Application of Nanomagnetic Particles in Hyperthermia Cancer Treatment

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ABSTRACT

This research focuses on developing uniform particles with a Curie temperature that is similar to the therapeutic one for the purpose of cancer treatment. Such particles will self-regulate the temperature of the tumor during magnetic hyperthermia (MH), thus avoiding the use of temperature controls. MH is based on a defined transfer of power onto magnetic nanoparticles in an alternate magnetic field that is determined by the frequency, magnetic field's strength, materials and the size of the particles, which result in localized generation of heat. This heat will either destroy the tumor cells directly or results in a synergic reinforcement of radiation efficacy, depending on the equilibrium temperature set in the tumor tissue. MH involves the local deposition of tumor cell specific magnetic nanoparticles and an external alternating current magnetic field applicator system. Nanoferrite particles can be easily applied interstitially for minimum invasive application. In this study more uniform nanoparticles have been manufactured and they were tested for their Curie temperature for self–regulated MH. Materials which have been investigated for such procedure are Gd-Zn ferrite, $MnZnFe_2O_4$ and $La_{3/4}Sr_{1/4}MnO_3$ and many others. Finally, the concept of discrete magnetic heating is addressed.

Keywords: magnetic hyperthermia, magnetic nanoparticles, pulsed magnetic field, Curie temperature, ac magnetic field.

1 INTRODUCTION

Hyperthermia is a technique which is rapidly developing in cancer therapy. As a medical treatment it relies upon locally heating tissue to greater than 42^0C for approximately 30 min to destroy the tissue, particularly tumors [1].

The difficulty in applying this therapeutically is due to the difficulty of selectively heating diseased tissue. Magnetic particle hyperthermia is appealing because it offers a way to ensure that only the intended target tissue is heated.

The concept is based on the principle that a magnetic particle can generate heat by hysteresis loss when placed in a relatively high-frequency magnetic field. The heating of magnetic particles has been investigated for decades as a possible approach to selectively heating cancerous tumors [2]. The most obvious method of heating through the use of magnetic particles is to take advantage of the hysteresis in ferro/ ferrimagnetic particles to provide heat. The loss in energy due to hysteresis (the resulting induced magnetic domain reversal dissipates thermal energy) is represented by the area inside the *B-H* hysteresis loop.

The heating power, P_{hyst}, generated by hysteresis loss in a unit volume of ferromagnetic material that is subjected to an applied magnetic field with amplitude H, alternating at frequency f, is given by:

$$P_{hyst} = f\left(\int H \, \mathrm{d}B\right) \tag{1}$$

where B is the magnetic induction.

The value of the integral, termed the hysteresis area, varies with H in a manner that depends critically on the magnetic characteristics of the ferromagnetic material. The hysteresis area, and hence P_{hyst}, generally increases non-linearly with increasing H until the material is magnetically saturated. Any further increase in H beyond the saturating value has no effect on P_{hyst}.

Materials with low coercive strength, H_c, generally achieve saturation at relatively low field amplitudes and hence are characterized by hysteresis loops with relatively small area. On the other hand, materials with high H_c are characterized by hysteresis loops with large area and require high field amplitudes to reach saturation.

This energy expenditure manifests itself as heat, and if particles are appropriately localized, an area of tissue can be selectively heated. In this approach highly hysteretic particles are clearly desirable.

Another approach to heating through magnetic particles employs superparamagnetic particles. Superparamagnetic particles lack hysteresis on the timescale of typical magnetic measurements, but in high-frequency ac fields the particles may not be able to reorient at the rate of oscillation of the field. In a ferrofluid, the reorientation can occur through two mechanisms, Brownian relaxation (rotation of the particle) and Ne'el relaxation (rotation of the moment within the particle).

