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# Preparation and investigation of potentiality of different soft ferrites for hyperthermia applications

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Water-based ferrofluids of substituted ferrites  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$  ( $0 \leq x \leq 1$ ) have been prepared by the co-precipitation method and characterized. Particles are superparamagnetic with an average particle size of about 10–12 nm. The specific absorption rate (SAR) was measured by calorimetric measurement at a frequency of 300 kHz and a field of 10–45 kA/m. The variation of SAR and magnetization of  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$  with Mn concentration shows similar dependence. Innocuousness studies of  $\text{MnFe}_2\text{O}_4$  ferrofluids to the living cells have been carried out with BHK-21 cells. *In vitro* studies showed that threshold biocompatible concentration is dependent on the nature of ferrites and coating. © 2005 American Institute of Physics. [DOI: 10.1063/1.1855131]

## INTRODUCTION

Heating (41–46 °C) of specific tissues or organs for treatment of cancer known as hyperthermia, has attracted a lot of attention in recent years. For this, superparamagnetic–ferrimagnetic  $\text{Fe}_3\text{O}_4$  or  $\gamma\text{-Fe}_2\text{O}_3$  particles have been extensively studied as they are biocompatible. But the feasibility of other ferrites, e.g., “ $\text{M}_{1-x}\text{Zn}_x\text{Fe}_2\text{O}_4$ , M=Mn, Co, Fe” and “ $\text{Fe}_{1-x}\text{B}_x\text{Fe}_2\text{O}_4$  (B=Mn)” for this purpose is yet to be explored.<sup>1–3</sup> The most challenging work is to maximize the specific absorption rate (SAR) in hyperthermia, which allows reduction of ferrofluid dose *in vivo* (tumor). The dependence of SAR on parameters like magnetization, size, and distribution of particles, magnetic-field strength, and frequency of the AC field has been discussed.<sup>4</sup> The power losses ( $P$ ) will be maximized when  $\omega\tau \sim 1$  after Debye<sup>5</sup> for relaxation process. By appropriately choosing  $\omega$  and  $\tau$ , it is possible to maximize the SAR values. Further enhancement of SAR is possible by increasing the magnetic moment. In this context, we have synthesized  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$  ( $0 \leq x \leq 1$ ) system with a view to improve the SAR without adversely affecting the biocompatibility. The results are discussed in this paper.

## EXPERIMENTAL

The substituted ferrites were prepared by co-precipitation technique in  $\text{N}_2$  atmosphere using ammonium hydroxide (specific gravity=0.96) under identical preparation conditions.<sup>6</sup> The fatty acid coated dilution insensitive ferrofluid was centrifuged at 5000 rpm for 15 min to separate out the unstable particles followed by dialysis of ferrofluid against distilled water using cellulose membrane

(12 kDa) for 72 h. The resultant fluid is again centrifuged at 3000 rpm for 10 min and filtered. The resultant fluid contains well-dispersed nano size particles in an aqueous solution without coagulation for several months. Thermogravimetric analysis (TGA) has been used to determine the ferrite concentration in ferrofluid. Samples were characterized using x-ray diffraction (XRD), vibrating sample magnetometer (VSM), transmission electron microscopy (TEM), and particle size analyzer.

The heating ability (SAR) of the different ferrofluids was measured from the time-dependent calorimetric measurements.<sup>6</sup> The RF generator used for this experiment has a variable field from 10 to 45 kA/m with a fixed frequency of 300 kHz. For the identification of the contribution of viscous loss (Brownian loss) to SAR, the ferrofluid was mixed with an aqueous solution of acrylamide to form a gel where viscosity of the medium increased by several orders of magnitude. Thus, the loss due to Brownian motion of particles has been eliminated.<sup>7</sup>

Cytotoxicity assays of ferrofluids ( $\text{MnFe}_2\text{O}_4$ ) were done using BHK 21 (Syrian Baby Hamster Kidney cell line) cell using BME (Basal Medium Eagle) as culture media.<sup>6</sup> Exponentially growing cells were incubated with different ferrofluid concentrations (1.2–0.00004 mg ferrite/ml) up to 96 h.

## RESULTS AND DISCUSSION

XRD confirms the formation of single phase for all the ferrites. The crystallite diameter is calculated using XRD line broadening and TEM. The TEM micrograph shows that the spherical particles are well dispersed. The average crystallite size for different ferrites is 10–12 nm. The hydrodynamic diameter as determined from dynamic light scattering method (DLS) varies between 70 and 80 nm. Figure 1 shows

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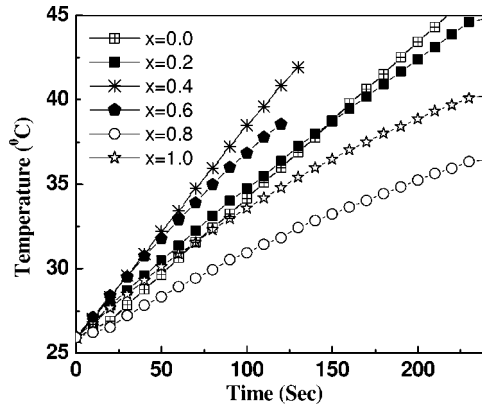


