

Magnetic Nanoparticles for Self Controlled Hyperthermia Treatment of Tumors

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ABSTRACT

Hyperthermia has been gaining a lot of interest as a method for treating cancer particularly as an adjunct to other modalities such as radiotherapy and chemotherapy. Self controlled magnetic hyperthermia takes advantage of producing localized heating by subjecting nanomagnetic particles to an alternating magnetic field. The temperature rise at the cancer tissue is controlled by the particles Curie temperature. In the present paper $Mn_{0.5}Zn_{0.5}Gd_xFe_{(2-x)}O_4$ nanoparticles were synthesized using chemical co precipitation technique to obtain particles with Curie temperature of 42 and with high value of magnetization. These particles showed high promise for self controlled magnetic hyperthermia application.

INTRODUCTION

Hyperthermia is temperature elevation of tissue with the aim of receiving therapeutic benefits. Knowledge about heat treatment of tumors is as old as the written text in medicine [1]. Unfortunately, the enthusiasm of modern cancer research for this modality has been sporadic until recently. In the 1960s, researchers confirmed that cancer cells are more vulnerable to heat than their normal counterparts. In the U.S., the hegemony of the three official modalities -- surgery, radiation and chemotherapy -- lasted until the 70s, when hyperthermia was taken off the ACS blacklist (Unproven Therapies List). In late 70s and early 80s several trials had shown that hyperthermia combined with radiation produced superior results over radiation alone. Recently, the results of three European and one American phase III trials have become available. All these trials were well controlled, showing that the use of hyperthermia in combination with radiation therapy results in superior tumor response, tumor control,

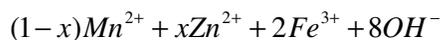
and survival as compared with radiation therapy alone [2]

Magnetic hyperthermia is the method of heating body tissue using magnetic materials [3,4,5]. In this process magnetic material is introduced near the tumor then subjected to an oscillating magnetic field that will cause the material to heat. Self controlled hyperthermia controls the spot overheating that causes necrosis [6]. The self control of overheating is provided by controlling the materials Curie temperature. Nanomagnetic particles with Curie temperature of 42-43°C are suitable for producing biocompatible heat source at the tumor site when subjected to an alternating field. Once the particles temperature reaches the Curie temperature they will stop responding to the applied field, hence the heating will be maintained at the Curie temperature. This study is aimed at producing nanomagnetic particles with Curie temperature of 42-43°C.

Mn-Zn Ferrite nanoparticles have gained a lot of consideration mainly because of the ability to vary their properties by varying the proportions of the constituent metals [7-9]. These particles are of the form $Zn_xMn_{(1-x)}Fe_3O_4$ and are synthesized by physical as well as chemical means. Chemical co-precipitation is one of the various methods used to synthesize nanoparticles. Gd-substituted Mn-Zn ferrite particles are made by chemical co precipitation method. The particles formed are of the nature $Mn_{0.5}Zn_{0.5}Gd_xFe_{(2-x)}O_4$. The effect of varying Gd proportions on the Curie temperature of the nanoparticles is reported.

MATERIALS AND METHODS

Mn-Zn-ferrite particles and Gd substituted Mn-Zn-Ferrite particles are obtained via chemical co-precipitation and ferritization. First the metal salts are co-precipitated into hydroxides. This is done by addition of aqueous solution of metal salts in water to the co precipitating base (e.g. NaOH, CH_3NH_3OH etc.). For the case of Mn-Zn Ferrite particles the reaction occurs as follows:



Then this precipitate is transformed into ferrite by heating in the precipitation alkaline solution (ferritization). The reaction for Mn-Zn ferrite particles is as follows:



FeCl₃ 6H₂O, GdCl₃ 6H₂O, MnCl₂ 4H₂O and ZnSO₄ 7H₂O were used to obtain Fe³⁺, Gd³⁺, Mn²⁺ and Zn²⁺ ions in the aqueous solution. This salt solution at 90°C was added to 8M NaOH solution at 90°C followed by vigorous stirring. The stirring and heating at 90°C was continued for a minimum of 40 mins [7-9]. It has been reported by Auzans et. al. [7-9] that heating for over 40 mins does not produce any significant changes in the particles properties. The product was then filtered, washed with distilled water and finally washed and dried with acetone.

The samples made were of the form $Mn_{0.5}Zn_{0.5}Gd_xFe_{(2-x)}O_4$. The following Mn-Zn-Gd ferrite particle samples were made:

Sample Name	Proportion of Gd: x
S	0
T	0.2
U	0.5
V	0.7
W	1
X	1.5

The hysteresis curves were obtained at room temperature using a vibration sample magnetometer (VSM). A Quantum Design SQUID was used to study the temperature dependence of the magnetization.

RESULTS

All the samples were examined by X-ray powder diffraction (XRD). XRD diagrams for the samples are shown in fig. 1. All major peaks were indexed to the standard pattern for Mn-Zn Ferrite.

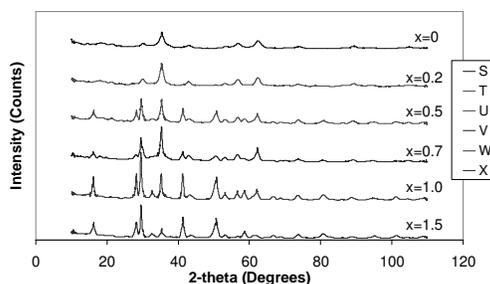


Fig 1. XRD Analysis

Hysteresis curves:

The hysteresis curves at room temperature for the samples S, U, W and X were obtained using a vibration sample magnetometer by subjecting them to a field in the range of 0 to 5,000 G (fig. 2). All these samples were observed to be soft-magnetic.