Ne'el relaxation is very strongly dependent upon particle size, and for small particles occurs rapidly, severely limiting achievable heating rates. The mathematics of heating in suspensions of super-paramagnetic particles was treated in detail by Rosenweig [3]. In a relatively high frequency magnetic field the magnetization lags the magnetic field, leading to a complex susceptibility for the ferrofluid ($\chi=\chi^{|}-\chi^{||}$). Analogous to refractive indices, $\chi^{||}$ represents the out of phase, loss susceptibility. Again, the power is dissipated as heat, warming the system.

There are two reasons why maximizing the response from particles is so desirable. The first is to minimize the amount of foreign material that must be injected (reduced cost & reduced unwanted side effects).

The second reason is that there are limits on the ac magnetic field that can be applied to a patient (to avoid muscular simulation & heart arrhythmias).

Frequencies are usually used between 0.05 and 1.2 MHz, and fields are kept to lower than 15 kAm^{-1} [1]. Optimizing particle properties will allow the minimum amount of foreign material to be introduced, while providing for sufficient heating within the appropriate field parameters.

2 MATERIALS AND METHODS

Ongoing investigations in MH are focused on the development of magnetic nanoparticles that are able to self-regulate the temperature they attain. The ideal temperature for hyperthermia is 43-45^{0}C. Particles with a Curie temperature in this range have been described by Kuznetsov [4].

Indeed, Curie temperature (T_c) is the temperature at which ferromagnetic materials lose their magnetic properties, thus they do not convert electromagnetic energy into heat. T_c is therefore the maximal temperature that could be reached by magnetic particles.

Tuning the T_c at a value just above T_t (treatment temperature) would be the smartest way to control hyperthermia as in this case the nanoparticles would be acting, both, as fuses as well as heaters.

Various nanoparticles can be synthesized using physical as well as chemical methods. Chemical methods are advantageous over physical methods because they offer a mixing of elements at molecular level and the synthesized particles directly obtained in nanosize range.

The nanoparticles thus synthesized could be checked for magnetic properties such as Curie temperature and magnetic saturation using SQUID and VSM. The constituents can be estimated using XRD. Also the nanoparticles morphology may be observed using TEM.

2.1 Gd-Zn Ferrite Nanoparticles

In this study, Gd substituted Zn ferrite nanoparticles were synthesized using chemical co-precipitation method so as to increase the Curie temperature up to the desired 315K and also to increase its pyromagnetic co-efficient. It was observed in an earlier experiment of this group that, the Curie temperature of Zn ferrite synthesized by chemical co-precipitation method was 240 K.

In this method, a 0.1 M solution of the metal salts Fe_2SO_4, $GdCl_3$ and $ZnSO_4$ was added to an 8 M solution of NaOH. The mixture was stirred vigorously at 100^{0}C for 45 min. The particles were then quenched by immersing the flask containing these particles in an ice-water bath. Thereafter the nanoparticles were filtered and washed three times with distilled water and three more with acetone. The particles were then allowed to dry in air at room temperature.

These particles were of the form: $ZnGd_xFe_{(2-x)}O_4$. Three batches of samples using x=0.02, 0.05 and 0.1 were prepared. The characterization results of these particles are presented below in Figure 1 (temperature dependence of magnetization for Gd-Zn with x=0.02 is only shown here):

Gd substituted Zn ferrite with x=0.02

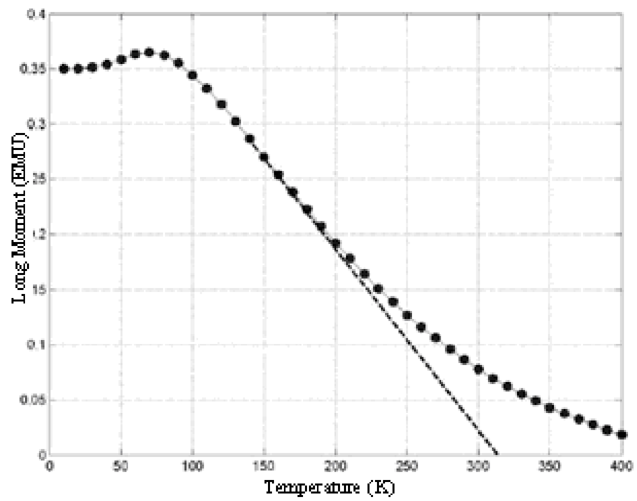

Figure 1: Temperature dependence of magnetization for Gd substituted Zn Ferrite with x=0.02.