FIG. 1. Time-dependent temperature curve of different  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$  ( $x = 0-1$ ) ferrofluid samples at 300 kHz frequency and 20 kA/m field.

the time-dependent temperature curves of the six ferrofluid samples with varying Mn concentration (0 to 1) in the presence of an AC magnetic field (300 kHz, 20 kA/m). SAR was calculated using following equation:

$$\text{SAR} = C \frac{\Delta T}{\Delta t} \frac{1}{m_{\text{ferrite}}}. \quad (1)$$

Where  $C$  is the specific heat of ferrofluid and sample holder taken together.  $\Delta T/\Delta t$  is the initial slope of the time-dependent temperature curve.  $m_{\text{ferrite}}$  is the total ferrite content in the fluid. In our experiment, ferrofluids used had a ferrite concentration of 20 mg/ml. From the initial slope of Fig. 1, SAR is calculated. Figure 2 shows the variation of SAR of different ferrofluids with AC field. The dependence of SAR of different ferrofluids on  $H$  varies from linear to second order, which may be attributed to change in composition of ferrofluid. The square laws were already reported for various ferrofluids.<sup>7</sup>

The  $M$  vs  $H$  curve for all the samples shows absence of hysteresis, confirming the superparamagnetic nature. Figure 3 shows the variation of magnetization at a field of 1.8 T with substitution of Fe with Mn. The magnetization initially increases with  $x$  up to a value of  $x=0.4$  and then it decreases.  $\text{Mn}^{2+}$  is isoelectronic with  $\text{Fe}^{3+}$ ; so for small  $x$ ,  $[\text{Fe}_{1-x}^{3+}\text{Mn}_x^{2+}](\text{Fe}_{1-x}^{3+}\text{Fe}_{1-x}^{3+})$  give a magnetic moment of  $(4+x)\mu_B$  (Bohr magneton) per formula unit. This accounts for

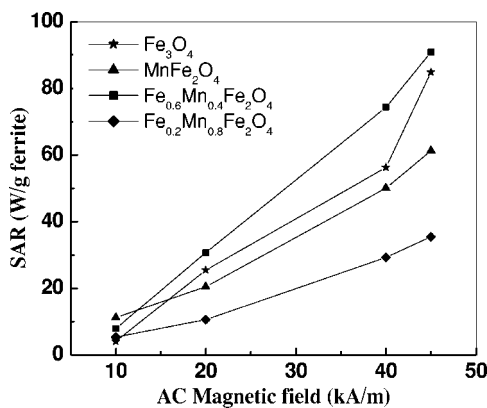


FIG. 2. Variation of SAR with AC magnetic field amplitude measured at 300 kHz for different ferrofluid samples.

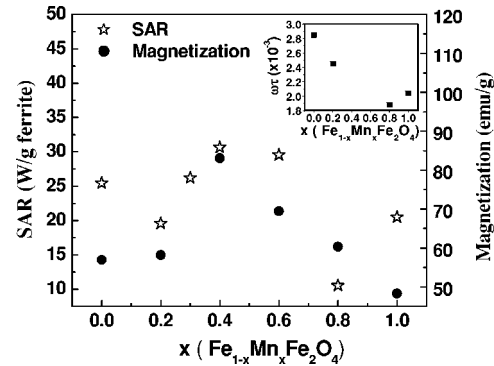


FIG. 3. Variation of magnetization and SAR with Mn (II) concentration in  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$ . The inset showing variation of  $\omega\tau$  with  $x$  in the same ferrite system.

the initial linear increase of magnetic moment with Mn substitution. The decrease beyond  $x=0.4$  is due to weakening of the AB interaction when  $\text{Fe}^{3+}$  is substituted by  $\text{Mn}^{2+}$  in the A site.<sup>8</sup>

Figure 3 shows the variation of SAR with Mn concentration in  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$ . It is noteworthy that SAR also goes through a maximum as the magnetization goes up. For superparamagnetic particles, SAR will result from relaxation processes. These processes in ferrofluids are either due to reorientation of the magnetization into the particle (Neel losses) or due to frictional losses (Brown losses). The Brownian relaxation time is

$$\tau_B = \frac{4\pi\eta r^3}{kT}, \quad (2)$$

and Neel relaxation time is

$$\tau_N = \tau_0 \exp \frac{KV}{kT}, \quad (3)$$

where  $\eta$  is viscosity of carrier liquid,  $r$  hydrodynamic radius of particles,  $k$  the Boltzmann's constant,  $\tau_0$  the time constant ( $\sim 10^{-9}$  s),  $V$  the particle volume, and  $K$  the anisotropy constant. The power loss corresponds to Néel and/or Brownian relaxation and is approximately given by<sup>5</sup>

