facilitating comparison of measurements carried out under different field conditions. This normalized energy dissipation rate is called the intrinsic loss power (ILP) [5]. There have been many recent excellent studies aiming to obtain magnetic nanoparticles with high SAR and ILP values, through control of particle clustering, shape, and/or internal exchange interactions. Typical ILP values for iron oxide nanoparticles are usually below 5 and 12 nH m^2 kg^{-1} for commercial and synthetic preparations, respectively [5]. For example, superparamagnetic iron oxide nanocubes with a wide range of sizes have been reported with SAR values of up to 2277 W/g_{Fe} (700 kHz, 24 kA/m, ILP=5.7 nH m^2 kg^{-1}). However, despite their high SAR the authors state that the synthesis of nanocubes in a wide size range is not straightforward [6], which could limit their biomedical potential. Improvements in both heating power and MRI relaxivity have been achieved by formation of clusters or aggregates of single core cube-shaped nanoparticles [7]. In some cases ferromagnetic nanocube aggregates have been encapsulated in biocompatible polymers, achieving SAR values up to 2614 W/g_{Fe} (1000 kHz, 0.66 kA/m, ILP=6000 nH m^2 kg^{-1}), but aggregation is a major obstacle to their use in vivo [8,9]. However, according to the authors, this exceptionally high SAR was achieved using an alternating magnetic field with frequency of 1000 kHz and amplitude of 0.66 kA/m, which yields a highly unlikely ILP value of 6000 nH m^2 kg^{-1}. Bacterial magnetosomes have been proposed as an alternative to the preparation of magnetic materials using chemical methods. For example, magnetosomes consisting of chain-like aggregates of iron oxide nanoparticles have resulted in SAR values of 875 W/g_{Fe} (183 kHz, 32 kA/m, ILP=4.7 nH m^2 kg^{-1}). However, the isolation of individual magnetosomes from these chain-like aggregates remains a challenge to their clinical application [10]. An alternative approach is to tune heat dissipation rate by introducing exchange-coupling in nanoparticles with core–shell structure. Core–shell nanoparticles with a $CoFe_2O_4$ core and Fe_3O_4 shell were reported to have SAR values of up to 1120 W/g_{Fe} (500 kHz, 37.3 kA/m, ILP=1.6 nH m^2 kg^{-1}) [11]. However, to achieve this effect the biocompatibility of the nanoparticles is compromised by the introduction of cobalt into the structure. Other nanoparticle shapes have been reported to yield high energy dissipation rates. Maghemite nanoflowers have been reported with SAR values of ~1900 W/g_{Fe} (700 kHz, 21.5 kA/m, ILP=5.9 nH m^2 kg^{-1}) using a modified thermal decomposition procedure [12]. Similarly to nanoflowers, maghemite assemblies with superparamagnetic behavior have been reported to have SAR values of ~1500 W/g_{Fe} (520 kHz, 29 kA/m, ILP=3.4 nH m^2 kg^{-1}). The role and benefits of multi-core interactions can be explained in terms of reduced magnetocrystalline anisotropy and enhanced magnetic moment which helps preserve the superparamagnetic behavior of the clusters, potentiating thermal losses [13]. Finally, and perhaps of greatest relevance to the work reported here, Fortin et al. reported maghemite nanoparticles obtained using a post-synthesis size-sorting step which had SAR values of up to 1650 W/g (24.8 kA/m, 700 kHz, ILP=3.8 nH m^2 kg^{-1}). However, without the post-synthesis treatment, the study revealed that SAR dropped to 135 W/g (ILP=0.98 nH m^2 kg^{-1}) [14] .

Despite the overall high heating efficiency provided by exchange-coupled, size-sorted and clusters of nanoparticles with different morphologies, the experimental protocols used to obtain these particles are often complex, time consuming, and can face challenges in scalability. In contrast, it is widely known that a simple, inexpensive, and efficient method for the synthesis of magnetic nanoparticles is the co-precipitation of iron salts in alkaline media under an inert atmosphere, attributed to Massart [15]. The main advantage of the co-precipitation method is that a single synthesis batch easily yields gram quantities of nanoparticles. The SAR of iron oxide nanoparticles obtained by co-precipitation fluctuates in a wide range of values, typically from 40 to 300 W/g_{Fe} [16–18] for co-precipitation method without post-synthesis size-selective treatments, and about 10–100 W/g_{Fe} for commercial nanoparticle preparations [5,19]. This wide range of values and the variability in the co-precipitation synthesis represent major limitations to eventual clinical application if high energy dissipation rates cannot be consistently obtained.

There have been various studies aiming to optimize magnetic nanoparticle synthesis by the aqueous co-precipitation route, with the aim of controlling the physical size of the inorganic iron oxide cores. Among these studies, different parameters have been considered such as media composition, reactant injection rates, temperature, stirring rates, pH, molar ratios, etc. [20–22]. However, although energy dissipation rates are expected to be a function of the physical size and magnetic properties of the iron oxide nanoparticles, systematic optimization studies of the co-precipitation synthesis to achieve high energy dissipation rates are still lacking.

Among the many examples of preparation of iron oxide nanoparticles by the co-precipitation method we found that to date the highest value obtained without any post-synthesis size-fractionation appears to be that reported by Kossatzet al. [23], who reported SAR values of 900 W/g_{Fe} (435 kHz, 15.4 kA/m, ILP=8.7 nH m^2 kg^{-1}) and 650 W/g_{Fe} (435 kHz, 15.4 kA/m, ILP=6.3 nH m^2 kg^{-1}) for iron oxide nanoparticles suspended in water and agar, respectively, using a post-synthesis peptization step with kerosene at high temperature. These energy dissipation rates are higher than other commonly reported values in the range of 40–300 W/g_{Fe} (ILP ~1–3 nH m^2 kg^{-1}). Unfortunately, Kossatz et al. do not explain the reasons behind their enhanced energy dissipation rate, or what they did differently from other groups in terms of experimental protocols. In addition, the lack of magnetic characterizations makes it difficult to compare the magnetic behavior of their particles to those of others and to evaluate its impact on the observed SAR values.

Motivated by a need for improvement of the co-precipitation synthesis to obtain particles with high energy dissipation rates, the present work demonstrates that high energy dissipating nanoparticles can be reproducibly obtained by optimizing the co-precipitation synthesis conditions and the subsequent peptization step. Three parameters were studied for optimization purposes: temperature, iron ion precursor concentration, and sonication conditions during peptization. These parameters were chosen based on results from our own preliminary experiments and based on observations described elsewhere [24,25]. The preliminary experiments showed that by simultaneously increasing the synthesis temperature and using ultra-sonication during the peptization step at a fixed iron concentration, higher SAR values could be obtained. A series of nanoparticle synthesis batches were synthesized by varying the above parameters between pre-set levels, and the combination of these levels and their factors was studied using SAR as the response variable. Optimal results were obtained when the synthesis temperature was 85 °C, total iron concentration was 0.30 M, and when ultra-sonication was used during the peptization step. As for the specific absorption rate, values of up to 1048 W/g_{Fe} (341 kHz, 36.5 kA/m, ILP=2.3 nH m^2 kg^{-1}) were obtained. When fixed in agarose these particles reached up to 719 W/g_{Fe} (341 kHz, 36.5 kA/m, ILP=1.6 nH m^2 kg^{-1}), demonstrating that they can dissipate a high amount of energy even when they are restricted from physical rotation. These results were confirmed by conducting additional experiments under the optimal conditions, and high SAR