It was observed that, the substitution of Gd in Zn ferrite leads to an increase in its Curie temperature and pyromagnetic co-efficient. Also, the Curie temperature has increased with increasing Gd substitution. Addition of Gd^{3+} ions results in their occupancy of the octahedral sites.

The preference for octahedral sites may be attributed to their large ionic radii. Since the ionic radii of the Gd^{3+} ions is large, there is a decrease in the distance between these and the oxygen ions when adding Gd ions consequently strengthening the B-B interaction [5].

As a result, the ions at the octahedral sites no longer have their moments parallel to each other. A part of these ions have moments aligned antiparallel to other atoms on these octahedral sites. This results in a reduction in the net magnetic moment of the octahedral atoms.

As the Gd substitution is increased, more and more octahedral atoms have their moments antiparallel. This leads to strengthening the B-B interaction which consequently results in an increase in the Curie temperature. The effects of changes in Gd proportion on the Curie temperature of the nanoparticles is shown in Figure 3 below.

Change in T_c with change in Gd proportion

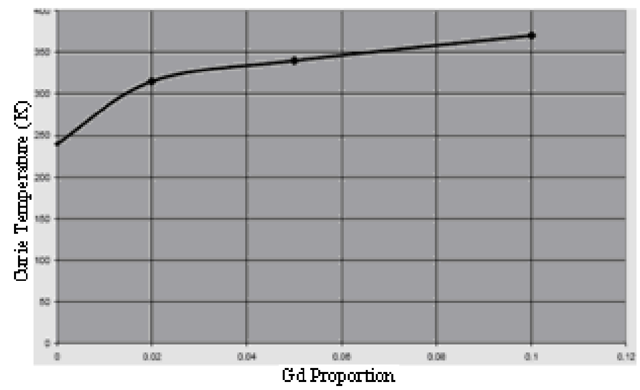

Figure 3: Change in Curie temperature (T_c) with change in Gd proportion.

The Curie temperature of the Gd substituted Zn ferrite nanoparticles with x=0.02 was found to equal to the desired 315 K for hyperthermia application. Also, the pyromagnetic co-efficient was higher than that of Zn ferrite and hence was a complementing factor for its possible use in hyperthermia applications. For other samples the Curie temperatures were beyond the desired 315 K, as shown in Table 1. Figure 2 shows the Gd-Zn ferrite with Gd=0.02 particles as seen under TEM. The average size of these particles was found to be approximately 200 nm.

Sample	Curie Temperature (K)
x=0.02	315
x=0.05	340
x=0.1	370

Table 1: Curie temperatures of Gd substituted Zn ferrite nanoparticles synthesized using co-precipitation method.

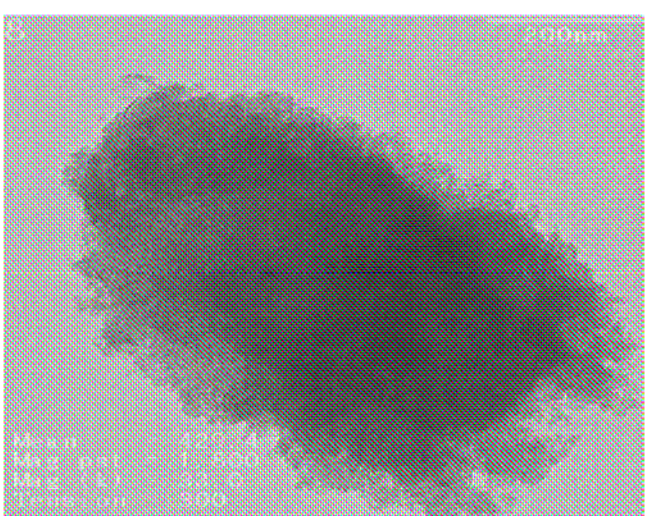

Figure 2: Morphology of Gd substituted Zn ferrite particles with x=0.02 under TEM.