$$P = (mH\omega\tau)^2 / [2\tau kT\rho V(1 + \omega^2\tau^2)], \quad (4)$$

where  $m$  is the particle magnetic moment,  $\omega$  the angular frequency,  $H$  the AC field amplitude, and  $\rho$  the density of ferrite.  $P$  will reach a maximum when  $\omega\tau=1$ <sup>5</sup>. In our system ( $d_h=70-80$  nm,  $f=300$  kHz), the contribution due to Brownian losses is very small as also confirmed by the polyacrylic gel experiment. If we consider SAR due to Néel losses, the relaxation time is dependent on  $V$  and  $K$ . Here, the size of magnetic particles obtained from XRD and TEM shows that there is no notable variation with varying Mn concentration. Hence a change of  $\tau_N$  with  $V$  is ruled out. If  $K$  does not change with Mn concentration, then the variation of  $P$  with  $x$  should be the same as the magnetic moment. But the sudden drop of SAR around  $x=0.8$  may be due to variation in  $K$  with  $x$ . Penoyer and Shafer<sup>9</sup> reported the variation of  $K$  with Mn concentration, which reaches a minimum for Mn concentration of  $x=0.7$ . Taking the value of  $K$  from literature,<sup>8</sup> we have calculated  $\omega\tau$  and its variation with  $x$  is

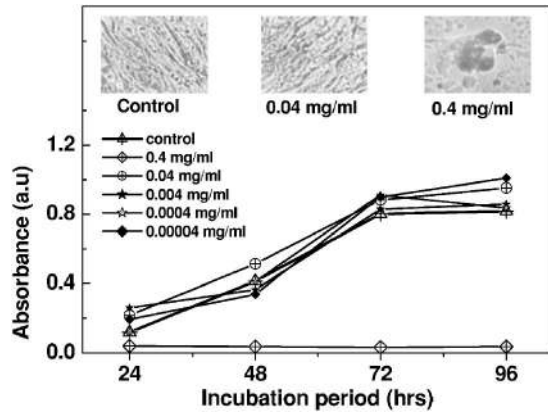


FIG. 4. Graph showing absorbance at 560 nm after different periods of incubation of different ferrite concentrations (0.4–0.0004 mg/ml) of  $\text{MnFe}_2\text{O}_4$  fluid. The inset photographs showing growth of BHK 21 cells (fixed with 50% Trichloroacetic acid) at 96 h for control (without ferrofluid), 0.04 mg/ml ferrite and 0.4 mg/ml.

given in the inset of Fig. 3. The effect of  $K$  on  $\tau_N$  as well as on SAR will reflect on the value of  $\omega\tau$  and hence its degree of deviation from (i.e.,  $\omega\tau=1$ ). The variation in magnetization and anisotropy together may explain the SAR values for different compositions. It is interesting to note that SAR is enhanced by 20% in  $\text{Fe}_{1-x}\text{Mn}_x\text{Fe}_2\text{O}_4$  ( $x=0.4$ ) compared to  $\text{Fe}_3\text{O}_4$ .

For comparative *in vitro* biocompatibility study,  $\text{MnFe}_2\text{O}_4$  is chosen where otherwise traditionally well-known biocompatible material  $\text{Fe}_3\text{O}_4$  is used. Figure 4 shows the BHK-21 cell proliferation in presence of different concentration of  $\text{MnFe}_2\text{O}_4$  ferrite. At the concentration of 0.4 mg/ml, it shows low cell viability, but at other concentration, it shows same viability as control. The inset in Fig. 4 shows the cell (BHK-21) morphology under phase contrast microscope ( $20\times 10$  magnification) in the presence of differ-

ent  $\text{MnFe}_2\text{O}_4$  concentrations after 72 h of incubation. At the higher concentrations, beyond threshold value (0.4 mg/ml), there are no viable cells. But at a concentration of 0.04 mg/ml, there is clear evidence of cell growth as the control. It has been observed that the threshold biocompatible limit of fatty acid coated  $\text{MnFe}_2\text{O}_4$  ferrofluid is the same as  $\text{Fe}_3\text{O}_4$ . This limit has been enhanced by several orders using different types of coating, e.g., dextran, liposome (data not shown here).

## CONCLUSION

The ferrofluid of Mn substituted  $\text{Fe}_3\text{O}_4$  has been prepared and SAR of these ferrites has been determined. We have noticed that the value of SAR increased by 20% in  $\text{Fe}_{0.6}\text{Mn}_{0.4}\text{Fe}_2\text{O}_4$  as compared to  $\text{Fe}_3\text{O}_4$ . The magnetization exhibits similar variation as SAR. The sudden drop of SAR for  $\text{Fe}_{0.2}\text{Mn}_{0.8}\text{Fe}_2\text{O}_4$  can be explained by considering anisotropy constant  $K$ . The biocompatibility and higher SAR may make these materials useful for hyperthermia applications.

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