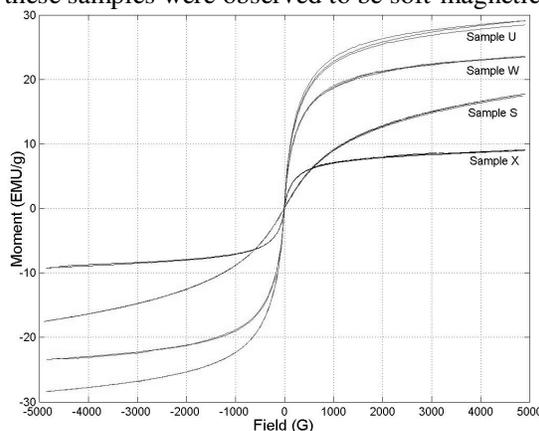


Fig. 2 Hysteresis curves

Temperature dependence of magnetization:

The temperature dependence of magnetization was observed by using a Quantum Design SQUID. For this a constant field of 100G was applied and the moment was measured by varying the temperature from 0K to 450 K.

Fig. 3 shows the superimposed Temperature Dependence on Magnetization plots for all the samples. The Curie temperature was calculated by extrapolation of the linear sections of the temperature dependence plots [7]. The variation in Curie temperature with increasing Gd proportion is plotted in fig. 4.

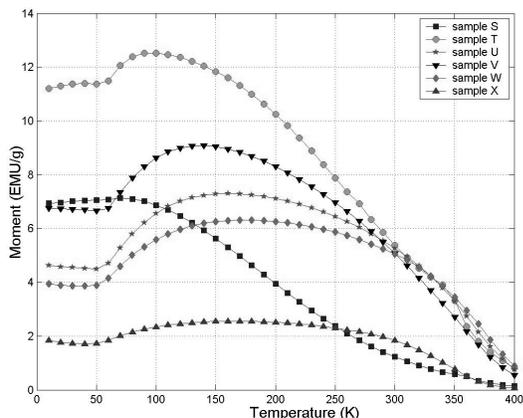


Fig. 3 Temperature dependence of magnetization for all samples

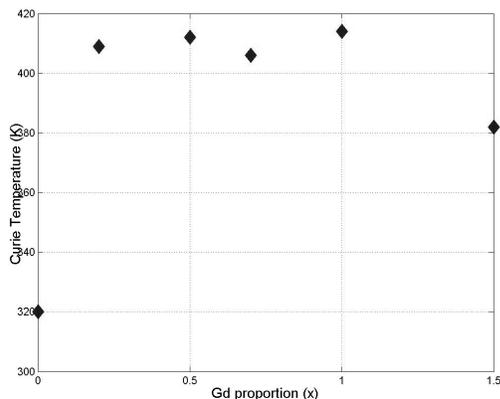


Fig 4 Curie temperature variation with Gd

Saturation Magnetization:

Table 1 lists the variation in saturation magnetization and Curie temperature with increasing Gd proportion.

Table 1 M_{sat} and T_c for samples

Sample Name	Saturation Magnetization (EMU/g)	Curie Temperature (K)
S	20	320
T	-	409
U	29	412
V	-	406
W	24	414
X	9.5	382

DISCUSSION

In this study Gd substituted Mn-Zn ferrites with various Zn and Gd proportions were synthesized to study the effect on the magnetic properties of these particles and also to find a combination which will result in particles having a Curie temperature suitable for hyperthermia application.

It is observed that the saturation magnetization of the particles drop with increasing Gd proportion. The initial increase in the saturation magnetization can be explained by considering that the Gd^{3+} ions have a large spin magnetic moment per atom ($7\mu_B$) as compared to that of Fe^{3+} ion ($5\mu_B$) [10-13]. Addition of Gd^{3+} ions results in their occupancy of the octahedral sites. The preference for octahedral sites maybe attributed to their large ionic radii. Since the ionic radii of the Gd^{3+} ions are large, there is a decrease in the distance between these and the oxygen ions when adding Gd ions [14]. 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 anti parallel to the 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 As a result the saturation magnetization drops.

Upadhyay et al. [15] have synthesized Gd substituted Mn-Zn Ferrite nanoparticles using chemical co-precipitation. They observed an increase in the pyromagnetic co-efficient ($(\partial M / \partial T)_H$) of the resultant particles. The increase in the pyromagnetic co-efficient is desirable because it results in a steeper slope of the magnetization v/s temperature plot which in turn ensures that the magnetization decreases rapidly as the temperature approaches the Curie temperature. This rapid decrease in magnetization means that the particles are heated up faster at temperatures below the Curie temperature and suddenly stop being heated near the Curie temperature which is a desirable property for Hyperthermia application. From Fig. 4 it can be seen that there is an increase in Curie temperature with Gd substitution. The Curie temperature increases from 320 K for Sample S ($x=0$) to about an average of 410 K for sample T (409 K), U (412 K), V(406 K) and W (414 K). Thus the Curie temperature remains almost constant for Gd proportions $x=0.2$ till $x=1.0$. But further addition of Gd results in a decrease in Curie temperature (Sample X: $x=1.5$: $T_c=382$ K).

CONCLUSIONS

Nanosize Mn-Zn ferrite and Gd substituted Mn-Zn ferrite particles have been synthesized by chemical co precipitation method. The samples are observed to be soft-magnetic. Addition of Gd^{3+} ions up to proportions of $x=0.5$ results in an increase in the net moment. Further addition of the Gd^{3+} ions results in a decrease in the net moment. The saturation magnetization increases then

decreases with increasing proportion of Gadolinium. The Curie temperature increases with addition of Gadolinium. But addition of Gd in proportions more than $x=1.0$ results in a decrease in Curie temperature.

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