2.2 Mn-Zn Ferrite Nanoparticles

Several samples of the form $Mn_{(1-x)}Zn_xFe_2O_4$ were synthesized using chemical co-precipitation method. In this method a 0.1 M solution of the metal salts Fe_2SO_4, $ZnSO_4$ and $MnCl_2$ was added to an 8 M solution of NaOH. The mixture was stirred vigorously at 90°C for 40 minus. Thereafter the synthesized nanoparticles were filtered and washed 3 times with distilled water and 3 times with acetone. The particles were then allowed to dry in air at room temperature. The characterization results of a significant few amongst them are presented in Table 2 below. Temperature dependence of magnetization for Mn-Zn ferrite with only x=0.5 is shown in Figure 4.

Sample	Curie Temp. (K)	Sat. Magnetization (EMU/g)
x=0.5	320	20
x=0.6	340	NA
x=0.8	285	NA

Table 2: Characterization data for Mn-Zn ferrite nanoparticles synthesized using co precipitation method.

Mn-Zn ferrite with x=0.5

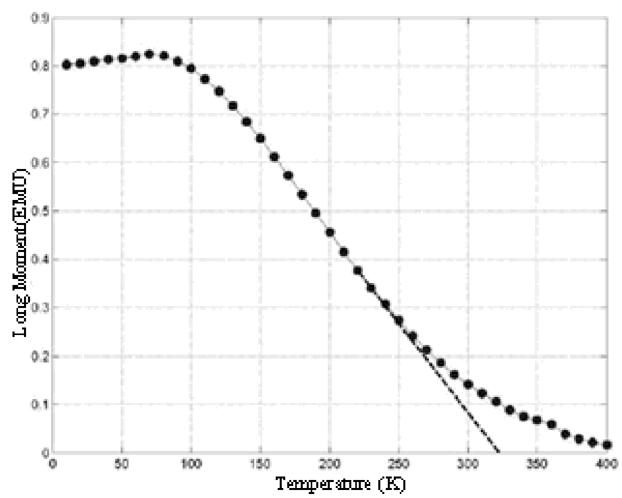

Figure 4: Temperature dependence of magnetization for Mn-Zn ferrite with x=0.5.

It was observed that the Curie temperature of the nanoparticles decreases for zinc proportions x > 0.6. The zinc atoms tend to occupy the smaller tetrahedral sites [5], and hence displace the Mn atoms at those sites. Since Zn does not contribute to the magnetic moment due to its filled 3d and 4s shells, it results in a weakening of the net magnetic moment of the particles thereby decreasing the B-B interaction and hence the Curie temperature. The Curie temperature of the sample with x=0.5 was found to be close to the desired 315 K. The Curie temperatures of other samples were either below or above this temperature.

2.3 $La_{2/3}Sr_{1/3}MnO_3$ Nanoparticles

In this method the starting compounds were $MnCO_3$, La_2O_3, and $SrCO_3$. They were separately dissolved in nitric acid and then mixed together with citric acid and ethylene glycol. The pH value was so adjusted to be 8 using NH_4OH. The moisture in the mix was evaporated at ~ 100^0C. Then it was dried and calcinated for three hours at 390^0C in air. The powder was then annealed in a temperature range, roughly of, 570-650^0C for three hours and then cooled down. Magnetic measurements were carried out by means of a SQUID magnetometer at a temperature range of 290-340 K in fields of up to two Tesla. Temperature was monitored by alcohol thermometer to avoid any electrical or magnetic heating of the temperature probe. XRD analysis revealed for the samples annealed at 570-650^0C the single phase composition was achieved for $T \geq 650^0$C as shown in Figure 5.

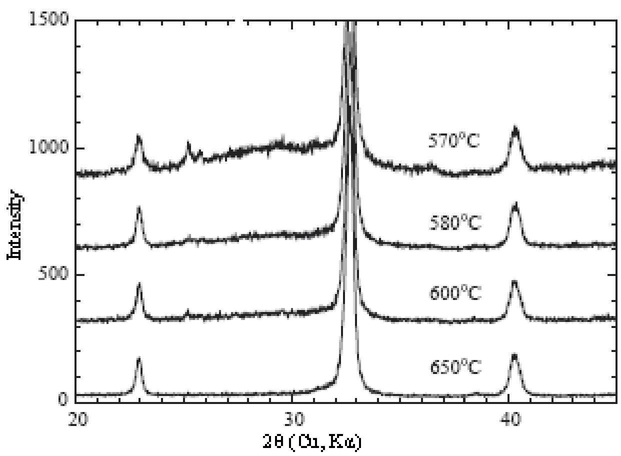

Figure 5: XRD patterns of samples annealed in the range of 570-650^0C for three hours.

Simultaneous decrease of the T_c indicates destabilization of the magnetic ordering with decreasing particle size as shown in Figure 6:

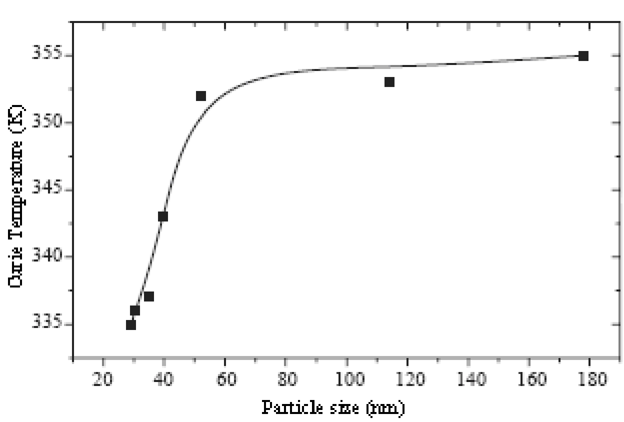

Figure 6: Evolution of the Tc with particle size.

It is important to note that, Gilchrist and coworkers in 1957-1965, used pulsed AC magnetic fields which yielded a steady state temperature of 50^0C in the lymph nodes of a dog for at least 30 minutes. More studies yet to be made to compare the advantages and drawbacks of pulsed field over the continuous, well studied, magnetic field.

3. CONCLUSIONS

The use of hyperthermia to artificially elevate body tissue temperatures is now a well established technique for the treatment of cancer. Of particular interest to this group is the method of heating nano-size ferro/ferrimagnetic particles by magnetic hysteresis and Ne'el relaxation methods. A therapeutically significant amount of heat can be generated by magnetic hysteresis in ferro/ferrimagnetic nanoparticles using, relatively, high field strengths and low or relatively high frequencies. In general, the hysteresis area increases non-linearly with the amplitude of the applied field, so a correct choice of ferro/ferrimagnetic material has to be made. In this paper, different magnetic nanoparticles have been fabricated mostly by chemical methods, and tested for their magnetic properties, especially the Curie temperature. The aim of this paper was to find out materials for magnetic nanoparticles which will have properties suitable for use in self-controlled magnetic hyperthermia, i.e.: Curie temperature of 315 K, a high pyromagnetic co-efficient. To achieve these goals, various magnetic nanoparticles were synthesized using mostly chemical means. For most of the particles, numerous samples were made by varying the constituent proportions to study the effect on their properties. Accordingly, various trends were observed in the properties for which reasons were sought by utilizing solid state physics approach.

Biocompatibility, toxicity and method of administering the nanoparticles to the cancerous tumor site issues have not been considered here.

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